Low molecular weight heparins
in the treatment of adult patients with COVID-19

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ITALIAN MEDICINES AGENCY

Useful information is hereby provided to guide the prescription and to define a risk/benefit balance for the individual patient.	
For which patients are they possibly recommended?	• **Prophylactic doses** The use of low molecular weight heparins in the prophylaxis of thrombo-embolic events in patients with acute respiratory infection, both bedridden and with reduced mobility, is recommended by the main guidelines in the absence of contraindications. In the presence of the aforementioned characteristics, this applies both to hospitalized patients and to patients treated at home or in nursing homes. • **Intermediate/high doses** The use of intermediate/therapeutic doses in severe cases of COVID-19, classifiable in phase IIB or III of the clinical evolution of the disease, can be considered by evaluating the relationship between benefits and risks in the individual patient. In particular, levels of D-dimer much higher than normal (4-6 times) and/or a SCI score≥ 4, high ferritin (> 1000 mcg/L) or a high BMI (>30) seem to indicate conditions whereby the use of intermediate/high doses of LMWHs or unfractionated heparins correlates with clinical benefit, although there is no evidence from RCTs.
At which dosages is it preferably prescribed and in which forms?	Within the permitted indications, the recommended dose (prophylactic or therapeutic) will depend on the medicine chosen and on the characteristics of the patient as indicated in the drug technical data sheet.
Who can prescribe the medicine in this emergency phase?	LMWHs are **not** subject to prescription limitations in authorized uses, therefore they can be prescribed (with expenditure borne by the NHS) by the GP or by any NHS specialist and can be distributed locally according to the procedures established by the Regions.
What are the major risks in terms of adverse reactions?	***Warnings*** (from data sheet) Adverse events common to all LMWHs include: haemorrhage, thrombocytopenia, thrombocytosis, allergic reaction, headache, elevated liver enzymes, urticaria, itching, erythema, hematoma, pain or other injection site reactions. For a thorough analysis, please refer to the respective technical data sheets.
Can it be prescribed with other medicines?	***Main interactions*** (from Liverpool drug Interaction group): • No significant interactions are reported with medicines used in CoViD-19 trials. • The concomitant use of other anticoagulant medicines is not suggested and caution is recommended in the use of antiplatelet medicines. For further information on interactions, please refer to the website: https://www.covid19-druginteractions.org/

Background

Low molecular weight heparins (LMWH) are glycosaminoglycans obtained by fractionation of heparin; fondaparinux, a synthetic heparin, can also be found on the market. They are used in the prophylaxis of post-surgical venous thromboembolism and venous thromboembolism in NON-surgical patients suffering from an acute disease (such as acute heart failure, respiratory failure, severe infections or rheumatic diseases) and reduced mobility at an increased risk of venous thromboembolism. They are also used in the treatment of deep vein thrombosis, pulmonary embolism and acute coronary syndrome.
The medicines with permitted indication for prophylactic use in non-surgical patients are:

- Enoxaparin
- Parnaparin
- Fondaparinux

All LMWHs (extractive or synthetic) are indicated for the treatment of venous thrombosis. Enoxaparin and bemiparin are also indicated for the treatment of pulmonary embolism.
For all indications the dosages are present in the technical data sheet.
Finally, unfractionated heparins are indicated for the prophylaxis and therapy of venous and arterial thromboembolic disease.

Rationale

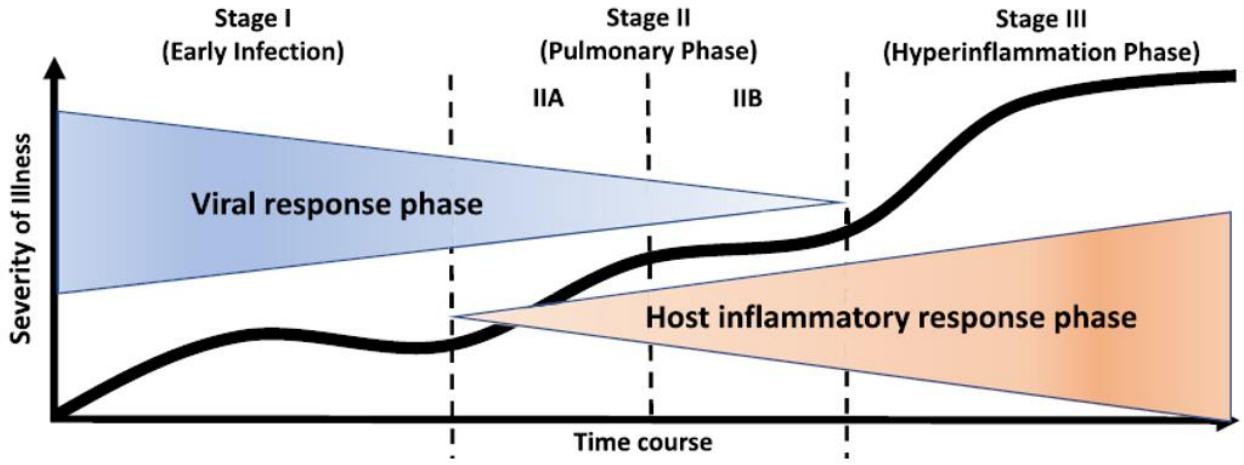
The clinical course of COVID-19 is divided into three distinct clinical stage:

1. An initial phase when the virus replicates within the host's cells. This phase is clinically characterized by the presence of presence of the classic flu-like symptoms (general malaise, fever, dry cough, etc.). The cases where the infection stops at this stage have an absolutely benign course.

2. The disease can then evolve into a second phase characterized by morpho-functional alterations in the lungs caused both by the direct effects of the virus and by the host's immune response. This phase is characterized by a pattern of interstitial pneumonia, very often bilateral, associated with respiratory symptoms which in the early phase are stable and without hypoxemia (phase IIA), but which may subsequently lead to progressive clinical instability (phase IIB).

3. This scenario, in a limited number of people, can evolve towards a worsening clinical picture dominated by the cytokine storm and the consequent hyperinflammatory state causing local and systemic consequences, which represents a negative prognostic factor producing, at the pulmonary level, pictures of arterial and venous vasculopathy with thrombosis of small vessels and evolution towards severe and sometimes permanent pulmonary lesions (pulmonary fibrosis). The final stages of this very serious clinical picture lead to severe ARD and in some cases DIC. In this phase, a progressive alteration was observed of some inflammatory parameters such as PCR, ferritin, and pro-inflammatory cytokines (IL2, IL6, IL7, IL10, GSCF, IP10, MCP1, MIP1A and TNFα) as well as of coagulative parameters such as increased levels of the fragments of fibrin degradation such as D-dimer, consumption of coagulation factors, thrombocytopenia, etc.

This picture, from both a clinical and an haematochemical point of view, is similar to haemophagocytic lymphohistiocytosis (rare clinical picture often triggered by a viral infection).
While the therapeutic choices of the first phase and the second initial phase (IIA) should aim at the containment of viral growth, in the second advanced phase (IIB) and in the third phase of the disease the goal should be the containment of hyperinflammation and its consequences. LMWHs or unfractionated heparins at therapeutic doses may have a role in the different phases of the disease, by also exploiting their anticoagulant properties.



Mod. da Siddiqi HK and Mehra MR. J Heart Lung Transplant. 2020

In particular, LMWHs should be used:

- in the initial phase of the disease, in presence of pneumonia and hypomobility of the bedridden patient. In this phase, LMWHs shall be used at a prophylactic dose in order to prevent venous thromboembolism, according to permitted indications;
- in the most advanced phase (hyperinflammation), in hospitalised patients, to treat thrombotic or thrombo-embolic phenomena of the venous or arterial system. In this case, LMWHs shall be used at therapeutic doses, according to permitted indications;
- in the advanced stages of the disease the usefulness of higher doses of LMWHs has been hypothesized to contain the effects on coagulation of the cytokine storm, even if to date the optimal dosages have not been specified of LMWH or unfractionated heparin, nor the specific indications nor the methods and times of administration.

Several RCTs are ongoing at both national and international level (see https://www.aifa.gov.it/sperimentazioni-cliniche-covid-19), with an aim to answer the above questions.

Available evidence

A retrospective analysis of 415 consecutive cases of severe pneumonia during COVID-19 (patients with at least one of the following characteristics were considered in serious medical conditions: RR≥30 breaths/min; SpO2 ≤93% at rest; PaO2/FiO2≤300 mmHg) admitted to the Wuhan hospital suggests that in patients with coagulation activation, the administration of heparin (unfractionated or LMWH) for at least 7 days could result in a survival advantage. The positive therapeutic effect is

apparently evident only in patients with a very high level of D-dimer (6 times the maximum values) or a high score on a "sepsis-induced coagulopathy" scale (SIC score≥4), which takes into account laboratory and clinical parameters. A greater number of haemorrhagic adverse events were observed in patients treated with heparin with normal D-dimer values.
This study shows an important series of limitations (it is retrospective, it displays selection bias with respect to associated therapies, etc.).

Many other studies followed the above observational study; the results of some of them, deemed relevant, are summarized below:

- *Nadkarni GN et al.*: A retrospective study conducted at Mount Sinai in New York compared the outcomes of mortality, intubation or major bleeding in a cohort of subjects stratified by type of anticoagulant (no anticoagulants -AC; therapeutic-dose anticoagulants and low-dose anticoagulants). The analysis was performed on a total of 4,389 patients: compared to no AC therapy (n = 1,530; 34.9%), the use of AC at therapeutic dose (n = 900; 20.5%) and AC at prophylactic dose (n = 1,959; 44.6%) were associated with lower hospital mortality (aHR: 0.53; 95% CI 0.45-0.62 and aHR: 0.50; 95% CI 0.45- 0.57, respectively), and at a lower rate of intubation (aHR: 0.69; 95% CI 0.51-0.94 and aHR: 0.72; 95% CI 0.58-0.89, respectively). When initiated within 48h from admission, there was no statistically significant difference between therapeutic (n=766) and prophylactic dose of AC (n=1,860) (aHR: 0.86; 95% CI 0.73 -1.02; p = 0.08). Overall, 89 patients (2%) experienced a major bleeding episode: 27/900 (3.0%) in the therapeutic dose group, 33/1,959 (1.7%) in the prophylactic dose group and 29/1,530 (1.9%) in the non-treatment group.
- *Paolisso P et al.: A retrospective study, conducted in Italy (S. Orsola Hospital of Bologna) from 1* March to 10 April 2020, investigated the effect of enoxaparin on 450 patients hospitalized for COVID-19, comparing the in-hospital all-cause mortality in patients treated with standard LMWH dosage for DVT prophylaxis (enoxaparin 40-60 mg/day, 361 patients) versus an "intermediate" therapeutic dose (enoxaparin 40-60 mg/bid, 89 patients), treated for 7 days. The patients included in the two treatment groups showed no significant difference relating to both key demographic characteristics at baseline and disease severity [defined as SpO2 <93% at rest; PaO2/FiO2 <300 mmHg]. Intermediate LMWH dosage was associated with lower in-hospital all-cause mortality than observed with the standard dose (5.8% vs. 18.8%, p = 0.02). The advantage in favour of intermediate LMWH dosage remained statistically significant after adjustment for the confounding factors observed between the two groups (age, hypertension, haemoglobin value, PaO2/FiO2 ratio, administration of hydroxychloroquine and tocilizumab, respectively +11.5% and +13.7% for the two drugs in the intermediate dose group) [OR = 0.260, 95% CI 0.089 - 0.758, p = 0.014)].
- *Motta JK et al.*: A retrospective observational study conducted in Western Connecticut on 374 patients compared 2 pre-emptive administration cohorts with prophylactic doses (enoxaparin 30 or 40 mg sc per day) or with therapeutic doses of unfractionated heparins or LMWHs (enoxaparin 1 mg/kg sc twice a day or 1.5 mg/kg sc once a day appropriately adjusted in case of renal insufficiency or higher doses by monitoring the anti-factor X activity). In this case, a higher mortality was observed (confirmed after adjustment for confounding factors), which

raised from 14.4% with prophylactic doses to 38.7% with therapeutic doses [adjusted RR = 2.3 95% CI 1.0-4.9 p= 0.04]

- *Paranjpe S et al*.: A retrospective observational study conducted at the Mount Sinai Health System of New York on 2,773 patients, which compares the administration of anticoagulants (oral, SC or IV) vs the non-administration of anticoagulants in hospitalized patients. The study, despite not showing a difference as for in-hospital mortality, highlights a reduction in the death risk in patients undergoing anticoagulant treatment for prolonged periods [adjusted HR 0.86/day; 95% CI: 0.82-0.89; P <.001]. The study underlines a modest increase in haemorrhagic events with a higher incidence in ventilated patients and concludes that the choice of the therapeutic strategy shall take into account the characteristics of the individual patient.
- *Hanif A et al*.: a retrospective observational study on 921 patients admitted consecutively to some US hospitals evaluated 4 cohorts: patients already on anticoagulant treatment upon admission (it is not specified with which drugs), patients who started the anticoagulant drug at therapeutic doses upon admission, patients who started prophylactic doses on admission and patients who did not start anticoagulant therapy. The study shows a reduction in mortality only in intubated patients who started therapeutic doses of an anticoagulant upon admission, compared to those who started prophylactic doses (63% vs 86.2%, p <0.0001). The study confirms previous observations where the presence of high levels of D Dimer on admission and a higher peak during hospitalization correlate with higher mortality, higher probability of intubation or thrombotic events.
- *Mattioli M et al*.: a safety study on the use of LMWHs, carried out in Italy on 105 hospitalized patients with COVID-19 pneumonia (according to WHO criteria), evaluated the effect of different doses of enoxaparin at 40 mg/day, 80 mg/day and 100 mg/day, selected on the basis of renal function and body mass index, in a population with an average age of 73 years and with severe disease in 64% of cases. The most commonly used dosage was 40 mg/day (63% of the population vs 33% for the 80 mg/day dose and 4% for the 100 mg/day dose). After a 36-day follow-up, an overall mortality of 21% was observed, stratifying by age (<85 years and> = 85 years), mortality was 13% and 40% respectively (p = 0.002). Despite an increased mortality with increasing age, no increased risk of bleeding was observed in the two age groups (<85 years and >= 85 years). Overall, one thrombotic event and 2 major bleeding events were observed. No mortality events due to haemorrhage were reported.

The studies described, albeit observational in nature, with possible confounding bias as for the basal characteristics and concomitant therapies and considering cases which are not exactly overlapping, but mainly refer to severe patients, show an advantage for LMWHs, in terms of mortality reduction. However, it seems evident that the choice of the dose of anticoagulant is not to be defined a priori, but shall consider the balance between the risks and benefits in the individual patient.
These studies, which are to date the only information available, lay the foundations for randomized clinical trials. The numerous ongoing RCTs at both international and national level are expected to give a short-term response to outstanding questions concerning in particular the dosages (prophylactic and therapeutic) to be used in the various clinical scenarios and the duration of anticoagulant treatments.

National and international recommendation guidelines

The main treatment guidelines recommend the use of venous thromboembolism prophylaxis in hospitalized patients. The main recommendations are as follows:

- **National Institutes of Health (NIH)**: For non-hospitalized patients with COVID-19, anticoagulant therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless other indications are provided (AIII).
  Adults hospitalized with COVID-19 should receive VTE prophylaxis according to the standard of care for other hospitalized adults (AIII). Continuation of venous thromboembolism prophylaxis after hospital discharge is not recommended (AIII).
- **American Society of Haematology**: The panel suggests the use of prophylactic-dose anticoagulants in all patients with acute COVID-19-related disease who have no suspected or confirmed VTE (conditional recommendation based on very low certainty regarding evidence for effects).
- **American College of Chest Physicians (CHEST)** (*Moores LK et al. CHEST Journal 2020*): in the absence of contraindications, all adult subjects with acute disease in progress should receive anticoagulant thromboprophylaxis, preferring the use of LMWHs or fondaparinux to unfractionated heparin.
- **International Society on Thrombosis and Haemostasis** (*Spyropoulos AC et al. J Thromb Haemost. 2020*): A universal strategy of routine thromboprophylaxis, preferably with standard dose of LMWHs (rather than UFH), is recommended in non-hospitalized subjects, after careful evaluation of the bleeding risk. In hospitalized subjects, LMWH prophylaxis must always be initiated by providing for the use of intermediate dosages in the case of risk factors (e.g. obesity).
- **Italian Society on Thrombosis and Haemostasis (SISET)** (*Marietta M et al. Blood Transfus 2020*): The use of LMWH, UFH or fondaparinux at the doses indicated for the prophylaxis of venous thromboembolism (VTE) is strongly recommended in all COVID-19 hospitalized patients. Thromboprophylaxis should be administered for the entire duration of the hospital stay and should also be continued at home for 7-14 days after hospital discharge or in the pre-hospital phase, in case of pre-existing or persistent risk factors for VTE (e.g. reduced mobility, body mass index (BMI)> 30, previous VTE, active cancer, etc.). The use of intermediate dose LMWHs (i.e., enoxaparin 4,000 IU subcutaneously every 12 hours) may be considered on an individual basis in patients with multiple risk factors for VTE (i.e., BMI> 30, prior VTE, active cancer, etc.).

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