South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: A REVIEW OF THE OPTIMAL DOSE OF EITHER UNFRACTIONATED HEPARIN OR LOW MOLECULAR WEIGHT HEPARIN IN THE PREVENTION OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH SEVERE COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 3 September 2020; Update of first version (19 June 2020).

Key findings

- A rapid review was conducted to assess the safety and efficacy of therapeutic intensity doses of heparin (including unfractionated heparin and low molecular weight heparin) as thromboprophylaxis in hospitalised patients with COVID-19.
- No controlled studies (randomised or other) were found on this topic in either adult or paediatric populations.
- There is conflicting data on whether therapeutic anticoagulation doses increases or decreases the risk of mortality in patients with severe COVID-19, however the data quality is too low to draw any definitive conclusions.
- Observational data shows an increased risk of major bleeding and clinically relevant non-major bleeding associated with treatment doses of heparin.
- There is currently insufficient evidence to recommend the use of therapeutic doses of either unfractionated or low molecular weight heparin as thromboprophylaxis in treatment guidelines for COVID-19 in South Africa until more robust evidence pertaining to efficacy and safety is published.
- Therapeutic doses for use as thromboprophylaxis in patients with severe COVID-19 should only be considered for use within the context of a clinical trial setting.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	X				

Recommendation: Based on this evidence review, the NEMLC Subcommittee recommends against the use of therapeutic doses of heparin for venous thromboembolism prophylaxis. Prophylactic doses should be used as recommended in the Standard Treatment Guidelines and Essential Medicines List.
Rationale: There is currently insufficient evidence to recommend the use of therapeutic doses of either unfractionated or low molecular weight heparin as thromboprophylaxis in children or adult patients with severe COVID-19. Additionally, there is a signal of potential harm. Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.
Level of Evidence: III Observational study

(Refer to appendix 4 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair).

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available

BACKGROUND

Severe COVID-19 may induce a hypercoagulable state[1-5], although the pathogenesis is poorly understood. Furthermore, coagulopathy secondary to coronavirus infection is associated with a higher mortality [4, 6]. Several coagulation abnormalities have been observed in patients with COVID-19 including increased D-dimer (a degradation product of cross-linked fibrin indicating augmented thrombin generation and fibrin dissolution by plasmin), increased fibrin and fibrin degradation product (FDP), longer prothrombin time and longer activated partial thromboplastin time. These derangements are associated with poor outcome. [4, 6-8] Elevated D-dimer has been the most consistent prognosticator of a poor outcome [10, 11].

Clinical guidelines recommend that all hospitalised patients with COVID-19 receive thromboprophylaxis with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). [12-15] (see Appendix 1). However, the risk of venous thromboembolism (VTE) remains high despite heparin prophylaxis. VTE has been observed in up to one-third of COVID-19 patients in intensive care units, even when prophylactic anticoagulation was used [1, 16]. It has been suggested that higher heparin doses i.e. doses of intermediate or therapeutic intensity may be used to prevent thromboembolism [1, 11, 15-17]. This is despite observations in two retrospective case series wherein the risk of VTE in ICU patients remained despite the use of of higher doses of LMWH [8, 17]. Consequently, neither the optimal dosing nor clinical benefit of heparin prophylaxis in patients with severe COVID-19 are known[11]. We review evidence to date that may inform recommendations regarding the dosing of heparin to prevent VTE in severe COVID-19 patients in South Africa.

A recent systematic review on the incidence of thromboembolism in patients with COVID-19 and whether antithrombotic therapies improve outcomes[18], found that, overall, there are a small number of applicable studies each with serious methodological limitations or inadequate reporting relating to the incidence of thromboembolic events in acutely and critically ill hospitalized patients. Evidence regarding dosing of heparin or LMWH was equally weak.

RESEARCH QUESTION:

What is the optimal heparin dose for the prevention of venous thromboembolism in patients with severe COVID-19, including those with and without requirement for oxygen therapy/ ventilatory assistance?

METHODS

This is an update of a rapid review conducted in June 2020. The original evidence search involved systematic searching of four electronic databases (PubMed as well as the Epistemonikos, Cochrane COVID Study Register and L-OVE Working Group databases). One reviewer screened records and extracted data. A second reviewer screened records independently and checked the data extraction. References listed in narrative reviews on this subject were also reviewed. Relevant records were extracted in a narrative table of results (see Table 1). No appraisal or meta-analysis was done. The search strategy is shown in Appendix 2. All reviewers checked the information that was extracted into the table of results.

For this update, the search included the Epistemonikos (https://app.iloveevidence.com/ in the COVID-19 evidence platform) and Cochrane's COVID-19 study register (https://covid-19.cochrane.org/). All results were uploaded into Covidence, a reference management software for reviews. Two reviewers screened the records. Mismatches in abstract selection was settled by consensus. Search details provided in appendix 2B.

Eligibility criteria for review

Population: Patients with confirmed or suspected COVID-19 with or without the requirement for oxygen therapy/ ventilatory assistance and receiving either UFH or LMWH as thromboprophylaxis. No restriction on age. Disease severity such that hospitalisation and/or admission to ICU is required.

Intervention: Therapeutic intensity doses of either unfractionated or low molecular weight heparin used as thromboprophylaxis.

Comparators: Prophylactic doses of either unfractionated or low molecular weight heparin.

Outcomes: Mortality; number of thromboembolic events, bleeding events, duration of hospitalisation; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse reactions and adverse events.

Study designs: Case series, non-randomised cohorts as well as randomised controlled trials, and systematic reviews of studies in humans.

RESULTS

We searched Epistemonikos and the Cochrane COVID Study Register on 12 August 2020. The results were uploaded into Covidence, a reference management software for reviews. We identified 235 records, 189 were screened independently after removing duplicates. Discrepancies were addressed by a joint re-evaluation of the abstracts. Five studies were [8, 17, 21-23]. compatible with the predefined PICO criteria described above and thus included for review. **Table 1** reports the main characteristics and outcomes of the included studies.

The original review included 2 studies. The first [8] was a retrospective, observational study investigating the incidence of venous thromboembolism in 198 hospitalised COVID-19 patients. All patients received VTE prophylaxis with the LMWH, nadroparin. 20% of patients (n = 39) developed a VTE despite prophylaxis. 35 of these 39 events occurred in ICU patients.

The second [17] was also a retrospective, observational study investigating the incidence of venous thromboembolism. In this instance, 26 anticoagulated ICU patients with severe COVID-19 and respiratory failure admitted to ICU were systematically assessed for VTE using complete duplex ultrasound (CDU). Anticoagulation dose was at the discretion of the treating physician based on the individual thrombosis risk and patients were classified as treated with prophylactic anticoagulation or therapeutic anticoagulation. Patients treated with therapeutic anticoagulation received either LMWH or unfractionated heparin with anti-Xa monitoring. The cumulative incidence of peripheral VTE was 69% (n = 18), and pulmonary embolism was diagnosed in six patients (23%). The proportion of VTE was significantly higher in patients treated with prophylactic anticoagulation when compared with the higher dose group (100% vs 56%, respectively, P = 0.03). However, for patients treated with therapeutic anticoagulation, 56% were found to develop VTE with six pulmonary emboli.

Three new studies have been included in this updated review.

Motta and colleagues[21] conducted a retrospective cohort study to determine the impact of anticoagulation on mortality in patients who received therapeutic versus prophylactic anticoagulant doses. (Anitcoagulants: enoxaparin or unfractionated heparin)

They found that patient mortality was 2.3 times higher when patients received pre-emptive therapeutic anticoagulation (AC. aRR = 2.3 (95% CI = 1.0, 4.9). Multivariable model adjusted for age, ethnicity, diabetes, history of cancer or heart disease, hyperlipidaemia, peak CRP, intensive care, mechanical ventilation and antibiotic use)

The authors concluded that "since the thrombotic effects of COVID 19 are not completely understood, it may very well be the case that therapeutic anticoagulation is an ineffective treatment with worse clinical outcomes for this syndrome."

Pesavento et. al.[22] conducted a retrospective cohort study to assess the risk/benefit of anticoagulation in 324 non-critical COVID-19 positive patients. (Anticoagulants: unfractionated heparin/fondaparinux/enoxaparin). Patients with critical disease (i.e. patients requiring intubation for ventilatory support or intensive care) were excluded from the study.

Incidence rate of bleeding (including both major bleeding and clinically relevant non-major bleeding) was 6.9 per 100 person/months (95% CI, 3.9 to 11.5) in patients receiving prophylactic heparin doses versus 26.4 per 100 person/months (95% CI; 15.6 to 41.6) in patients receiving treatment doses (all doses higher than prophylaxis).

Two fatal bleeding events occurred in each group (prophylactic group = 0.9 fatal bleeds per 100 person/months; treatment group = 2.9 fatal bleeds per 100 person/months).

Treatment doses of anticoagulation were also associated with a higher all-cause mortality [Prophylaxis incidence rate = 12.2 per 100 person/months (95% CI, 8.1 to 17.8); treatment dose incidence rate = 20.1 per 100 person/months (95% CI, 11.0 to 33.8)].

Stessel and colleagues[23] conducted a longitudinal controlled before and after study to investigate the impact of implementing an individualised thromboprophylaxis protocol in critically ill ICU patients with COVID-19. The before group received routine low dose pharmacological VTE prophylaxis, i.e. once-daily subcutaneous nadroparin calcium 2850 IU (n = 46). The after group received more aggressive thromboprophylaxis protocol including nadroparin calcium 3800 IU 12 hourly plus duplex ultrasonography twice a week to assess the presence of DVT in the large veins as well as daily measurements of anti-factor Xa (anti-Xa) activity (n = 26). Primary outcome was one-month mortality.

One-month mortality was 39.1% (18/46) of patients in the before group and 3.85% (1/26) of patients the after group ($p < 0.001$).

Incidence of VTE was 41.3% (19/46) and 15.4% (4/26) in the before and after groups, respectively ($p = 0.03$).

Length of ICU stay was reduced by 2 days in the After group (13 versus 11 days; $p = 0.03$).

Study limitations and quality assessment
All included studies were observational, non-randomised and uncontrolled thus subject to bias and confounding.

The studies included as part of the initial review[8, 17] had small patient numbers and were therefore insufficiently powered to draw robust conclusions from their findings. The benefits and harm of heparin dosing were not pre-specified endpoints. In the study by Middeldorp and colleagues [8], the heparin dose was amended midway through the study period.

In addition to the general limitations highlighted above, the studies included in this updated review[21 - 23] also have a number of weaknesses:

The study by Pesavento et. al.[22] excluded critically ill patients. The study groups were poorly matched in that the prophylaxis group had a younger median age (median age = 70 years versus 77 years for the treatment dose group). Additionally, the treatment dose group included double the proportion of patients with a history of venous thromboembolism (Prophylaxis = 4.2% versus Treatment dose = 8.3%). The health status of the treatment dose group was worse than the prophylaxis group: treatment group had a higher average D-dimer value and 27.4% of patients in the treatment group required ICU admission versus 2.9% of patients in the prophylaxis group.

In Stessel et. al.[23], the “After” group was younger than the “Before” group (62.0 years versus 69.5 years, $p = 0.03$), and although not statistically significant, had proportionately fewer patients with hypertension and diabetes (hypertension = 42.3% versus 63.0%; diabetes = 23.1% versus 30.4%). There may have been other changes in clinical management between the “before” and “after” periods that contributed to improved outcomes in the “after” group-details of such confounders are not reported in the publication.

Future clinical trials
As of 18 August 2020, 23 clinical trials investigating the role of optimal dose of LMWH's for thromboprophylaxis in patients with COVID-19 are registered. A short summary of planned and ongoing studies is included in Appendix 3.

CONCLUSION

There is currently insufficient evidence to support the use of a therapeutic dose of heparin as thromboprophylaxis in hospitalised patients with severe COVID-19, unless clinically indicated for other reasons. Although Stessel and colleagues[23] report a mortality benefit with a more aggressive approach towards anticoagulation as well as decreased ICU lengths of stay, the quality of this data is weak in that it was a single-centre observational study with low patient

numbers and no control. Moreover, new data from Motta et. al.[21] and Pesavento et. al.[22] suggests that higher anticoagulant doses may be associated with excess harm. Overall, the data is weak and is associated with significant methodological limitations.

Therefore, the original recommendation to apply the guideline outlined in the Adult Hospital Level Standard Treatment Guidelines and Essential Medicines List for thromboprophylaxis in patients with moderate to high risk of developing venous thromboembolism[20] remains (See Appendix 1). Therapeutic-intensity heparin dosing strategy should only be considered as part of randomised clinical trials so as to generate robust data on efficacy and safety of higher dose heparin in this clinical setting and to inform treatment policies in future.

Reviewers: Roger Wiseman (Liberty Health (Pty) Ltd, South Africa), Shelley McGee (South African Medical Association), Karen Cohen (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town).

Declaration of interests:

RW and KW have no interests to declare. SM is employed by the South African Medical Association, sponsored by various pharmaceutical and device companies for CPD activities, exhibition at conferences and advertising in SAMJ. RW is employed by a private sector health insurance company.

Acknowledgements:

Dr Tamara Kredo and Ms Joy Oliver of the MRC for their assistance in conducting the evidence searches.

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Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings
Published, peer-reviewed Middeldorp, Coppens, van Haaps, et. al[8] Journal of Thrombosis and Haemostasis 2020 Incidence of venous thromboembolism in hospitalized patients with COVID-19 https://onlinelibrary.wiley.com/doi/10.1111/jth.14888	Retrospective case series. Single centre observational study 02 March 2020 to 12 April 2020	Setting: The Netherlands, 1 medical institution in Amsterdam, The Netherlands. Patients: hospitalized patients with COVID-19. Patients with a negative PCR test were considered 'confirmed' if they presented with symptoms and a disease course consistent with COVID-19, an alternative diagnosis was absent, and a CT-scan of the chest demonstrated abnormalities highly suspicious of typical pulmonary involvement of COVID 19 (n = 25 patients). Sample size: 198 patients (130 males, 68 females) Median age: 61 years (SD 14 years) 75 patients were admitted to ICU, 123 patients were admitted to a regular ward 19 patients were receiving anticoagulation prior to admission for other clinical indications	All patients received nadroparin 2,850 IU once-daily or 5,700 IU for patients with a body weight of ≥100 kg. From April 3 onwards, ICU patients received a double dose nadroparin i.e. 2,850 IU twice-daily for patients with a body weight <100 kg and 5,700 IU bid for those ≥100 kg.	Primary outcome: objective diagnosis of distal or proximal DVT, PE, or venous thrombosis at other sites including catheter-related thrombosis. After a median follow up of 7 days, 39 of 198 patients (20%; 95% CI, 15-26%) were diagnosed with venous thromboembolism. 35 of these 39 events occurred in ICU patients. Dose of heparin was not a pre-specified endpoint, however, the authors noted: "All VTE were diagnosed in patients receiving thrombosis prophylaxis. The risk of VTE in ICU patients was not lower during the period when the standard dose of nadroparin prophylaxis was doubled (58%) than in the first follow-up period (41%)." No statistical analysis was reported for this finding. None of the 19 patients on therapeutic anticoagulation for indications other than COVID-19 developed VTE compared to 39 of 179 of the remaining patients (22%; SHR, not estimable; Fisher's exact test P=0.03). No analysis on adverse reactions was provided.

Citation	Study design	Population (n)	Treatment	Main findings
Published research letter Llitjos, Leclerc, Chochois, et. al.[17] Journal of Thrombosis and Haemostasis 2020 High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients.	Retrospective case series. Multicentre observational study. 19 March 2020 to 11 April 2020	France: 2 centres Patients: Hospitalised patients with severe COVID-19 admitted to ICU with respiratory failure. COVID-19 confirmed by RNA detection of SARS-CoV-2. Sample size: 26 patients (20 males, 6 females) Average age: 68 years (Range 51.5 - 74.5 years) Eight patients received prophylactic dose of LMWH, 18 patients received therapeutic doses of LMWH.	This was a systematic assessment of venous thromboembolism (VTE) using complete duplex ultrasound (CDU) in anticoagulated COVID-19 patients. Anticoagulation dose was left to the discretion of the treating physician based on the individual risk of thrombosis and patients were classified as treated with prophylactic anticoagulation or therapeutic anticoagulation. Patients treated with therapeutic anticoagulation received either low molecular weight heparin or unfractionated heparin with anti-Xa monitoring, with therapeutic levels of 0.3 to 0.7 U/mL of anti-Xa activity.	Incidence of VTE in severe COVID-19 patients: Cumulative incidence of peripheral VTE of 69% (n = 18), and pulmonary embolism was diagnosed in six patients (23%). The overall mortality was 12%, 16 patients were discharged from the ICU, and seven continued to receive mechanical ventilation. The proportion of VTE was significantly higher in patients treated with prophylactic anticoagulation when compared with the other group (100% vs 56%, respectively, P = 0.03). However, for patients treated with therapeutic anticoagulation, 56% were found to develop VTE with six pulmonary embolisms. No analysis on adverse events was provided.

Citation	Study design	Population (n)	Treatment	Main findings
Published, not peer-reviewed Motta, Ogunnaike, Shah, et. al[21] medRxiv, 2020 Clinical Outcomes With the Use of Prophylactic Versus Therapeutic Anticoagulation in COVID-19 https://onlinelibrary.wiley.com/doi/10.1111/jth.14888	Retrospective cohort study 01 April 2020 to 25 April 2020	Connecticut, USA: 2 centres Patients: Hospitalised adult patients (18 years and older) diagnosed with COVID-19 and treated with anticoagulant therapy during their inpatient stay, which was started preemptively at the time of admission. Patients who received anticoagulation other than heparin or enoxaparin, or no anticoagulation, were excluded Patients who received therapeutic anticoagulation "specifically for a thrombotic indication" were excluded Sample size: 374 patients (220 males, 154 females) Average age: 64.7 years (SD 18.1) 299 patients received prophylactic dose of anticoagulation, 75 patients received therapeutic doses of anticoagulation. 93.5% of patients received LMWH at some time during their admission, 14.8% received heparin.	Comparison: treatment versus prophylactic dose of enoxaparin or unfractionated heparin Doses used: **Enoxaparin:** Therapeutic dosage: 1 mg/kg SC twice daily or 1.5 mg/kg SC daily Prophylactic dosage: 30 or 40 mg SC daily. **Heparin:** Therapeutic dosage: Intravenous heparin titrated to an activated partial thromboplastin time (aPTT) between 70 and 110 sec. Prophylactic dosage: 5000 units SC 8 hourly. Patients were assigned to the therapeutic group if they received a therapeutic dosage of either medication at any time. They were assigned to the prophylaxis group if they only received prophylaxis for the duration of their inpatient stay. Sensitivity analysis to address bias due to dichotomization of time-varying variable: defined anticoagulation as prophylactic based on dose at time of admission.	Primary objective: determine the impact of anticoagulation on mortality in patients who received therapeutic versus prophylactic doses of enoxaparin or heparin anticoagulation (AC). Secondary objective: determine the difference between the two groups in in-hospital mortality, among subgroup of patients with a peak CRP $\geq$ 200 mg/L. The risk of mortality was higher in patients on therapeutic AC than those on prophylactic AC. aRR = 2.3, 95% CI = 1.0, 4.9, p = 0.04) For patients with a CRP $\geq$ 200 mg/L, there was no difference in mortality between patients on therapeutic and prophylactic AC (aRR = 1.0, 95% CI = 0.2, 4.5, p = 0.97).

Citation	Study design	Population (n)	Treatment	Main findings
Published, peer-reviewed Pesavento, Ceccato, Pasquetto, et. al.[22] J Thromb Haemost. 2020 The hazard of (sub)therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: the Padua province experience. https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.15022	Retrospective cohort study 26 February 2020 to 06 April 2020	Monselice, Northern Italy: 2 centres Patients: Hospitalised patients with laboratory confirmed COVID-19. Exclusions: Patients with critical disease (i.e. patients requiring intubation for ventilatory support or intensive care) were excluded, as were those who could not receive antithrombotic prophylaxis and those on indefinite treatment with vitamin K antagonists or direct oral anticoagulants (DOAC). Sample size: 324 patients (181 males, 143 females) Median age: 71 years (IQR 59 - 82 years) 240 patients received prophylactic dose of anticoagulation, 84 patients received therapeutic doses of anticoagulation. 83.6% of patients received LMWH, 15.7% received unfractionated heparin.	Comparison: treatment versus prophylactic dosing of unfractionated heparin, enoxaparin or fondaparinux Prophylaxis doses: **Unfractionated heparin:** Daily doses up to 15 000 units **Enoxaparin:** Up to 4000 U daily **Fondaparinux:** Up to 2.5mg daily Treatment doses: Higher daily doses than the prophylaxis doses, usually adjusted to body weight or laboratory parameters were aggregated in one group [(sub)therapeutic group] regardless of the drug amount. Note: The authors term these doses as "(sub) therapeutic". In the analysis, all patients receiving daily doses that were higher than the prophylaxis doses, as defined above, were aggregated into the "(sub)therapeutic" group. The term "(sub)therapeutic" can be easily misunderstood as this group included all doses of heparin that were higher than prophylaxis For the purposes of this review, doses that this group received are therefore referred to as "treatment doses". Choice of antithrombotic agent was at discretion of the attending physician. Selection of agent was noted from information retrieved from patient clinical charts.	Primary endpoint: Composite of major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) occurring during the administration of antithrombotic agents (and up to two days after discontinuation). Secondary outcomes: -Single components of primary endpoint -Objectively confirmed symptomatic VTE -All-cause mortality. Prophylactic dose group: primary endpoint event in 15/240 patients (LMWH = 11, fondaparinux = 4). Incidence rate = 6.9 per 100 person/months (95% CI, 3.9 to 11.5). 8 major bleeds (MB) and 7 CRNMBs. Treatment doses group Primary endpoint event in 18/84 patients (17 on LMWH and 1 on fondaparinux). Incidence rate = 26.4 per 100 person/months (95% CI; 15.6 to 41.6). 8 MBs and 10 CRNMBs. Two fatal bleeding events occurred in each group: Prophylactic group: 0.9 fatal bleeds per 100 person/months: Treatment group: 2.9 fatal bleeds per 100 person/months). Death from any cause: 27 patients receiving prophylactic doses: incidence rate = 12.2 per 100 person/months (95% CI, 8.1 to 17.8). 14 patients receiving treatment doses: Incidence rate = 20.1 per 100 person/months (95% CI, 11.0 to 33.8)

Citation	Study design	Population (n)	Treatment	Main findings
Published, peer-reviewed Stessel, Vanvuchelen, Bruckers et. al.[23] Thrombosis Research, 2020 Impact of implementation of an individualised thromboprophylaxis protocol in critically ill ICU patients with COVID-19: A longitudinal controlled before-after study	Single-centre, investigator-initiated, longitudinal, controlled, before-after study 13 March 2020 to 20 April 2020	Hasselt, Belgium: 1 centre Patients: Patients with PCR-confirmed COVID-19 admitted to ICU. Sample size: 78 patients (69 males, 9 females) **Before group** (13 March to 30 March 2020): n = 46 Median age: 69.5 years (range 62 to 76 years) **After group** (31 March to 20 April 2020): n = 26 Median age: 62 years (range 56 to 73 years)	**Before group:** Patients admitted to ICU from 13 March until 30 March 2020 These patients received routine low dose pharmacological VTE prophylaxis, i.e. once-daily subcutaneous nadroparin calcium 2850 IU. **After group:** An individualised, more aggressive thromboprophylaxis protocol took effect from 31 March. This included: • Patients received nadroparin calcium to 3800 IU 12 hourly subcutaneously. Adjustments were made for severe kidney failure (eGFR < 30 ml/min) and cachectic patients (total body weight < 40 kg). • All patients were screened with duplex ultrasonography twice a week for the presence of DVT in the large veins • Daily measurement of anti-factor Xa (anti-Xa) activity in all patients	<u>Primary endpoint:</u> One-month mortality. <u>Secondary outcomes</u>: - One week mortality - Two week mortality - Three-week mortality - Incidence of VTE - ICU length of stay (LOS). One-month mortality was 39.13% (18/46) in the before group and 3.85% (1/26) in the after group ($p < 0.001$). Secondary outcomes: One-week mortality was 19.6% (9/46) in before group and 3.9% (1/26) in the after group ($p = 0.08$), Two-week mortality was 30.4% (14/46) in the before group and 3.9% (1/26) in the after group ($p = 0.01$) Three-week mortality was 37.0% (17/46) in the before group and 3.9% (1/16) in the after group ($p = 0.01$). Incidence of VTE was 41.3% (19/46) and 15.4% (4/26) in the before and after groups, respectively ($p = 0.03$). Length of ICU stay was reduced by 2 days in the After group (13 versus 11 days; $p = 0.03$).

Excluded studies:

1. Systematic review by Moldanado et. al.[18], which aimed to synthesize evidence on the incidence of thromboembolism in patients with COVID-19 and whether antithrombotic therapies improve outcomes. The authors noted a high risk of bias due to potential confounders and inconsistent patient follow-up, the studies low applicability to treatment setting where thromboprophylaxis is the standard of care and inconsistent result. Specifically pertaining to dose, this study was unable to offer insight into whether patients with COVID-19 should be treated with different thromboprophylaxis protocols than those previously recommended for hospitalized patients.
2. The systematic review by Hasan et. al. [24], which investigated venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation. It was not possible to differentiate the differences in clinical outcomes for therapeutic versus prophylactic doses of anticoagulation since the included original studies did not stratify their data based on the intensity of anticoagulation.

Appendix 1: GUIDELINE CONSIDERATIONS

NIH COVID-19 Treatment Guidelines (updated 30 July 2020)[12]

Venous Thromboembolism Prophylaxis

Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults **(Level of Evidence: Expert Opinion)**

There are currently insufficient data to recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19 in patients who are admitted to a hospital **(Level of evidence: moderate recommendation based on expert opinion)**.

World Health Organization: Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected. Interim guidance (27 May 2020)[13]:

Prevention of complications in hospitalized and critically ill patients with COVID-19

In patients (adults and adolescents) hospitalized with COVID-19, use pharmacological prophylaxis, such as low molecular weight heparin (such as enoxaparin), according to local and international standards, to prevent venous thromboembolism, when not contraindicated. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices).

Monitor patients with COVID-19, for signs or symptoms suggestive of thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism or acute coronary syndrome. If these are clinically suspected, proceed immediately with appropriate diagnostic and management pathways.

American Society of Hematology: (updated 20 July 2020)[14]

Recommendation for VTE prophylaxis in patients with COVID-19

All hospitalized adults with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH over unfractionated heparin to reduce contact, unless the risk of bleeding outweighs the risk of thrombosis. In the setting of heparin-induced thrombocytopenia, fondaparinux is recommended. Dose adjustment for obesity may be used per institutional guidance. In patients where anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (e.g. pneumatic compression devices). Combined pharmacologic and mechanical prophylaxis is not generally recommended.

Despite the lack of quality published evidence, many institutional protocols have adopted an intermediate-intensity (i.e., administering the usual daily LMWH dose twice daily) or even a therapeutic-intensity dose strategy for thromboprophylaxis based on local experience. We recommend participation in well-designed clinical trials and/or epidemiologic studies when they become available.

Recommendation regarding empiric therapeutic-intensity anticoagulation for VTE prophylaxis in seriously ill COVID-19 patients (i.e. in the absence of confirmed or suspected VTE)

Microvascular thrombosis is hypothesized to be involved in hypoxemic respiratory failure in some patients with COVID-19. Autopsy studies to date have been limited but they do show large vessel and microvascular thrombosis, pulmonary hemorrhage and high prevalence of VTE. Although retrospective cohort studies of patients treated or not treated with anticoagulation have been published, such observational data should not be used to support changes in practice due to the survivor bias, confounding by indication, and lack of adjustment for important patient comorbidities and other treatments. Whether critically ill COVID-19 patients should receive therapeutic-intensity anticoagulation in the absence of confirmed or suspected VTE is currently unknown. Multiple randomized controlled trials are investigating the effects of different doses of heparin on patient outcomes. We encourage participation in clinical trials rather than empiric use of therapeutic-dose heparin in COVID-19 patients with no other indication for therapeutic dose anticoagulation.

Australian guidelines for the clinical care of people with COVID-19. Version 17.0 (updated 13 August 2020)[15]

10 Anticoagulants

10.1 Venous thromboembolism (VTE) prophylaxis

Consensus recommendation

Use prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) in **adults with moderate COVID-19 or other indications**, unless there is a contraindication, such as risk for major bleeding. Where eGFR is less than 30 mL/min/1.73m2, unfractionated heparin or clearance-adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily or dalteparin 2500 IU once daily).

10.2 Increased-dose venous thromboembolism (VTE) prophylaxis

Consensus recommendation

Consider using increased prophylactic dosing of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily) in **adults with severe or critical COVID-19 or other indications**, unless there is a contraindication, such as risk for major bleeding or platelet count < 30 x 10^9/L. Where eGFR (see below) is less than 30 mL/min/1.73m2, unfractionated heparin or clearance-adjusted doses of LMWH may be used (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily).

Hospital level (Adults) Standard Treatment Guidelines and Essential Medicines List[20]

2.8 VENOUS THROMBO-EMBOLISM

MEDICINE TREATMENT

PROPHYLAXIS

Risk Assessment

Risk assessment is essential, and treatment needs to be individualised. Risk factors for VTE can be divided into predisposing factors (i.e. patient characteristics) and exposing factors (i.e. underlying medical conditions, nature of surgical intervention, etc.).

SUBCATEGORIES OF VTE RISK IN SURGICAL AND NON-SURGICAL PATIENTS

	Surgical patients	***Medical patients***
Low VTE risk	» Surgery lasting <30 minutes » Injuries without or with only minor soft-tissue trauma » No or only minor additional predisposing risk factors	» Infection or acute inflammatory diseases without bed rest » Central venous catheters » No or only minor additional predisposing risk factors
Moderate VTE risk	» Surgical procedures of longer duration » Immobilisation of lower limb with plaster cast » Lower limb arthroscopic procedures. » No or only minor additional predisposing risk factors	» Acute cardiac insufficiency (NYHA III/IV) » Acute decompensated COPD without ventilation » Infection or acute inflammatory diseases with bed rest » Malignant disease » No or only minor additional predisposing risk factors
High VTE risk	» Major surgical procedures for malignancy » Multiple trauma or severe trauma of the spine, vertebra or » lower limbs » Major orthopaedic surgery, e.g. hip or knee replacement » Major surgical procedure of cardiothoracic and pelvic region	» Stroke with paralysis » Acute decompensated COPD with ventilation » Sepsis » ICU patients

Source: Jacobson BF, Louw S, Büller H, Mer M, de Jong PR, Rowji P, Schapkaitz E, Adler D, Beeton A, Hsu HC, Wessels P, Haas S; South African Society of Thrombosis and Haemostasis. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013 Feb 15;103(4 Pt 2):261-7.
https://www.ncbi.nlm.nih.gov/pubmed/23547704

Some risk assessment models for assessing VTE risk:

Model	Url link to tool
Padua Prediction Score	https://www.mdcalc.com/padua-prediction-score-risk-vte
IMPROVE VTE risk score	https://www.outcomes-umassmed.org/IMPROVE/risk_score/vte/index.html
Geneva risk score	https://www.mdcalc.com/geneva-risk-score-venous-thromboembolism-vte-prophylaxis

Prophylactic treatment

Prophylaxis is indicated for medical patients with moderate to high risk of VTE (see table above), with restricted mobility during acute illness/ surgical patients.

- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.

In morbid obesity dosing of LMWH should be individualised, in discussion with a specialist
In renal failure (eGFR <30 mL/minute), the recommended dose of
LMWH is 1 mg/kg daily.

OR

Unfractionated heparin, SC, 5 000 units 12 hourly.

Although the risk of bleeding is small, in the following patients prophylaxis should only be used under exceptional circumstances:

» active bleeding
» intraocular, intracranial or spinal surgery
» lumbar puncture or spinal/epidural anaesthesia within 12 hours after prophylactic dose or 24 hours of full therapeutic dose, [Timing of anticoagulants for patients receiving anaesthesia: See section 12.8: Spinal (intrathecal) anaesthesia]
» renal insufficiency
» coagulopathy
» uncontrolled hypertension

Accessible at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Appendix 2: Search strategy

A: Original Review (June 2020):

Epistemonikos

(title:(heparin* OR "heparinic acid" OR liquaemin OR UFH OR "low-molecular-weight heparin" OR LMWH OR dalteparin OR enoxaparin OR nadroparin OR tinzaparin) OR abstract:(heparin* OR "heparinic acid" OR liquaemin OR UFH OR "low-molecular-weight heparin" OR LMWH OR dalteparin OR enoxaparin OR nadroparin OR tinzaparin)) AND (title:(coronivir* OR coronavirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR "COVID-19" OR COVID19 OR "2019-nCOV" OR 2019nCov OR "cv-19" OR"n-COV" OR ncov* OR hCOV* OR "SARS cov-2" OR "SARS-coronavirus" OR "SARS-cov" OR "MERS-cov" OR "MERS cov" OR "severe acute respiratory syndrome coronavirus") OR abstract:(coronivir* OR coronavirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR "COVID-19" OR COVID19 OR "2019-nCOV" OR 2019nCov OR "cv-19" OR"n-COV" OR ncov* OR hCOV* OR "SARS cov-2" OR "SARS-coronavirus" OR "SARS-cov" OR "MERS-cov" OR "MERS cov" OR "severe acute respiratory syndrome coronavirus"))

Records retrieved: 23 records

PubMed

((heparin[mh] OR heparin*[tiab] OR heparinic acid[tiab] OR liquaemin[tiab] OR UFH[tiab] OR heparin, low-molecular-weight[mh] OR LMWH[tiab] OR dalteparin[tiab] OR enoxaparin[tiab] OR nadroparin[tiab] OR tinzaparin[tiab]) AND (coronavir*[tiab] OR coronovirus*[tiab] OR corona virus[tiab] OR virus corona[tiab] OR corono virus[tiab] OR virus corono[tiab] OR COVID-19[tiab] OR COVID19[tiab] OR 2019-nCov[tiab] OR 2019nCov[tiab] OR cv-19[tiab] OR n-cov[tiab] OR ncov*[tiab] OR hCOV*[tiab] OR SARS cov-2[tiab] OR SARS-coronavirus[tiab] OR SARS-cov[tiab] OR (wuhan*[tiab] AND (virus[tiab] OR viruses[tiab] OR viral[tiab])) OR (COVID*[tiab] AND (virus[tiab] OR viruses[tiab] OR viral[tiab])) OR MERS-cov[tiab] OR MERS cov[tiab] OR COVID-19[NM] OR severe acute respiratory syndrome coronavirus 2[nm])) NOT ((animals[mh] NOT humans[mh])) AND (2019/12/01:2020/05/27[dp])

Records retrieved: 55 records

L-OVE Working Group (https://app.iloveevidence.com/**)**

Type of question: Treatment or prevention
Population: Coronavirus infection
Treatment: Heparins

Records retrieved: 4 records

Cochrane COVID Study Register (https://covid-19.cochrane.org/)

heparin* OR "heparinic acid" OR liquaemin OR UFH OR "low-molecular-weight heparin" OR LMWH OR dalteparin OR enoxaparin OR nadroparin OR tinzaparin

Records retrieved: 46 records

Total: 88 records excluding duplicates

B: Updated review (August 2020):

Cochrane COVID Study Register (https://covid-19.cochrane.org/) heparin* OR "heparinic acid" **Records retrieved:** 111 records, 45 duplicates
Epistemonikos (https://app.iloveevidence.com/**)** antithrombotic agents **Records retrieved:** 116 records, 1 duplicate

Total: 189 records excluding duplicates

Appendix 3: Summary of planned and ongoing studies

The review also identified several studies which are planned or ongoing to examine the outcomes of high versus low dose Heparin or Low Molecular weight Heparin in COVID-19 patients.

A total of 58 studies were identified Clinicaltrials.gov, 13 of which are examining high dose versus low dose of heparin or LMWH in patients with severe COVID-19 disease. These range from Phase 3 randomised controlled trials to observational cohort studies. Eleven of these studies are actively recruiting with planned completion dates ranging from October 2020 to January 2022. Outcomes include mortality, disease progression, ICU admission, incidence of VTE and bleeding.

Ten additional studies identified in Epistemonikos are also examining the different impacts of a prophylactic and therapeutic dose. Studies range from RCTs evaluating the impact of therapeutic dose LMWH on clinical worsening, death, VTE, need for mechanical ventilation, bleeding risk, to randomised open label trials comparing the efficacy of Therapeutic dose LMWH to standard prophylaxis in prevention of VTEs.

Appendix 4: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X]	Although systematic reviews have been published with respect to the used of increased doses of LMWH in ICU patients, the base data is limited to retrospective, observational studies which are regarded as low quality and subject to bias. Although Stessel and colleagues[23] report some mortality benefit with a more aggressive anticoagulation patient number are small and quality of this data is weak. In contrast, new data from Motta et. al.[21] and Pesavento et. al.[22] suggests that higher anticoagulant doses may be associated with excess harm.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X]	Data from Motta et. al.[21] and Pesavento et. al.[22] suggests that higher anticoagulant doses may be associated with excess harm however the quality of data is low.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [X]	See statement above.

<table>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the certainty/quality of evidence?
High | Moderate | Low | Very low
[ ] | [ ] | [ ] | [X]
High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect</td><td>Evidence base currently consists of five small observational studies subject to bias and confounding.</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes | No | Uncertain
[X] | [ ] | [ ]</td><td>Enoxaparin and unfractionated heparin are medicines listed on the National EML.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive | Less intensive | Uncertain
[X] | [ ] | [ ]</td><td>Price of medicines/day:
<table><tr><th>Medicine</th><th>Tender price</th><th>Price - SEP</th></tr><tr><td>Enoxaparin, SC, 40 mg daily</td><td>R41.39*</td><td>R91.49**</td></tr><tr><td>Unfractionated heparin, SC, 5000u 12 hourly</td><td>R8.28*</td><td>R16.28**</td></tr></table>*Contract circular RT297-2019 [Accessed 01/08/2020]
- Heparin Sodium Fresenius 5000iu/5ml = R45.70
** SEP database, excluding dispensing fees, March 2020 https://mpr.code4sa.org/
Bio-Heparin Sodium Fresenius 5000iu/ml = R16.28
Additional resources: n/a</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor | Major | Uncertain
[X] | [ ] | [ ]

Is the option acceptable to key stakeholders?
Yes | No | Uncertain
[ ] | [X] | [ ]</td><td>Patients: No specific research surveying patients' value of this therapeutic agent is currently available, and NEMLC Subcommittee judged this as "minor".

Healthcare workers: Currently therapeutic doses of heparin for VTE prophylaxis are used in clinical practice for critically ill patients, based on local experience.</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
First	19 June 2020	RW, SM, KC	Recommend against using therapeutic doses of heparin for VTE prophylaxis for hospitalised COVID-19 patients; as currently there is insufficient evidence for routine use - consider in context of clinical trial setting.
Second	3 September 2020	RW, SM, KC	Recommend against using therapeutic doses of heparin for VTE prophylaxis for hospitalised COVID-19 patients; as currently there is insufficient evidence for routine use - consider in context of clinical trial setting.