Use of heparins in adult patients with COVID-19

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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?	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, by using prophylactic doses. To date, there is no solid evidence/sufficient data to recommend a routine use of intermediate or therapeutic doses of LMWH as an alternative to prophylactic doses in COVID-19 patients hospitalized and classifiable in phase IIB or III of the clinical evolution of the disease, if there is no evidence of thrombo-embolic manifestations in progress. In this setting, the use of intermediate or high doses can be decided on a case-by-case basis in relation to the individual patient's medical condition after a careful assessment of the benefit/risk balance or take place in the context of clinical studies. In the presence of suspected or confirmed thromboembolic manifestations, LMWH or unfractionated heparins should be used at therapeutic dosage and for the appropriate times to be defined case by case. As regards the possible continuation of thromboprophylaxis with LMWH at home after discharge, the evidence available in the literature is still too limited to recommend or not its use, even if preliminary data from retrospective studies seem to suggest its use in high-risk patients, carefully evaluating, case by case, the benefit/risk balance.
At which dosages is it preferably prescribed and in which forms?	The dose used will depend on the medicine chosen and on the characteristics of the patient, and must take into account what is 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

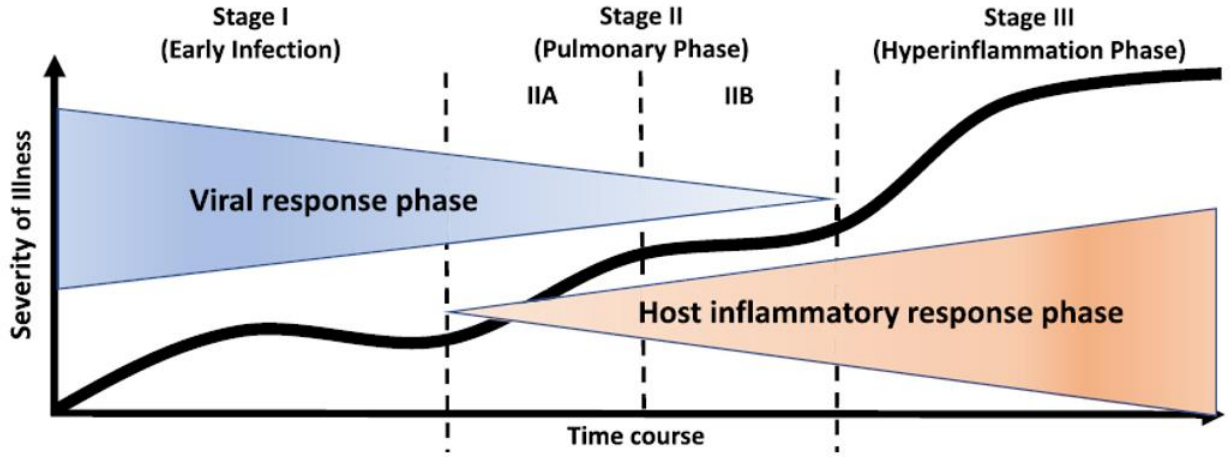
The clinical course of COVID-19 is divided into three distinct clinical stage:

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, both clinically and

from a haematochemical point of view, is similar to haemophagocytic lymphohistiocytosis (a rare medical condition often triggered by a viral infection).

In particular, microvascular and macrovascular thrombotic complications, including venous thromboembolism (VTE) and arterial thromboembolism, are common manifestations of COVID-19 disease, with an overall incidence of 17% (95% C 13.4-20.9) for venous thromboembolism, with a marked increase in subjects admitted to intensive care (28% vs 7%) (*Jimenz D et al 2021*).

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.



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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, in order to contain the effects of cytokine storm on coagulation, the most recent evidence in the literature indicates that the use of prophylactic doses may be preferred to intermediate/therapeutic doses.

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

Randomised trials

- *Multiplatform trials ATTACC, ACTIV-4 and REMAP-CAP*: The pre-print results have recently been made available of the interim analysis of a multi-platform randomized clinical trial, resulting from the collaboration between 3 large independent international studies (ATTACC, ACTIV-4 and REMAP-CAP),

related to the safety and efficacy of the therapeutic dose compared to the standard dose of thromboprophylaxis in hospitalized patients with COVID-19. In patients with severe disease (i.e. those admitted to intensive care who received organ support, such as invasive medical ventilation or vasopressor therapy), in December 2020, the DSMB decided to discontinue enrollment for futility. In fact, an interim analysis of the 1,074 enrolled subjects showed no improvement in terms of organ support free days in patients treated with therapeutic dose anticoagulants compared to those treated with prophylactic dose (3 vs 5 days; AdOR 0.87; 95% CI 0.70-1.08 with an *a-posteriori* probability of futility of 99.8%) compared to a greater number of major bleeding (3.1% vs 2.4%). Conversely, a subsequent January 2021 press release announced the enrollment discontinuation of patients with moderately severe disease (hospitalized but initially not requiring ICU care or organ support) for superiority after an interim analysis on 1,772 subjects enrolled found that anticoagulation at therapeutic dosage was more effective than standard thromboprophylaxis with regard to the number of free days of organ support, regardless of the basal D-dimer level.

These results are on the whole still too preliminary to establish with certainty the dosage to be used and only further detailed analyses on specific subgroups will allow us to establish the usefulness of an approach with intermediate/high doses in hospitalized patients.

- *INSPIRATION Trial*. On 18 March 2021 the results were published of the INSPIRATION study, a randomized controlled clinical trial, which, with a 2x2 multifactorial design, aimed to evaluate the efficacy of standard prophylactic or intermediate dose anticoagulant therapy (main analysis) and statin therapy (secondary analysis not yet available) versus placebo in adults admitted to intensive care for COVID-19. The primary efficacy outcome was a composite endpoint of venous or arterial thrombosis, recourse to extracorporeal oxygenation (ECMO) treatment, or mortality within 30 days. A total of 562 subjects were randomized to treatment with intermediate doses (enoxaparin, 1mg/kg per day) (n = 276) vs standard prophylactic doses (enoxaparin, 40mg per day) (n = 286). The primary endpoint occurred in 126 patients (45.7%) in the intermediate dose group and 126 patients (44.1%) in the standard dose prophylaxis group (absolute risk difference, 1.5% [CI 95%, -6.6%; 9.8%]; OR 1.06 [95% CI, 0.76-1.48]; P = .70). Similarly, no significant differences were observed in terms of mortality, venous thromboembolic events, or length of stay in therapy. In terms of safety, major bleeding episodes occurred in 7 patients (2.5%) in the intermediate dose group and 4 patients (1.4%) in the standard dose prophylaxis group (risk difference, 1.1% [One-sided 97.5% CI, - ∞ to 3.4%]; OR 1.83 [One-sided 97.5% CI, 0.00-5.93]), not satisfying the non-compliance criteria inferiority (P for non-inferiority> .99). Acute thrombocytopenia occurred only in patients assigned to the intermediate dose group (6 vs 0 patients; risk difference, 2.2% [95% CI, 0.4% -3.8%]; P = .01) . These results have also recently been confirmed in the analysis of the 90-day data *(Bikdeli B et al. 2021)*.
- *Lemos ACB et al*. Small, randomized, open-label phase II study in which COVID-19 patients requiring mechanical ventilation were randomized to receive therapeutic (n = 10) or prophylactic (n = 10) enoxaparin doses. There was a statistically significant increase in the PaO2 / FiO2 ratio over time, a greater likelihood of discontinuing mechanical ventilation, and a longer duration of ventilation-free days in the therapeutic dose group than in the prophylactic dose group. Due to the limitations of the study, conducted in a single center on an extremely small number of people, the results obtained can only be considered exploratory.
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Observational studies

The following are the main observational studies published in chronological order starting from the most recent:

- *Giannis D et al.* (The CORE-19 Registry): prospective registry in which all 4,906 subjects hospitalized in the period 1 March-31 May at the Northwell Health System were registered. After 90 days of post-discharge observation, the following rates of onset of thromboembolic events were found: venous

(VTE: 1.55%), arterial (ATE: 1.71%). All-cause mortality was 4.83% and major bleeding was 1.73%. In a multivariate analysis, post-discharge thromboprophylaxis was associated with a 46% reduction in the risk of thromboebolic events (combined definition of VTE, ATE, and all-cause mortality) (OR 0.54; 95% CI 0.47-0.81).

- *Al-Samkari H et al.*: Multicenter cohort study conducted in 67 hospitals in the US. The study included 3,239 adult patients admitted to intensive care for COVID-19 in the period March-April 2020. Within the general population 204 subjects (6.3%) developed a venous thromboembolic event and 90 subjects (2.8%) presented a major bleeding event. Of the 2,809 subjects included in a target trial emulation, 384 (11.9%) had received early anticoagulant therapy (within 2 days of admission to intensive care). During a median follow-up of 27 days (IQR, 15-35), 1,066 subjects (38.0%) died: 179 (46.6%) in the early anticoagulant group and 887 (36.6%) in the untreated group (HR 1.12 ; 95% Ci 0.92-1.35).
- *Tacquard C et al.*: retrospective study in which the data were analyzed of all subjects with COVID-19 admitted to intensive care in the period March-April 2020 in eight French hospitals. All subjects had performed anticoagulant prophylaxis, which was stratified retrospectively into standard or high dose. Compared to the 538 subjects enrolled, 104 patients presented 122 thrombotic events with an incidence of 22.7% (95% CI 19.2-26.3%). The use of high-dose prophylaxis was associated with a significantly reduced risk of thrombotic events (HR 0.81; 95% CI 0.66-0.99) without a significant increase in the risk of bleeding (HR 1.11; 95% CI 0.70-1.75%).
- *Di Castelnuovo A* et al.: retrospective observational study in which 2,574 unselected COVID-19 patients were analyzed who had been admitted to 30 clinical centers in Italy from 19 February 2020 to 5 June 2020. The hospital death rate in patients receiving less heparin were respectively 7.4 and 14.0 per 1,000 days-person. After appropriate adjustment for the propensity score, the use of heparin was associated with a 40% lower risk of death (RR 0.60; 95% CI 0.49-0.74). This association was particularly evident in patients with higher disease severity or strong coagulation activation.
- *Martinelli I* et al.: observational cohort study conducted in adult subjects admitted consecutively in the period March-April 2020. The study evaluated the efficacy of different doses of LMWH: 1 mg/kg BID for subjects admitted to intensive care, 0.7mg/kg BID in low intensity wards, and 1 mg/kg QD in high intensity wards. At day 21, the incidence rate of death and clinical progression were lower in patients treated with higher doses than in those with standard doses (RR 0.39, 95% CI 0.23-0.62), similarly the incidence of venous thromboembolism was lower (hazard ratio 0.52, 95% confidence interval 0.26-1.05). A major bleeding episode occurred in 4/127 patients (3.1%) with a high dose of enoxaparin.
- *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 bsa per day) or with therapeutic doses of unfractionated heparins or LMWHs (enoxaparin 1 mg/kg bsa twice a day or 1.5 mg/kg bsa 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]
- *Pesavento R* et al.: retrospective analysis of all COVID-19 patients admitted consecutively between February and April 2020. Major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) were obtained from patient medical records and are been judged by an independent committee. Of the 324 patients recruited, 240 had been treated with prophylactic doses and 84 with higher doses of anticoagulants. The incidence of a composite endpoint of major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) was 6.9 per 100 person/month in patients given prophylactic doses and 26.4 per 100 people/month in those who were prescribed higher doses (HR 3.89; 95% CI, 1.90-7.97). The corresponding overall mortality rates were respectively 12.2 and 20.1 per 100 person/month.
- *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). If started 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.

- *Hanif A et al.*: a retrospective observational study on 921 patients admitted consecutively to some US hospitals evaluated four 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 two major bleeding events were observed. No mortality events due to haemorrhage were reported.
- *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/ per 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 dosing was associated with lower in-hospital all-cause mortality than observed with the standard dose (5.8% vs. 18.8%, p = 0.02). 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)].
- *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]. P < .001]. The study highlights a modest increase in bleeding events with a higher incidence in ventilated

patients and concludes by stating that the choice of the therapeutic strategy must be made considering the characteristics of the individual patient.

- *Tang N et al.* 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.).

Systematic reviews and meta-analyses

- *Parisi R et al.*: meta-analysis on 25,719 hospitalized COVID-19 patients conducted to evaluate the association of anticoagulants and their dosage with hospital all-cause mortality in COVID-19 patients. The use of anticoagulants was associated with a 50% reduction in the risk of hospital mortality (RR 0.50, 95% CI 0.40-0.62; I^2: 87%). Both anticoagulant regimens (therapeutic and prophylactic dosage) reduced hospital mortality from all causes, compared to the absence of anticoagulants. Particularly in ICU patients, the anticoagulant regimen was associated with a reduced risk of hospital mortality (RR: 0.30, 95% CI: 0.15-0.60; I^2: 58%) compared to the prophylactic one. However, the former was also associated with a higher risk of bleeding (RR: 2.53, 95% CI: 1.60-4.00; I^2: 65%). The authors conclude that the use of anticoagulants, primarily heparin, reduced all-cause mortality in COVID-19 patients during hospitalization. Due to the higher risk of bleeding associated with the use of therapeutic doses, the use of prophylactic dosages of anticoagulant is probably preferable in non-critical COVID-19 patients.

The studies described, albeit with possible confounding bias with respect to the basal characteristics and concomitant therapies, and on not exactly overlapping cases, but mainly on severe patients, show an advantage, in terms of mortality reduction, for LMWH. With regard to the choice of dosage to be used, the first evidence from large randomized studies seems to support, at least in subjects with severe pathology, the use of a standard prophylaxis regimen compared to intermediate/therapeutic dosages.
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.

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).
    - There are currently insufficient data to make recommendations for or against the use of thrombolytics or intermediate/therapeutic dose anticoagulants for VTE prophylaxis in hospitalized COVID-19 patients outside a clinical trial.

- Continuation of venous thromboembolism prophylaxis after hospital discharge is not recommended (AIII).

- **American Society of Hematology** *(Cuker A et al.* Blood Adv *2021)*:
  - The panel suggests using prophylactic versus intermediate/therapeutic dose anticoagulants in all patients with COVID-19-related critical illness who have no suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence for effects).
  - The panel suggests using prophylactic versus intermediate/therapeutic dose anticoagulants in all patients with COVID-19-related critical illness who have no suspected or confirmed VTE (conditional recommendation based on very low certainty in the 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 LMWH or fondaparinux over use of 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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