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COVID-19 – KCE CONTRIBUTIONS

THROMBOPROPHYLAXIS AND TREATMENT

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This document is a rapid review of scientific literature retrieved from several publicly funded COVID-19 resource collections. The literature included in these repositories is not always peer-reviewed or externally validated. KCE synthesised the evidence in short time frames to respond to urgent questions and could therefore not follow its regular methodological procedures. This work is used to inform guidance of other governmental and professional agencies.

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■ RAPID REVIEW BY KCE

1 SUMMARY

1.1 Background

COVID-19, a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to thromboembolic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis.

Guidance on thromboprophylaxis for Belgium was provided by the Belgian Society of Thrombosis and Haemostasis (BSTH) prepared by the Centre Hospitalier Universitaire de Liège, Sciensano and the Belgian Centre for Pharmacotherapeutic Information (BCFi / CBiP). This rapid review and summary describes results available on May 4th 2020 (on May 30th, new BSTH guidance and algorithms were published online).

- For all patients, BSTH advised to continue thromboprophylaxis for 14 days minimum and possibly up to 45 days after reassessment. This should always be discussed on a case-by-case basis.
- For **patients with COVID-19 treated at home**, the (old) BSTH algorithm offers detailed guidance on how to decide on a case-to-case basis; it provides prophylaxis dosing, advice on bleeding risk, use of stockings, and advice for pregnant women and women on oestrogens. The BSTH risk factors order of priority to take a step in the algorithm are: 1. BMI ≥ 30 kg/m²; 2. History of venous thromboembolism (VTE), active cancer and intake of selective oestrogen receptor modulation (SERM) medication; 3. Bedrest, immobility, thrombophilia
- For **patients with COVID-19 treated in hospital outside intensive care units (ICU)**, the advice is to switch oral anticoagulant treatment (prior to admission) by curative low-molecular-weight heparins (LMWH) therapy. For other patients the decision tree is based on D-dimers level, fibrinogen, and BMI taking into account patient weight, renal function, previous history of VTE and active cancer. At discharge, prophylaxis is continued on a case-by-case basis.
- For **patients with COVID-19 treated in ICU**, the (old) BSTH algorithm makes a distinction in BMI <30 , and respiratory support needed to advice for therapeutic or prophylactic dosing of LMWH.
- For **pregnant patients with COVID-19** treated at home, the BSTH algorithm is currently been reviewed but for now it is advised to review risk factors individually and discuss thromboprophylaxis with all COVID-19 pregnant and post-partum women.

1.2 Objectives

The evidence evolves on a daily basis. The aim of this rapid review is to search for recent evidence to provide additional information towards the (old) BSTH algorithms, the guidance by Sciensano and the BCFi for management of patients with COVID-19 who develop venous or arterial thrombosis, and of those with preexisting thrombotic disease who develop COVID-19, or those who need prevention or care for their thrombotic disease during the COVID-19 pandemic including pregnant women.

1.3 Methods

We evaluated the literature in a non-systematic way for new evidence. We searched Belgian and International recognised organisations for haematology, cardiology and emergency medicine, and obstetric emergency care, Cochrane database, the Lancet, NEJM, NIH, and Pubmed. The websites were searched on April 29th and updated till May 4th 2020.

1.4 Key results

No new evidence from primary studies was found. Guidance for non-hospitalised and hospitalised COVID-19-patients are widely available, are not diverging from each other, are stating dosing of therapeutic and prophylactic LMWH and the need to adjust for weight and renal function. For

pregnant and post-partum women guidance is available from France and Spain. Both consider risk factors in the decision of starting thromboprophylaxis with Spain starting all women due to confinement inactivity and also considering starting treatment in suspected cases when a test is not yet performed.

1.5 Conclusion

The importance of providing thromboprophylaxis is recognised by all international guidance for the patient with COVID-19 for patients at home and hospitalised. The (old) BSTH algorithms are of good quality and in agreement with international guidance. BSTH guidance for pregnant women is needed and will be available soon.

2 PROBLEM DESCRIPTION

Evidence is emerging that COVID-19 is associated with an increased risk of thromboembolic disease, with pulmonary embolism (as well as cerebrovascular accident or myocardial infarction) regarded as an important risk factor for increased mortality.

On April 7th Sciensano recommended to replace oral anticoagulant treatment (prior to admission) by curative LMWH (low molecular weight heparin) therapy for hospitalized patients, due to multiple potential drug interactions and difficulties to monitor oral anticoagulation. The Belgian Society on Thrombosis and Haemostasis (BSTH) further published therapeutic algorithms for hospitalised patients in and outside of intensive care, and for non-hospitalized patients. These were prepared by the Centre Hospitalier Universitaire de Liège and were due a consensus revision. Finally, the Belgian Centre for Pharmacotherapeutic Information (BCFi / CBiP) provided new guidance on April 30th for ambulatory patients. The evidence evolves on a daily basis. This rapid review aims to complement the literature review conducted to date and to determine whether current recommendations need to be revised or supplemented with specific recommendations for particular patient groups (e.g. pregnant women).

2.1 Background

COVID-19, a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis.[1] Indirect effects of infection e.g., severe inflammatory response, critical illness, traditional risk factors may also contribute to risk for thrombotic disease.[1] In addition, many patients receiving antithrombotic therapy for thrombotic disease may develop COVID-19, which can have implications for choice, dosing, and laboratory monitoring of antithrombotic therapy.[1]

Venous thromboembolism has been reported in 25% to 69% of patients with severe COVID-19 in the intensive care unit, and may be associated with poor prognosis.[2, 3, 4] Acute pulmonary embolism (CT angiography) has been reported in 30% of patients in a study in France with a D-dimer threshold of 2660 micrograms/L detecting all patients with pulmonary embolism.[5] The American Society of Hematology recommended to institute venous thromboembolism prophylaxis measures for patients at risk. Low molecular weight heparin is preferred over unfractionated heparin to reduce patient contact time.[6] In particular, Fondaparinux is recommended in patients with a history of heparin-induced thrombocytopenia.[6] Direct oral anticoagulants can interact with the experimental antivirals used to treat COVID-19; therefore, a suitable alternative parenteral anticoagulant should be started.[7] The optimal anticoagulant dose in COVID-19 in patients is unknown; intermediate- or full-dose regimens rather than prophylactic doses may be needed but could lead to bleeding events.[1]

Non-survivors had significantly higher D-dimer levels and longer prothrombin time and activated partial thromboplastin time compared with survivors in one study.[8] Targeting the fibrinolytic systems to improve pulmonary function in the patients with Acute Respiratory Distress Syndrome (ARDS) is under discussion.[2]

2.2 Belgian situation

2.2.1 Retrieved guidance

In Belgium, guidance is provided (Table 1 - Appendix 1) by the BSTH prepared by the *Centre Hospitalier Universitaire de Liège* for the prevention of thrombosis and anticoagulation of the COVID-19-patient. A distinction is made between hospitalised patients (in ICU or not) and non-hospitalised patients. For each of the three situations an algorithm is provided dated April 15th 2020. The website presenting the old algorithms on May 4th, 2020 (<https://bsth.be/professionals>) provided also links to the following recommendations (see also below):

- the guidance by Sciensano version 7,[9]
- a review supported by several international organisations,[1]
- a rapid review by the Veterans Affairs US government evidence synthesis program,[10]
- and ISTH recommendations.[11, 12]

Sciensano provided guidance on anticoagulation in COVID-19 patients on April 7th (Table 2 - Appendix 1).[9] The guidance is based on the French document by the Société Française d'Anesthésie et de Réanimation (SFAR) from April 3th (see also below).[13]

The Belgian Centre for Pharmacotherapeutic Information (BCFi / CBiP) provided guidance on April 30th for ambulatory patients (Table 3 - Appendix 1).[14] The recommendations are based on the Sciensano guidance,[9] the Dutch incidence paper by Klok et al.[3], and the Société Française de Médecine Vasculaire.[15] The BCFi / CBiP distinguishes advice for patients who are discharged from hospital after a COVID-19 infection and patients with COVID-19 infection who are treated at home.

Moreover, the BSTH gives limited guidance for pregnant women.

2.2.2 Summary of Belgian guidance

The three guidance documents give advice that is in line with each other. Nevertheless, the (old) BSTH guidance is more detailed, nicely presented and the step by step advice is easy to follow.

For **patients with COVID-19 treated at home**, the BSTH algorithm offers detailed guidance on how to decide on a case-to-case basis. The guidance from BCFi / CBiP stipulates similar risk factors but no priority is given and details on the dose of anticoagulants are lacking.

The BSTH risk factors order of priority to take a step in the algorithm are:

1. BMI ≥ 30 kg/m²
2. Previous history of VTE, active cancer and intake of selective oestrogen receptor modulation (SERM) medication
3. Bedrest, immobility, thrombophilia

Further advice to discuss thromboprophylaxis if **high bleeding risk** is present and in which situations to lower the dose is given. The following are high bleeding risk:

- Active bleeding,
- Severe bleeding < 3 months,
- Thrombocytopenia < 50 x10³/mm³,
- Dual Antiplatelet Therapy (DAPT).

Other bleeding risk factors are medications, age, cancer...

For women, the following advice is given:

- Discuss stopping menopausal hormone replacement therapy (except transcutaneous estradiol),
- Discuss temporary stop estroprogestative contraception or continue with thromboprophylaxis; or continue progestagen alone,
- Discuss thromboprophylaxis if pregnancy and/or postpartum in a COVID-19 positive patient.

Finally, compression stockings, class 1, 2 or 3 depending on medical history and contraindications, should be used during the day only.

For **patients with COVID-19 treated in hospital outside intensive care units (ICU)**, the BSTH algorithm gives detailed guidance on how to proceed. Both the BSTH and Sciensano advise to switch oral anticoagulant treatment (prior to admission) by curative LMWH therapy. The algorithm provides dose per weight for therapeutic LMWH taking into account renal function. For patients not on anticoagulation prior to admission the decision tree is based on D-dimers level, fibrinogen, and BMI. Again, the algorithm provides dose per weight for prophylactic LMWH taking into account renal function, previous history of VTE and active cancer. At discharge, the advice should be given on a case-by-case basis.

For **patients with COVID-19 treated in ICU**, the BSTH algorithm gives detailed guidance on how to proceed and makes a distinction in BMI <30, and respiratory support needed to advice for therapeutic or prophylactic dosing of LMWH.

For **pregnant patients with COVID-19** treated at home, the BSTH algorithm gives the following guidance: Discuss thromboprophylaxis if pregnancy and/or postpartum in a COVID-19 positive patient.

For all patients, BSTH advises to continue thromboprophylaxis for 14 days minimum and up to 45 days, when the patient needs to be reassessed. This should always be discussed on a case-by-case basis.

3 OBJECTIVE

This topic emerged very recently and papers are published daily in many scientific journals. The aim of this rapid review is to search for more recent evidence to provide additional information towards the (old) BSTH algorithms, the guidance by Sciensano and the BCFi for management of patients with COVID-19 who develop venous or arterial thrombosis, and of those with preexisting thrombotic disease who develop COVID-19, or those who need prevention or care for their thrombotic disease during the COVID-19 pandemic including pregnant women.

4 METHODS

We evaluated the literature in a non-systematic way for new evidence on the prevention and treatment of patients with COVID-19 who develop venous or arterial thrombosis, and of those with pre-existing thrombotic disease who develop COVID-19, or those who need prevention or care for their thrombotic disease during the COVID-19 pandemic. We searched Belgian and International recognised organisations for haematology, cardiology and emergency medicine, and obstetric emergency care, Cochrane database, the Lancet, NEJM, NIH, and Pubmed. The websites were searched on April 29st till May 4th 2020.

We tabulated primary studies that the guidance documents are referring to. The retrieved guidance documents are listed by country / organisation. A summary of the clinical guidance is provided in table format and discussed.

5 RESULTS

Extracts from the informative rapid response on 'Antithrombotic Therapies for COVID-19 Disease' by Tao et al. (the Veterans Affairs US government evidence synthesis program) are used in the result section below.[9] The full report with the references as used in the tables is referred in Appendix 3. The conclusion summary from this report states that: "New evidence on thromboembolism in COVID-19 does not warrant a change in current guidance on thromboprophylaxis among acutely and critically ill hospitalized patients. To date, the incidence of thromboembolism among patients with COVID-19 remains largely unknown. Evidence is limited to case reports and case series with methodological limitations including inadequate follow-up, which may have biased results towards underreporting of thromboembolism. Two studies have been published on antithrombotic therapies and clinical outcomes in patients with COVID-19. Several studies are planned to further evaluate the incidence of thromboembolism in COVID-19 and potential therapeutics. Of note, no trials comparing prophylactic dosing strategies of unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) have been registered on clinicaltrials.gov, although hematology experts have called for this type of trial".

5.1 Retrieved primary studies

Studies presented by Toa et al. on incidence and antithrombotic therapy are presented in Table 4 - Appendix 1. Other identified studies are listed in Table 5 - Appendix 1.

In the Netherlands, the venous thrombosis incidence study by Klok concluded to apply pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to the ICU, and suggested to increase the prophylaxis towards high-prophylactic doses, e.g. going from enoxaparin 40 mg OD to 40 mg BID, even in the absence of randomised evidence.[3]

In Italy, patients on direct oral anticoagulants (DOAC) treated with antiviral drugs showed an alarming increase in DOAC plasma levels.[7] In order to prevent bleeding complications, the authors suggested withholding DOACs from patients with SARS-CoV-2 and replacing them with alternative parenteral antithrombotic strategies for as long as antiviral agents are deemed necessary and until discharge.[7]

The French study by Helms et al. noted that despite coagulation, a high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications.[15] The authors suggested that higher anticoagulation targets than in usual critically ill patients should therefore probably be used.

Several studies are planned to further evaluate the incidence of thromboembolism in COVID-19 and potential therapeutics (Table 6 - Appendix 1).[10] One small study is set up at the Jessa Hospital, Belgium.

5.2 Retrieved recommendations

The guidance presented by Toa et al. from the rapid review (search date up to April 12th) is reported in Table 7 - Appendix 1.

An overview of the retrieved guidance is presented in Table 8 - Appendix 1. Only three documents, from France and Spain and the international consensus (Bikdeli et al.), were identified providing guidance on pregnant women.[16, 17] [1]

5.3 Recommendations

5.3.1 *Non-pregnant patients with COVID-19*

Table 9 summarises the recommendations from international organisations and countries.

5.3.2 *Pregnant patients with COVID-19*

The summary of the guidance is reported in Table 10.

6 CONCLUSION

The information in the guidance documents for starting prophylaxis in the **ambulant COVID-19 patient** is clearly provided by The French Société Française de Médecine Vasculaire and the BSTH. This can thus be applied e.g. to the elderly Belgian patients in residential care settings. The Spanish experts' advice and the international consensus (Bikdeli et al) argue to decide case by case to give a prophylactic LMWH. The Société Française de Médecine Vasculaire advises, similar to the BSTH, to start prophylaxis when risk factors (similar in both guidance documents) are present. After 14 days of prophylaxis this should be reviewed. Minimally the following advice should be given to the patient:

- Encourage ambulation and physical activity
- Avoid prolonged standing or sitting and avoid crossing your legs
- Change position every 30-60 min
- Exercise with the lower extremities (flexo-extension movements and circular movements of the feet)
- Avoid dehydration

For the **hospitalised patient** we conclude that the (old) BSTH algorithms are in agreement with the international proposed guidance. Some additional remarks from the international guidance may be of interest for **post-discharge** thromboprophylaxis:

- Aspirin could be considered for COVID-19 VTE prophylaxis if criteria for post-discharge thromboprophylaxis are met.[6]
- The individual patient's VTE risk factors, including reduced mobility and bleeding risk as well as feasibility should be considered when considering prophylaxis for up to 45 days post-discharge.[1, 6]

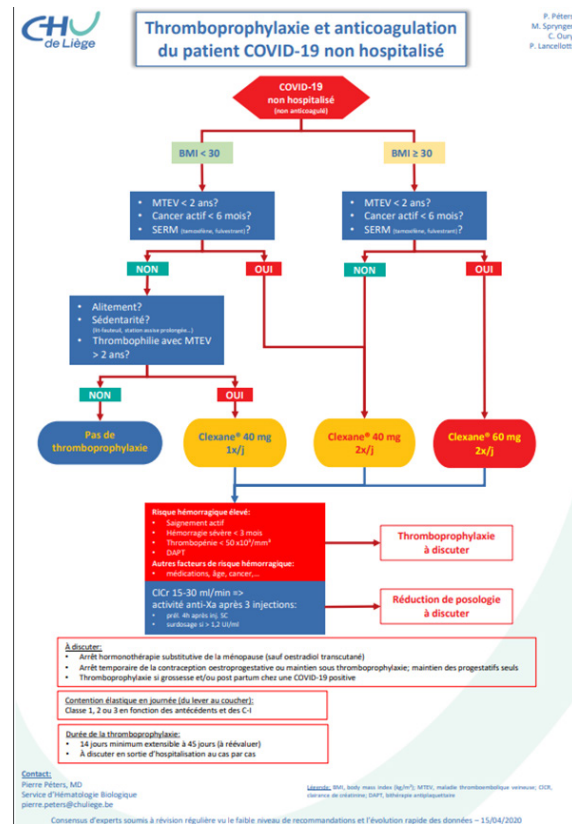
For **pregnant and post-partum women** detailed information is provided by the Spanish and French experts. In Spain, all pregnant women with COVID-19 are advised to start LMWH prophylaxis for at least 2 weeks. In France prophylaxis is started when at least 1 risk factor is present and this for COVID-19 confirmed and suspected pregnant women. We note that 'prolonged or complete immobility' is a risk factor in France. This is by the Spanish experts already counted as an important factor (taking into account the Spanish quarantine) and may explain the difference in approach. The French guidance is shorter, more convenient in use, and has a clearer risk factor strategy compared to the Spanish advice. The current (old) advice from BSTH is limited to discuss prophylaxis case by case. But, new guidance for pregnant women with confirmed COVID-19 is expected within a week (May 11th 2020) (personal communication Dr Pierre Péters, BSTH). The new guidance will use the French advice as the building block as it is closest to Belgian practice and dosing.

The dosing of therapeutic and prophylactic LMWH is comparable across guidance with adjusting for weight and renal function.

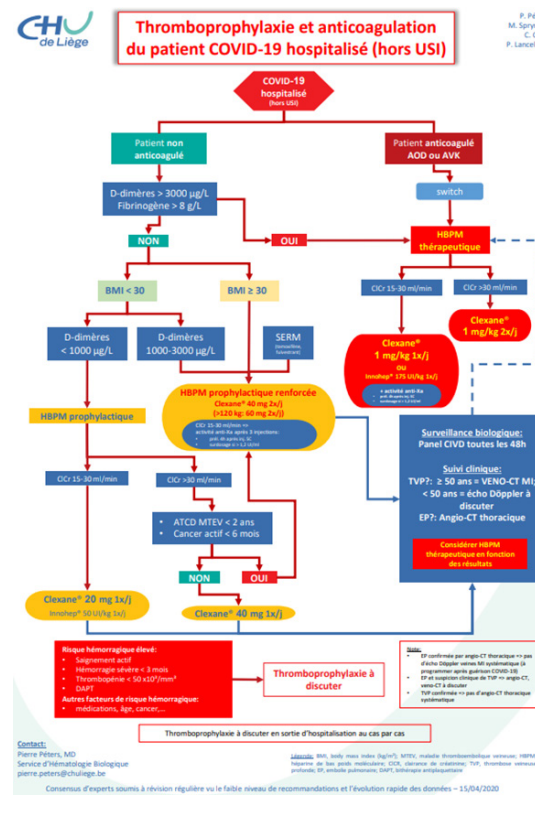
APPENDIX 1. EVIDENCE TABLES

Table 1 – Prevention of thrombosis and anticoagulation of a patient with COVID-19 in Belgium – old BSTH guidance*

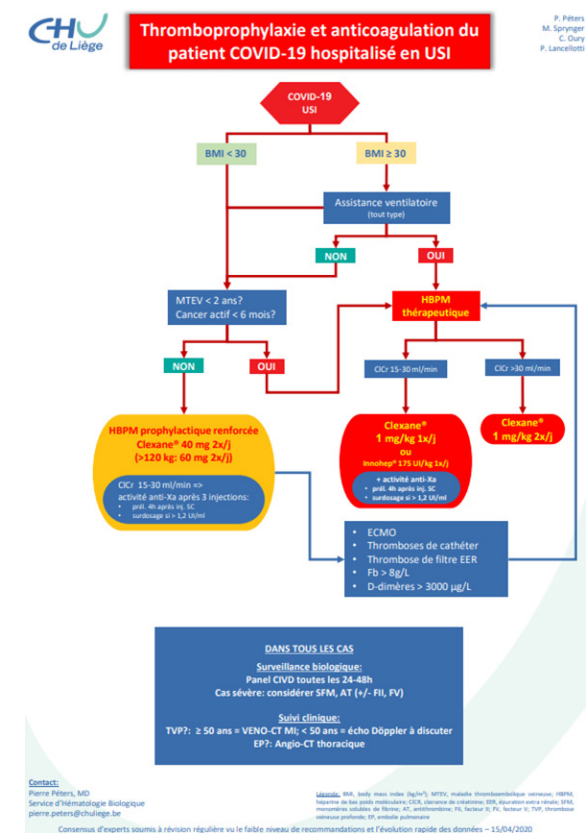
Outside hospital



In hospital outside intensive care



Admitted to intensive care



*these algorithms are no longer available online as they have been replaced by the consensus guidance on May 30th 2020. For the larger print versions and English version see Appendix 2.

Table 2 – Guidance Sciensano for anticoagulation in COVID-19 patients

Date of document	Guidance
April 14 th 2020[9]	• In COVID-19 hospitalized patients, oral anticoagulant treatment (prior to admission) is to be replaced by curative LMWH therapy, due to multiple potential drug interactions and difficulties to monitor oral anticoagulation. • Prophylactic LMWH is indicated in most (if not all) COVID-19 patients who require hospitalization, according to the local institutional protocols, with standard weight adjusted and renal failure dose adjustments. • Higher LMWH doses (enhanced prophylactic or therapeutic) are to be considered on a careful case by case analysis balancing potential risks and benefits. • Usual precautions with regards to LMWH safety are of course applicable.

Table 3 – Belgian Centre for Pharmacotherapeutic Information (BCFi / CBiP) guidance for coagulopathy in ambulatory patients

Patient population	Guidance April 30 th 2020[14]
Patients discharged after hospitalisation for COVID-19	• patients who experienced a pulmonary embolism or venous thromboembolism: ◦ the anticoagulation treatment is continued after their discharge ◦ long-term anticoagulation treatment of at least 3 months • patients who did not experience a pulmonary embolism or venous thromboembolism during admission: decision must be taken on a case-by-case basis.
Patients with COVID-19 who are treated on an outpatient basis only	The decision to proceed with thrombosis prophylaxis LMWH or Fondaparinux is to be taken on a case-by-case basis, based on a weighing of the thrombosis risk and the bleeding risk. Thrombosis risk: • reduced mobility due to illness • BMI > 30 kg/m² • age > 70 years • ongoing cancer treatment • personal history of venous thromboembolism • major surgery in the last 3 months D-dimer determinations for the detection of an increased thrombosis risk are currently not recommended.

Table 4 – Published/released studies of VTE incidence among COVID-19 patients and antithrombotic therapy[10]

Author/Year	Location/Setting (ie, hospital, country)	Dates	Number of Cases	Patient Characteristics (ie, age, gender)	Outcomes Assessed
Question 1: In patients with COVID-19, what is the incidence of thromboembolism?					
Cui 2020	ICU of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology in China	January 30 – March 22, 2020	n=81	• Age (mean): 59.9 years • Gender (% Male): 46% • Comorbidities (%): ◦ Hypertension: 25% ◦ Diabetes: 10% ◦ Coronary artery disease: 12% ◦ Smoking: 43%	• Development of ultrasound-confirmed lower extremity venous thrombosis
Klok 2020	ICUs at Leiden University Medical Center, Erasmus University Medical Center, Amphibia Hospital Breda in the Netherlands	March 7 – April 5, 2020	n=184	• Age (mean): 64 years • Gender (% male): 76% • Active cancer (%): 2.7% • Coagulopathy* during admission (%): 38% • Therapeutic anticoagulation at admission (%): 9.2% • Renal replacement therapy during admission (%): 13%	• Composite of thromboembolic phenomena (acute pulmonary embolism, deep vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism)
Chen 2020	Central Hospital of Wuhan in Wuhan, China	January 2020 – February 2020	n=25	• Age (median): 65 years • Gender (% male): 60% • Comorbidities (%): ◦ Hypertension: 40% ◦ Diabetes: 20% ◦ Cardiovascular disease: 16% ◦ Smoking: 24% ◦ Prior DVT: 4%	• CT-proven acute pulmonary embolism • D-dimer, lymphopenia, CRP, B-type BNP, CMP
Danzi 2020 ²³	European hospital (details not reported)	NR	n=1	75 year-old woman; past medical history not reported	• Diagnosis of PE • Treatment with LMWH
Xie 2020 ²⁴	Wuhan, China	NR	n=2	57 year-old man and 70 year-old man; past medical history not reported	• Diagnosis of PE
Question 2: In patients with COVID-19 disease, do antithrombotic therapies improve outcomes?					
Tang 2020	Tongji Hospital in Wuhan, China	January 1 – February 13, 2020	n=449	• Age (mean): 65 years • Gender (% male): 60% • Comorbidities (%): ◦ Hypertension: 40% ◦ Diabetes: 21% ◦ Cardiovascular disease: 9.1%	• 28-day mortality • Sepsis-induced coagulopathy (SIC) score and D-dimer result
Wang 2020	US hospital (details not reported)	NR	n=3	Case 1: 75 year old man with hypertension, hyperlipidemia, type 2 diabetes mellitus, and coronary artery disease Case 2: 59 year old female with hypertension Case 3: 49 year old male with no known medical history	• Use of tPA +/- heparin

*Coagulopathy: spontaneous prolongation of prothrombin time (PT) > 3 seconds or activated partial thromboplastin time (APTT) > 5 seconds

Table 5 – Additional studies on VTE incidence or antithrombotic therapy among COVID-19 patients

Author	Peer reviewer	Date Published / online	Title document	Link
Testa[7]	Yes	April 23 th 2020	Direct oral anticoagulant plasma levels striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents. The Cremona experience	https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14871
Helms[18]	Yes	April 14 th 2020	High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study.	https://www.esicm.org/wp-content/uploads/2020/04/863_author_proof.pdf

Table 6 – Ongoing/planned clinical trials on thromboembolism in COVID-19 disease and treatment[10]

Agent	Sponsor	Title	ClinicalTrials.gov Identifier	Study Type	Primary Outcome	Secondary Outcome(s)
NA	Jessa Hospital	COVID-19 and Deep Venous Thrombosis: a Cross-sectional Study	NCT04338932 ²⁶	Observational	Prevalence and possible risk factors for DVT in ICU	None
Aspirin 75 mg, Clopidogrel 75 mg, Rivaroxaban 2.5 mg, Atorvastatin 40 mg, Omeprazole 20 mg	Imperial College London	Preventing Cardiac Complication of COVID-19 Disease With Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial.	NCT04333407 ²⁷	Interventional	All-cause mortality at 30 days after admission	Absolute change in serum troponin from admission to peak value, discharge rate, intubation rate.
Defibrotide	IRCCS San Raffaele Scientific Institute	Use of Defibrotide to Reduce Progression of Acute Respiratory Failure Rate in Patients With COVID-19 Pneumonia	NCT04335201 ²⁸	Interventional	Eval progression to acute respiratory failure.	Adverse events, duration of hospitalization, systemic inflammation, overall survival
Tissue Plasminogen Activator (tPA) ²⁹	Beth Israel Deaconess Medical Center	NR	Not registered	Interventional	NR	NR

Table 7 – Guidance retrieved by Toa et al.[10]

Source	Recommendation	Date Published	Date Accessed
Guidance specific to COVID-19			
World Health Organization ¹¹	Use pharmacological prophylaxis (LMWH [preferred if available] or heparin 5000 units subcutaneously twice daily) in adolescents and adults without contraindications. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices).	3-13-2020	4-12-2020
International Society of Thrombosis and Haemostasis ²⁵	Consider prophylactic dose LMWH in all patients (including non-critically ill) who require hospital admission for COVID-19 infection, in the absence of any contraindications	3-25-2020	4-12-2020
Centers for Disease Control and Prevention ¹²	No specific comment on anticoagulation in COVID-19 patients; refers to WHO guidance	4-3-2020	4-12-2020
Department of Defense	No specific comment on anticoagulation in COVID-19 patients; refers to WHO guidance	3-23-2020	4-12-2020
Infectious Disease Society of America ⁸	No specific comment on anticoagulation in COVID-19 patients	4-11-2020	4-12-2020
The Italian Society on Thrombosis and Haemostasis ¹⁰	- Use LMWH, UFH, or fondaparinux at doses indicated for prophylaxis of VTE in all COVID-19 hospitalised patients; patients with anticoagulant contraindications should be treated with limb compression. - Thromboprophylaxis should be administered for the entire hospital stay and maintained at home for 7-14 days after hospital discharge or in the pre-hospital phase, in case of pre-existing or persisting VTE risk factors. - The use of intermediate-dose LMWH (i.e., enoxaparin 4,000 IU subcutaneously every 12 hours) can be considered on an individual basis in patients with multiple risk factors for VTE. - Use of therapeutic doses of UFH or LMWH is not recommended as a standard treatment.	4-8-2020	4-14-2020
Guidance published prior to COVID-19			
American Society of Hematology ¹⁵	Use UFH, LMWH, or fondaparinux rather than nonparenteral anticoagulant in acutely ill medical patients and UFH or LMWH in critically ill medical patients.	11-2018	4-12-2020
Society of Critical Care Medicine ¹⁷	Recommend against the use of antithrombin for the treatment of sepsis and septic shock. No recommendation regarding the use of thrombomodulin or heparin for the treatment of sepsis or septic shock.	03-2020	4-12-2020

Table 8 – Overview of retrieved guidance documents

Country/Organisation	Date Published / online	Title document	Link website
Europe			
Switzerland / Casini [19]	April 2020	11 th Suggestions for thromboprophylaxis and laboratory monitoring for in-hospital patients with COVID-19	https://smw.ch/article/doi/smw.2020.20247
Spain : Working Group on Cardiovascular Thrombosis of the Spanish Society of Cardiology / Vivas[20]	April 2020	22 th Recomendaciones sobre el tratamiento antitrombótico durante la pandemia COVID-19. Posicionamiento del Grupo de Trabajo de Trombosis Cardiovascular de la Sociedad Española de Cardiología	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7176384/
Sociedad Espanola de Trombosis y Hemostasia[21]	April 2020	29 th Recomendaciones de tromboprofilaxis y tratamiento antitrombótico en pacientes con COVID-19 (Recommendations for thromboprophylaxis and antithrombotic treatment in patients with COVID-19) (The patients considered are hospitalised)	https://www.covid-19.seth.es/wp-content/uploads/2020/04/Recomendaciones-tromboprofilaxis-y-tratamiento-antitrombotico-pacientes-COVID-19-2020-04-29.pdf https://www.covid-19.seth.es/recomendaciones-de-tromboprofilaxis-y-tratamiento-antitrombotico-en-pacientes-con-covid-19/
Sociedad Espanola de Trombosis y Hemostasia[16]	April 2020	15 th Recomendaciones sobre profylaxis ETV en el embarazo y puerperio durante la pandemia COVID-19. (recommendations on prophylaxis of thromboembolic disease (VTE) in pregnancy and postpartum during COVID-19 pandemic)	https://www.covid-19.seth.es/wp-content/uploads/2020/04/Recomendaciones-sobre-profilaxis-ETV-en-embarazo-y-puerperio-COVID-19.pdf

Société Française de Médecine Vasculaire[15]	Not stated		MTEV -COVID19 patients non hospitalisés : Propositions de la Société Française de Médecine Vasculaire pour la prévention, le diagnostic et le traitement de la maladie thromboembolique veineuse des patients avec COVID 19 non hospitalisés	https://www.portailvasculaire.fr/sites/default/files/docs/sfmv_propositions_mt_ev_covid-19_texte.pdf https://www.portailvasculaire.fr/documents-covid19
Société Française d'Anesthésie et de Réanimation (SFAR), (by the GIHP and GFHT) / Susen[13]	April 2020	3 th	Traitement anticoagulant pour la prévention du risque thrombotique chez un patient hospitalisé avec Covid-19 et surveillance de l'hémostase	https://sfar.org/traitement-anticoagulant-pour-la-prevention-du-risque-thrombotique-chez-un-patient-hospitalise-avec-covid-19-et-surveillance-de-lhemostase/
Club Anesthésie Réanimation en Obstétrique(CARO) et Collège National des Gynécologues et Obstétriciens Français (CNGOF)[17]	April 2020	16 th	Gestion du risque thromboembolique chez les femmes enceintes COVID-19 + ou suspects	http://caro-club.univ-lyon1.fr/
United States of America				
American College of Cardiology[22]	April 2020	22 th	Thrombosis and COVID-19: FAQs For Current Practice	https://www.acc.org/latest-in-cardiology/articles/2020/04/17/14/42/thrombosis-and-coronavirus-disease-2019-covid-19-faqs-for-current-practice
The American Society of Hematology[6]	April 2020	17 th	COVID-19 and VTE/Anticoagulation: Frequently Asked Questions	https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation
China				
People's Liberation Army Professional Committee of Critical Care Medicine and Chinese Society on Thrombosis	April 2020	20 th	Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19.	https://www.ncbi.nlm.nih.gov/pubmed/32307014

and Hemostasis grouped experts /
Song [23]

International

Bikdeli[1] supported by: International Society on Thrombosis and Haemostasis (ISTH), North American Thrombosis Forum (NATF), European Society of Vascular Medicine (ESVM), International Union of Angiology (IUA). ESC Working Group on the Pulmonary Circulation and Right Ventricular Function (SR, SK).	April 17th 2020	COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164881/
International Society of Thrombosis and Haemostasis[11, 12]	March 2020	ISTH interim guidance on recognition and management of coagulopathy in COVID-19 Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19.	https://onlinelibrary.wiley.com/doi/10.1111/jth.14810 https://www.portailvasculaire.fr/documents-covid19

Table 9 – Summary of recommendations from international organisations and countries

Country/Organisation	Recommendations anticoagulants
Europe	
Switzerland / Casini [19]	The Working Party on Hemostasis (Swiss Society of Hematology) proposed their recommendations (version April 11th) based on the available literature and published recommendations from the International Society of Thrombosis and Hemostasis (https://www.isth.org), from the American Society of Hematology (https://www.hematology.org/covid-19) and from the Society for Thrombosis and Haemostasis Research (http://gth-online.org).[18] • All in-hospital COVID-19 patients should receive pharmacological thromboprophylaxis according to a risk stratification score, unless contraindicated. • In patients with creatinine clearance >30 ml/min, low molecular weight heparin (LMWH) should be administered according to the prescribing information. An increased dose should be considered in overweight patients (>100 kg). • In patients with creatinine clearance <30 ml/min, unfractionated heparin (UHF) subcutaneously twice or three times daily or intravenously should be administered according to the prescribing information. An increased dose should be considered in overweight patients (>100 kg). • Anti-Xa activity should be monitored when indicated (e.g., evidence of renal dysfunction). • Antithrombin needs not be monitored but this could be considered on an individual basis in cases of disseminated intravascular coagulation or sepsis-induced coagulopathy or heparin resistance. • We suggest regularly monitoring prothrombin time, D-dimers, fibrinogen, the platelet count, lactate dehydrogenase (LDH), creatinine and alanine aminotransferase (ALT) (daily or at least 2–3 times per week). • In patients in intensive care with a large increase in D-dimers, severe inflammation, or signs of hepatic or renal dysfunction or imminent respiratory failure, intermediate or therapeutic dosing of LMWH or UHF should be considered, according to the bleeding risk. • Heparin-induced thrombocytopenia (HIT) should be considered in patients with fluctuations in platelet counts or signs of heparin resistance. • In patients undergoing extracorporeal membrane oxygenation (ECMO) treatment we suggest maintaining UFH at doses bringing anti-Xa activity into the therapeutic range. There are no data on the use of direct oral anticoagulants.
Spain : Working Group on Cardiovascular Thrombosis of the Spanish Society of Cardiology / Vivas[20]	Presents a table of interactions of medication used to treat COVID-19 and antithrombotics (Appendix 4). Algorithm for hospitalized patients with COVID-19 with no previous antithrombotic: • The first step of the algorithm is to prescribe LMWH to all patients requiring hospital admission, with weight-adjusted doses for patients with body mass index > 35 and after assessing the bleeding risk and baseline platelet count.

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- The patient's thromboembolic risk and the severity of the disease due to COVID-19 should also be assessed, thus providing a guideline for an intermediate/extended or therapeutic dose of LMWH (however, there is no evidence in this regard)
 - Monitor proinflammatory and haemostatic parameters every 24-48 h (depending on the clinical severity of the patient), according to which the patient's risk and consequently the dose of LMWH will be reassessed.
 - Discharge from hospital: prudent to prolong the use of LMWH in prophylactic doses for 7-10 days after discharge.
 - If the diagnosis of VTE is established, LMWH should be administered at therapeutic doses;
 - an anti-Xa determination at 48 h after the start of anticoagulation could be of interest, to ensure efficacy and minimize bleeding risk.

Patients with indication for anticoagulation prior to SARS-CoV-2 infection (atrial fibrillation, mechanical valve prosthesis):

- Switch to parenteral anticoagulation is proposed (mainly due to the severity of the condition or drug interactions with drugs to treat COVID-19).
 - There is no clear evidence on the maintenance of oral anticoagulation in patients admitted for SARS-CoV-2 infection, although a priori it could be maintained in stable patients not taking any drug potentially causing an interaction. Therefore, the possible interactions and the severity of the patient should be carefully assessed in order to proceed according to the different algorithms to change oral anticoagulation to LMWH at anticoagulant doses to minimize thromboembolic and bleeding events from incorrect bridging treatment. Such a change should also be made when antiviral treatment is completed and anticoagulation can be re-administered.
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Sociedad Española de Trombosis y Hemostasia[21] To indicate **prophylaxis** with low molecular weight heparin (LMWH) in hospitalised patients with COVID-19 will be considered if they present any additional risk factor for thrombosis.

The following will be considered as **major risk factors for thrombosis** in patients with COVID-19:

- Forms of severe COVID-19 with the following alterations:
 - C-reactive protein (CRP) >150 mg/L
 - Dimer D >1500 ng/mL
 - Ferritin >1000 ng/mL
 - Lymphocytopenia <800×10⁶/L
 - IL-6 >40 pg/mL
 - D-dimer >3000 ng/ml
-

- Personal or family history of venous thrombotic disease
- Personal history of arterial thrombotic disease
- Known biological thrombophilia
- Recent surgery
- Gestation
- Hormone replacement therapy

Prophylaxis in patients with no major risk factors for thrombosis

All patients hospitalized with COVID-19 without increased risk factors for thrombosis should receive prophylactic doses of LMWH (see Table A) early, unless there is a contraindication.

Table A. Prophylactic dose LMWH

Dosis Profilácticas	Función renal	
	Aclaramiento de creatinina >30 mL/min	Aclaramiento de creatinina <30 mL/min
Enoxaparina	< 80 Kg: 40 mg / 24h s.c. 80 – 100 Kg: 60 mg / 24h s.c. > 100 Kg: 40 mg / 12h s.c.	< 80 Kg: 20 mg / 24h s.c. > 80 Kg: 40 mg / 24h s.c.
Tinzaparina	< 60 Kg: 3500 UI/ 24h s.c. > 60 Kg: 4500 UI / 24h s.c.	< 60 Kg: 3500 UI / 24h s.c. > 60 Kg: 4500 UI / 24h s.c.
Bemiparina	3500 UI/24h s.c.	2.500 UI/24h s.c.
Nadroparina	0,3 ml / 24h s.c.	----
Dalteparina	5000 UI / 24h s.c.	----

In case of heparin allergy or heparin-induced thrombocytopenia, use fondaparinux at a dose of: 2.5 mg / 24h s.c. if creatinine clearance is >50 mL/min 1.5 mg / 24h s.c. if creatinine clearance is <50 and >20 mL/min

Contraindicated if creatinine clearance is <20 mL/min Prophylactic treatment with LMWH will be maintained until the patient is discharged.

Prophylaxis in patients with higher risk factors for thrombosis

All patients hospitalized with COVID-19 and the presence of at least one of the major risk factors for thrombosis should receive LMWH at a prophylactic, weight-adjusted dose (or for patients at increased risk of thrombosis) (see Table B) early, unless there is a contraindication.

Table B. Prophylactic doses of LMWH for patients at increased risk

Dosis profilácticas para pacientes de mayor riesgo	Función renal	
	Aclaramiento de creatinina >30 mL/min	Aclaramiento de creatinina <30 mL/min
Enoxaparina	1 mg / Kg / 24h s.c.	0.5 mg / Kg / 24h s.c.
Tinzaparina	75 UI / Kg / 24h s.c.	75 UI / Kg / 24h s.c.
Bemiparina	5000 UI / 24h s.c.	3500 UI / 24h s.c.
Nadroparina	< 70 Kg: 0,4 ml / 24h s.c. > 70 Kg: 0,6 ml / 24h s.c.	---
Dalteparina	5000 UI / 24h s.c.	---

In case of heparin allergy or heparin-induced thrombocytopenia, use fondaparinux at a dose of: 5 mg / 24h s.c. if creatinine clearance is >50 mL/min 2.5 mg / 24h s.c. if creatinine clearance is <50 and >20 mL/min Contraindicated if creatinine clearance is <20 mL/min Prophylactic treatment with LMWH will be maintained until the patient is discharged.

After discharge, LMWH should be maintained at the usual dose of prophylaxis (Table A) in patients who are bedridden or have restricted ambulation, or who have persistent risk factors for thrombosis, for at least one week or until adequate mobility is achieved.

Treatment of thromboembolic disease

Patients with suspected clinical thromboembolic disease are considered to be those who present one of the following clinical situations:

- Sudden onset of hypoxemia with PO₂<90%, which is not justified by the radiological lesion, or tachycardia >100 ppm or hypotension with SAD <100 mmHg) or clinical DVT

- Elevated ventricular overload markers (NT-proBNP, troponin)
- Signs of right ventricular overload (VD/VE ratio >1) or pulmonary hypertension (speed of tricuspid regurgitation >2.8 m/s) on echocardiogram
- Persistently elevated D-dimer (>3000 ng/mL) that increases with dissociation of the evolution of the remaining acute phase reactants (C-reactive protein, ferritin).

If PTE is suspected, urgent pulmonary angiocentesis must be performed to confirm the diagnosis. If the diagnosis of PTE or DVT is confirmed, LMWH should be initiated at therapeutic doses (Table C).

Table C. Therapeutic doses of LMWH.

Dosis Terapéuticas	Función renal	
	Aclaramiento de creatinina >30 mL/min	Aclaramiento de creatinina <30 mL/min
Enoxaparina	1 mg / Kg / 12h s.c. (en la fase aguda) 1,5 mg / Kg / 24h s.c.	1 mg / Kg / 24h s.c.
Tinzaparina	175 UI / Kg / 24h s.c.	175 UI / Kg / 24h s.c.
Bemiparina	115 UI / Kg / 24h s.c.	85 UI / Kg / 24h s.c.
Nadroparina	86 UI anti Xa / Kg / 12h s.c. Si ClCr ≥30 y <50 mL/min reducir del 25% al 33%	Contraindicada
Dalteparina	100 UI / Kg / 12h s.c. 200 UI / Kg / 24h s.c.	Ajustar según nivel de anti-Xa

In the event of hemodynamic instability unfractionated heparin (sodium heparin) in continuous infusion will be used by adjusting the dose with TTPA.

In patients allergic to heparin or to heparin-induced thrombocytopenia, use fondaparinux at a dose of

- 5mg / 24h s.c. if <50 Kg and creatinine clearance >50 mL/min
- 7.5 mg / 24h s.c. if 50-100 Kg and creatinine clearance >50 mL/min
- 10 mg / 24h s.c. if >100 Kg and creatinine clearance >50 mL/min
- 5mg / 24h s.c. if creatinine clearance is <50 and >20 mL/min

- Contraindicated if creatinine clearance is <20 mL/min

In patients diagnosed with PET or DVT, it is recommended that anticoagulation treatment be maintained for a minimum of 3-6 months. The treatment of choice after discharge will be LMWH at anticoagulant dose every 24 h (Table C) without starting coumarin, to avoid displacement for INR control.

Patient not requiring hospitalization

An individualized assessment of the need for antithrombotic prophylaxis should be made based on clinical criteria, risk factors, and personal and family thrombotic history. If required, LMWH should be used at the usual dose of prophylaxis (Table A).

In any case, the patient should be given the following general recommendations:

- Encourage ambulation
- Avoid prolonged standing or sitting and avoid crossing your legs
- Change position every 30-60 min
- Exercise with the lower extremities (flexo-extension movements and circular movements of the feet).
- Avoid dehydration

Pregnant patient: This section also appears as a SETH document on the Society's website <https://www.covid-19.seth.es/wp-content/uploads/2020/04/Recomendaciones-sobre-profilaxis-ETV-en-embarazo-y-puerperio-COVID-19.pdf>

The pregnant patient is an increased risk group for VTE that in the case of COVID-19 infection requires adequate assessment in both pregnancy and postpartum. For the recommendations of the Sociedad Espanola de Trombosis y Hemostasia[16, 20] see Table 10 in the section **Error! Reference source not found.** on pregnant women.

Société Française de
Médecine Vasculaire[15]

Prévention de la MTEV en médecine et après hospitalisation en dehors du contexte du COVID-19

Thromboprophylaxie au cours de l'hospitalisation

- Les patients hospitalisés avec une affection médicale aiguë sont à risque de Maladie Thromboembolique Veineuse (MTEV). Ce risque se situe aux alentours de 2% à 40 jours après hospitalisation. Le bénéfice d'une prophylaxie médicamenteuse pendant 10 +/- 4 jours au cours d'une hospitalisation pour affection médicale aiguë a été validé dans l'essai MEDENOX. La thromboprophylaxie est actuellement recommandée dans tous les guides de bonne pratique nationaux et internationaux.
- Les facteurs de risque des patients candidats à une prophylaxie sont bien connus : • Age • Infection aiguë • Cancer actif • Antécédent de MTEV • Immobilisation prolongée • Insuffisance cardiaque chronique • Insuffisance respiratoire chronique.

Prophylaxie de la MTEV en cas de COVID-19 chez les patients restant à domicile

En l'état actuel des connaissances, il n'est pas licite de suivre l'évolution des dosages de D dimères pour décider une thrombo-prophylaxie.

Il n'est pas licite de réaliser de manière systématique des écho-Doppler répétés pour rechercher une thrombose veineuse profonde (TVP) en l'absence de signes cliniques évocateurs de MTEV.

Les auteurs ont choisi, pour les patients avec COVID-19 ambulatoires, d'appliquer ce modèle de thromboprophylaxie, étant proche de la situation des patients non COVID-19 pour lesquels des données validées existent.

On peut envisager une thrombo-prophylaxie chez les patients COVID-19 qui présentent en plus d'une réduction de mobilité importante au moins un facteur de risque parmi les suivants : IMC > 30kg/m², Age > 70 ans ; Cancer en cours de traitement; Antécédent personnel de MTEV ; Chirurgie majeure de moins de 3 mois ;

Dans ces cas, il est suggéré une thrombo-prophylaxie de 7 à 14 jours : par Héparine de Bas Poids Moléculaire (HBPM) ou fondaparinux à dose standard (Ex : Daltéparine 5000 UIx1/jour ou Enoxaparine 4000 UIx1/jour ou Fondaparinux 2.5mg x1/j) avec auto injections si possible pour limiter le recours à une Infirmière Diplômée d'Etat (IDE) à domicile et éviter les contacts. Les auteurs suggèrent donc de ne pas adapter la thromboprophylaxie au poids du patient.

Les patients ambulatoires suspects de COVID-19 présentant les facteurs suscités peuvent bénéficier de la même thrombo-prophylaxie que les patients avec COVID-19 confirmé : 7 à 14 jours puis ré-évaluation pour décider de la poursuite ou non de la thromboprophylaxie.

Diagnostic de la MTEV : Parcours du patient hors hospitalisation (see reference document)

Société Française
d'Anesthésie et de
Réanimation (SFAR),
(by the GIHPand GFHT)
/ Susen[13]

Prévention et traitement des complications thrombotiques en cas d'infection par le COVID-19 hospitalisé

	Pas d'oxygénothérapie	Oxygénothérapie	Oxygénothérapie nasale à haut débit ou ventilation artificielle	Monitoring de l'anticoagulant
IMC <30 kg/m ²	HBPM dose prophylactique standard ou fondaparinux (par ex : enoxaparine 4000 UI/24h SC; enoxaparine 2000 UI/24h SC si Clcr entre 15 et 30 ml/min; tinzaparine 3500 UI/24h SC si Clcr >20 ml/min; fondaparinux 2,5 mg/24h si Clcr >50 ml/min)			Surveillance de l'activité anti-Xa: - HBPM : éviter le surdosage (> 1,2 UI/ml pour l'enoxyaparine) - HNF : objectif 0,3-0,5 UI/ml
IMC ≥30 kg/m ² sans FDR*	enoxaparine 4000 UI/12h SC enoxaparine 6000 UI/12h SC si poids >120 kg HNF: 200 UI/kg/24h, si Clcr < 30 ml/min			
IMC ≥30kg/m ² avec FDR*				
Thromboses itératives de cathéter ou de filtre d'EER	HBPM à dose curative par ex. enoxaparine 100 UI/kg/12h SC (poids réel), sans dépasser 10 000 UI/12h. HNF 500 UI/kg/24h si Clcr <30 ml/min si ECMO Réévaluer la dose en cas de défaillance multiviscérale ou de coagulopathie de consommation.			Surveillance de l'activité anti-Xa: - HBPM : éviter le surdosage (> 1,2 UI/ml pour l'enoxyaparine) - HNF : objectif 0,5-0,7 UI/ml
Syndrôme inflammatoire marqué (par ex: fibrinogène >8 g/L)				
Hypercoagulabilité (par ex: D-dimères >3 µg/ml)				
ECMO				
Traitement anticoagulant au long cours				

Risque intermédiaire Risque élevé Risque très élevé
NB: le risque faible n'est pas représenté

*Facteurs De Risque (FDR) thromboemboliques : cancer actif, antécédent personnel de thrombose...
Clcr : Clairance de la créatinine; HBPM : héparine de bas poids moléculaire; HNF : héparine non fractionnée

Objective #1 DEFINIR LE NIVEAU DE RISQUE DE THROMBOSE CHEZ LES PATIENTS AVEC COVID-19

1. Rechercher chez tous les patients COVID-19, des facteurs de risque (FDR) thromboemboliques majeurs surajoutés, et notamment : un cancer actif (traitement au cours des 6 derniers mois), des antécédents personnels récents (< 2 ans) d'évènement thromboembolique. D'autres facteurs de risque peuvent être considérés (âge >70 ans, allègement prolongé, postpartum, contraception orale combinée...).
2. Définir et caractériser les facteurs de risque thrombotiques qui paraissent déterminants lors d'un COVID-19 - La sévérité du COVID-19 reflétée par l'intensité du traitement : absence d'oxygénothérapie (O2), oxygénothérapie, oxygénothérapie nasale à haut débit (ONHD) ou ventilation artificielle. - L'indice de masse corporelle (IMC)
3. En déduire 4 niveaux de risque thromboembolique (tableau): a. Risque faible : patient non hospitalisé avec IMC < 30 kg/m² sans FDR surajouté. b. Risque intermédiaire : IMC < 30 kg/m² avec ou sans FDR surajouté, sans nécessité d'OHND ni de ventilation artificielle. c. Risque élevé : - IMC < 30 kg/m² avec ou sans FDR surajouté, sous ONHD ou ventilation artificielle - IMC > 30 kg/m² sans FDR surajouté - IMC > 30 kg/m² avec FDR surajouté, sans nécessité d'OHND ni de ventilation artificielle d. Risque très élevé : - IMC > 30 kg/m² avec FDR surajouté, sous ONHD ou ventilation artificielle - ECMO (veino-veineuse ou veino-

artérielle) - Thromboses de cathéter itératives ou inhabituelles - Thromboses de filtre d'épuration extra-rénale - Syndrome inflammatoire marqué et/ou hypercoagulabilité (par ex : fibrinogène > 8 g/L ou D-Dimères > 3 µg/ml ou 3000 ng/ml)

OBJECTIF # 2 SURVEILLER L'HEMOSTASE DES PATIENTS HOSPITALISES AVEC COVID-19

1. Contrôler au minimum toutes les 48h les paramètres d'hémostase suivants : numération plaquettaire, temps de Quick (TQ ou TP), TCA, fibrinogène, et D-Dimères.
2. Dans les cas sévères, en cas d'aggravation clinique, de thrombopénie et/ou de diminution de la concentration de fibrinogène, contrôler aussi pour le diagnostic d'une CIVD la concentration des monomères de fibrine (si dosage disponible), des facteurs II et V, et de l'antithrombine.

OBJECTIF # 3 PRESCRIRE UN TRAITEMENT ANTICOAGULANT CHEZ LES PATIENTS AVEC COVID-19

1. Chez tous les patients hospitalisés, il est proposé de relayer les traitements anticoagulants oraux, AVK ou AOD (risque d'instabilité et interactions médicamenteuses), par une héparinothérapie curative.
 2. En cas de risque thrombotique intermédiaire, il est proposé de prescrire une prophylaxie par une héparine de bas poids moléculaire (HBPM) : par exemple, enoxaparine 4000 UI/24h SC ou tinzaparine 3500 UI/24h SC. Le fondaparinux 2,5 mg/24h SC est une alternative si la clairance de la créatinine (Clcr) est supérieure à 50 ml/min. En présence d'une insuffisance rénale sévère, on peut proposer comme alternative à la calciparine : enoxaparine 2000 UI/24h SC pour une Clcr entre 15 et 30 ml/min ou tinzaparine 3500 UI/24h SC pour une Clcr entre 20 et 30 ml/min.
 3. Chez les patients traités par HBPM à dose prophylactique standard, il est recommandé de NE PAS surveiller l'activité anti-Xa.
 4. En cas de risque thrombotique élevé, il est proposé de prescrire une prophylaxie renforcée par HBPM aux doses suivantes : enoxaparine 4000 UI/12h SC ou 6000 UI/12h SC si poids > 120 kg. En cas d'insuffisance rénale (Clcr < 30ml/min), il est proposé de prescrire de l'héparine non fractionnée (HNF) à la dose de 200 UI/kg/24h.
 5. Chez les patients traités par une posologie d'HBPM supérieure à la dose prophylactique standard, il est proposé de surveiller l'activité anti-Xa 4 heures après la 3ème injection, puis régulièrement en cas d'insuffisance rénale, pour rechercher un surdosage (valeur seuil variable selon l'HBPM) exposant à un risque hémorragique plus élevé.
 6. En cas de risque thrombotique très élevé, il est proposé de prescrire une héparinothérapie curative par une HBPM, par exemple enoxaparine à la dose de 100 UI/kg/12h SC, ou par HNF à la dose de 500 UI/Kg/24h en cas d'insuffisance rénale sévère.
 7. Chez tous les patients obèses (IMC > 30 kg/m²), le risque thrombotique étant élevé ou très élevé, les posologies d'héparine proposées sont: a. enoxaparine 4000 UI/12h ou 6000 UI/12h si poids > 120 kg. b. avec un FDR surajouté et ONHD ou ventilation artificielle : enoxaparine 100 UI/kg (poids réel) /12h SC sans dépasser 10 000 UI/12h ou HNF 500 UI/kg/24 h.
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8. Chez tous les patients sous HNF, contrôler au moins toutes les 48 heures et après chaque changement de dose l'activité anti-Xa, qui devra être maintenue si le risque de saignement est maîtrisé entre 0,3 et 0,5 UI/ml lors d'un traitement prophylactique renforcé (dose de départ 200 UI/kg/24h), et entre 0,5 et 0,7 UI/ml lors d'un traitement curatif (dose de départ 500 UI/kg/24h).

9. La mise en place d'une ECMO (veino-veineuse ou veino-artérielle) expose d'emblée à un risque thrombotique très élevé. Il est donc proposé de prescrire une anticoagulation curative par HNF dès l'initiation de l'ECMO (indépendamment du débit d'ECMO), pour un objectif d'anti-Xa entre 0,5 et 0,7 UI/mL.

10. En cas de syndrome inflammatoire ou d'hypercoagulabilité marqués (par exemple : fibrinogène > 8 g/L ou D-dimères > 3 µg/ml ou 3000 ng/ml) ou d'augmentation rapide de la concentration des D-Dimères, une héparinothérapie curative est proposée même en l'absence de thrombose clinique en tenant compte du risque hémorragique.

11. Sous HNF, il est recommandé de surveiller au moins toutes les 48 heures la numération plaquettaire. Une diminution de celle-ci de plus de 40% entre le 4ème et le 14ème jour de traitement impose un bilan de CIVD et la recherche d'une thrombopénie induite par l'héparine.

12. En cas de défaillance multiviscérale, ou de coagulopathie de consommation avec diminution brutale de la concentration en fibrinogène, de la numération plaquettaire et du taux de facteur V, il est proposé de réévaluer la posologie de l'héparinothérapie, ces événements étant associés à une majoration du risque hémorragique.

13. La durée et l'intensité de la thromboprophylaxie seront réévaluées en fonction de la sévérité de l'infection et des facteurs de risque.

OBJECTIF # 4 APPLIQUER D'AUTRES MESURES QUE LE TRAITEMENT ANTICOAGULANT POUR LA PREVENTION DU RISQUE THROMBOTIQUE

1. Interrompre tout traitement hormonal ou apparenté (contraception oestroprogestative, traitement hormonal substitutif, tamoxifène) chez les patientes avec COVID-19 nécessitant une thromboprophylaxie.

2. Organiser une filière de communication spécifique entre les services de soins et de réanimation et le laboratoire d'hémostase, pour une transmission optimale des résultats biologiques (notamment : numération plaquettaire, fibrinogène, D-Dimères et activité anti-Xa) pour une adaptation posologique rapide de l'héparinothérapie.

3. Suspecter une embolie pulmonaire chez tout patient présentant brutalement une aggravation respiratoire ou hémodynamique notamment en cas de dysfonction cardiaque droite.

4. Un echo-doppler veineux des membres inférieurs est à considérer lors de toute aggravation clinique inexplicée, ou en cas d'élévation brutale des D-Dimères. Cet examen peut aussi être réalisé plus tôt chez les patients avec un cathéter veineux central.

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5. Il n'y a pas d'arguments chez ces patients à faible risque hémorragique pour proposer une interruption cave temporaire.
 6. La compression pneumatique intermittente (CPI) est une option à discuter.
 7. En cas de thrombose chez un patient jeune et sans facteur de risque surajouté, un bilan de thrombophilie constitutionnelle pourra être envisagé après guérison. Un syndrome des anticorps antiphospholipides pourra être recherché, plus tôt, et quel que soit l'âge en cas de forte suspicion (thromboses itératives, survenant sous héparinothérapie curative, ou allongement inexpliqué du TCA).
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United States America

American College of Cardiology[22]

- The available data on thrombotic risk are quite limited.
 - Nonetheless, most experts agree that the signal for increased thrombotic risk is sufficient to recommend pharmacologic venous thromboembolism (VTE) prophylaxis in all hospitalized COVID-19 patients as long as there is no contraindication.
 - There is not a clear increased propensity for bleeding among COVID-19 patients with coagulopathy, though data are lacking.
 - Assessment for VTE should be performed and incorporate multiple elements of the patient condition, including interval history, physical exam and vital signs, currently administered treatments, and laboratory studies. The decision to order imaging for VTE should not be based on an elevated D-dimer alone.
 - All patients hospitalized with COVID-19 should receive pharmacologic VTE prophylaxis unless a specific contraindication (e.g., active bleeding) exists. Strategies to minimize frequent interactions between patients and health care providers (e.g., use of daily low-molecular-weight heparin rather than thrice-daily unfractionated heparin injections) may help to minimize infection risk and use of personal protective equipment when clinically appropriate.
 - Use of higher-intensity, non-standard VTE prophylaxis can be considered for patients with COVID-19, but ideally should be done within the context of a clinical trial given current lack of efficacy evidence.
 - Post-hospital VTE prophylaxis should be considered in patients with COVID-19. Experience from the MAGELLAN (<https://www.nejm.org/doi/full/10.1056/NEJMoa1111096>), APEX (<https://www.nejm.org/doi/full/10.1056/NEJMoa1601747>), and MARINER (<https://www.nejm.org/doi/full/10.1056/NEJMoa1805090>) studies suggest that in select patients without COVID-19, post-discharge thromboprophylaxis (particularly with a DOAC) may be beneficial if bleeding risk can be minimized. This may be even more important in COVID-19 because of the long duration of illness—a peak in symptoms around day 8-10 followed by a rather lengthy tail with increased likelihood of immobility and risk of superinfection. Use of a validated risk score (e.g., IMPROVE or IMPROVEDD score with D-dimer) may be particularly helpful in guiding decision-making.
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The American Society of Hematology[6]

Is COVID-19 associated with an increased risk for venous thromboembolism (VTE)?

The incidence of VTE in COVID-19 patients is not established. Like other medical patients, those with more severe disease, especially if they have additional risk factors (e.g. older, male, obesity, cancer, history of VTE, comorbid diseases, ICU care), have a higher risk of VTE than those with mild or asymptomatic disease. In a recently published Dutch study of 184 COVID-19 patients in the ICU, 25 had confirmed PE, 1 had DVT and 2 had catheter-related thrombosis.¹ These patients were severely ill with 13%

receiving renal replacement therapy and 38% with evidence of coagulopathy. Due to differences in duration of follow-up, the authors reported a cumulative incidence of VTE of 27% (95% CI 17-32). The patients in this study initially received nadroparin thromboprophylaxis, ranging from 2850 IU once daily to 5700 IU once daily (enoxaparin 40 mg is equivalent to nadroparin 4000 IU). Unpublished data suggest lower VTE incidence in ICU patients in other centers, and variation in rates may reflect differences in ICU admission criteria. There are no studies on VTE rate in outpatients or in patients on non-ICU hospital wards.

What is the recommended VTE prophylaxis in patients with COVID-19?

All **hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis** with LMWH or fondaparinux (suggested over unfractionated heparin to reduce contact) unless the risk of bleeding is judged to exceed the risk of thrombosis. Dose adjustment for obesity may be used per institutional guidance. In patients with a history of heparin-induced thrombocytopenia, use fondaparinux. 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.

Should seriously ill COVID-19 patients receive therapeutic-intensity anticoagulation empirically (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, with some suggesting microvascular thrombosis and others showing pulmonary hemorrhage. Consequently, **therapeutic anticoagulation has been contemplated for the treatment of critically ill patients** characterized by very high levels of D-dimer, abnormal coagulation parameters (coagulopathy/DIC), markedly elevated inflammatory markers (cytokine storm syndrome), and/or multiorgan failure. **Whether critically ill COVID-19 patients should receive therapeutic-intensity anticoagulation in the absence of confirmed or suspected VTE is currently unknown.**

How should we manage COVID-19 patients who experience recurrent clotting of access devices (e.g., central venous catheters, arterial lines) or extracorporeal circuits (e.g., Continuous Renal Replacement Therapy, ECMO) despite prophylactic anticoagulation?

Although of unproven benefit, it may be reasonable to increase the intensity of anticoagulation (i.e., from standard-intensity prophylaxis to intermediate-intensity prophylaxis or from intermediate-intensity prophylaxis to therapeutic-intensity prophylaxis) in these settings. Any decision to increase the intensity of anticoagulation should take into account the individual patient's bleeding risk.

Should COVID-19 patients receive post-discharge thromboprophylaxis?

Patients hospitalized for acute medical illness are at increased risk for VTE for up to 90 days after discharge. This finding should apply to COVID-19 patients, though data on incidence are not yet available. Therefore, it is reasonable to **consider extended thromboprophylaxis after discharge using a regulatory-approved regimen** (e.g., betrixaban 160 mg on day 1, followed by 80 mg once daily for 35-42 days; or rivaroxaban 10 mg daily for 31-39 days). Inclusion criteria for the trials studying these regimens included combinations of age, co-morbidities such as active cancer, and elevated D-dimer >2 times the upper normal limit. Any decision to use **post-discharge thromboprophylaxis should consider the individual patient's VTE risk factors**, including reduced mobility and bleeding risk as well as feasibility. "Home hospital" approaches for COVID-19 patients involving early discharge have been being suggested to free up inpatient beds. Status at discharge should be considered in any decision to use VTE prophylaxis in these unique patients. **Aspirin has been studied for VTE prophylaxis in low-risk patients after orthopedic surgery and could be considered for COVID-19 VTE prophylaxis if criteria for post-discharge thromboprophylaxis are met.**

If a patient with COVID-19 requires therapeutic anticoagulation for VTE or AFIB stroke prevention, are there any special considerations?

Multiple medications are under investigation for COVID-19. Sarilumab (KEVZARA) can increase cytochrome P450 enzyme activity. Apixaban (Eliquis®) and rivaroxaban (Xarelto®) should not be used with sarilumab and increased doses of warfarin may be required. Atazanavir and lopinavir/ritonavir will increase drug concentrations of apixaban and rivaroxaban and decrease the active metabolite of clopidogrel and prasugrel. The University of Liverpool has collated a list of drug interactions at <http://covid19-druginteractions.org/>. Use LMWH or UFH in hospitalized critically ill patients because of the shorter half-life and fewer drug-drug interactions compared with direct oral anticoagulants. Regular warfarin users who are unable to get INR monitoring during isolation may be candidates for direct oral anticoagulant therapy. Patients with mechanical heart valves, ventricular assist devices, valvular atrial fibrillation, antiphospholipid antibody syndrome, or pregnancy or lactation should continue treatment with warfarin therapy.

What hemostasis/coagulation test(s), if any, should be ordered in patients with suspected or known COVID-19 absent evidence of thrombosis or bleeding? Should tests like D-dimer be ordered?

- As we are still gathering information about the nature of the coagulopathy associated with COVID-19, it is reasonable to measure D-dimer, PT, aPTT, and fibrinogen levels in hospitalized patients; importantly INR is not sufficiently sensitive for coagulopathy.
 - Severe COVID-19 is associated with high D-dimer levels which appear to predict mortality. A relationship between elevated D-dimer levels and mortality, however, has been shown in previous cohorts of critically ill patients. Whether this is more significant in COVID-19 or more predictive of mortality in COVID-19 is currently unknown.
 - It is also unknown whether antithrombotic treatments aimed at D-dimer thresholds improve outcomes. How elevated D-dimer levels should guide management is highly uncertain, but this information may be helpful for clinical monitoring, characterizing the coagulopathy, and conducting clinical trials to rigorously test management strategies. Therapeutic anticoagulation is not
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mandatory for all patients based only on an elevated D-dimer test and there is no evidence supporting use of D-dimer values to guide intensity of anticoagulation.

Is VTE prophylaxis for a hospitalized patient with COVID-19 any different from a patient without COVID-19? Is there a role for post-discharge thromboprophylaxis?

- The best answer is yes and no. On the one hand, all medically ill patients admitted to the hospital should trigger screening to evaluate the need for VTE prophylaxis. However, two preliminary findings seem to distinguish patients with COVID-19 from other hospitalized medically ill patients, at least based on early reports from China and Europe. First, COVID-19 patients admitted to the hospital may have an additional procoagulant state compared to other hospitalized patients, including activation of coagulation through various infectious and inflammatory mechanisms. Second, many of these VTE events are occurring in patients receiving standard dose VTE prophylaxis.
- All patients hospitalized with COVID-19 should receive pharmacologic VTE prophylaxis unless a specific contraindication (e.g., active bleeding) exists. Strategies to minimize frequent interactions between patients and health care providers (e.g., use of daily low-molecular-weight heparin rather than thrice-daily unfractionated heparin injections) may help to minimize infection risk and use of personal protective equipment when clinically appropriate.
- Use of higher-intensity, non-standard VTE prophylaxis can be considered for patients with COVID-19, but ideally should be done within the context of a clinical trial given current lack of efficacy evidence.
- Post-hospital VTE prophylaxis should be considered in patients with COVID-19. Experience from the MAGELLAN (<https://www.nejm.org/doi/full/10.1056/NEJMoa1111096>), APEX (<https://www.nejm.org/doi/full/10.1056/NEJMoa1601747>), and MARINER (<https://www.nejm.org/doi/full/10.1056/NEJMoa1805090>) studies suggest that in select patients without COVID-19, post-discharge thromboprophylaxis (particularly with a DOAC) may be beneficial if bleeding risk can be minimized. This may be even more important in COVID-19 because of the long duration of illness—a peak in symptoms around day 8-10 followed by a rather lengthy tail with increased likelihood of immobility and risk of superinfection. Use of a validated risk score (e.g., IMPROVE or IMPROVEDD score with D-dimer) may be particularly helpful in guiding decision-making.

Should therapeutic anticoagulation be used in patients with COVID-19 absent confirmed or suspected thrombosis (i.e., ACS, VTE, stroke)?

- There is substantial controversy about the use of escalated doses of anticoagulants to prevent thrombotic events in COVID-19. Some have advocated that anticoagulants may help prevent other complications such as respiratory deterioration and mechanical ventilation due to pulmonary microvascular thrombosis. However, because therapeutic anticoagulation is also associated with an increased risk of bleeding, it should ideally be used in the context of a randomized trial for prevention of thrombosis based on our current state of knowledge.

People's Liberation Army Professional Committee of Critical Care Medicine and Chinese Society on Thrombosis and Hemostasis grouped experts / Song [23]

- Recommendation 1: Severe COVID-19-related coagulation dysfunction has a pathological basis
- Recommendation 2: The past medical history should be fully understood and the patients' coagulation function should be accurately evaluated in severe COVID-19 patients.
- Recommendation 3: Routine coagulation tests are recommended to screen coagulation function for severe COVID-19 patients
- Recommendation 4: ISTH/CDCC DIC scores are recommended to diagnose COVID-19-related coagulation dysfunction
- Recommendation 5: Viscoelastic tests are recommended for severe COVID-19 patients with coagulation dysfunction
- Recommendation 6: Anticoagulant therapy can be utilized without anticoagulant contraindications in severe COVID-19 patients with thrombosis
- Recommendation 7: In severe COVID-19 patients with coagulation dysfunction, anticoagulant therapy using unfractionated heparin/low-molecular-weight heparin are recommended to reduce the depletion of coagulation substrates
- Recommendation 8: In severe COVID-19 patients with coagulation dysfunction, a TEG heparinase comparison test is recommended to monitor unfractionated heparin dosage
- Recommendation 9: For severe COVID-19 patients with coagulation dysfunction requiring continuous renal replacement therapy, unfractionated heparin/LMWH for systemic anticoagulation or no anticoagulation is recommended
- Recommendation 10: Topical citrate anticoagulation is recommended for severe COVID-19 patients with active bleeding who require CRRT
- Recommendation 11: For severe COVID-19 patients with coagulation dysfunction requiring external membrane oxygenation therapy, unfractionated heparin is the preferred anticoagulant and there should be more monitoring of their coagulation status
- Recommendation 12: If heparin-induced thrombocytopenia occurs in severe COVID-19 patients, the anticoagulant argatroban/bivalirudin is recommended
- Recommendation 13: Goal-directed replacement therapy is recommended for severe COVID-19 patients with coagulation dysfunction
- Recommendation 14: If bleeding is not effectively stopped after active replacement therapy in severe COVID-19 patients, recombinant factor VII is recommended

The argumentation and explanations are discussed in the guidance.

International

Bikdeli[1] supported by: Presents a table of interactions of medication used to treat COVID-19 and antithrombotics / antiplatelets (Appendix 4).

International Society on Thrombosis and Haemostasis (ISTH), The following figure and table presents the consensus Recommendation on Antithrombotic Therapy During the COVID-19 Pandemic:

North American
Thrombosis Forum
(NATF),

European Society of
Vascular Medicine
(ESVM),

International Union of
Angiology (IUA).

ESC Working Group on
the Pulmonary
Circulation and Right
Ventricular Function
(SR, SK).

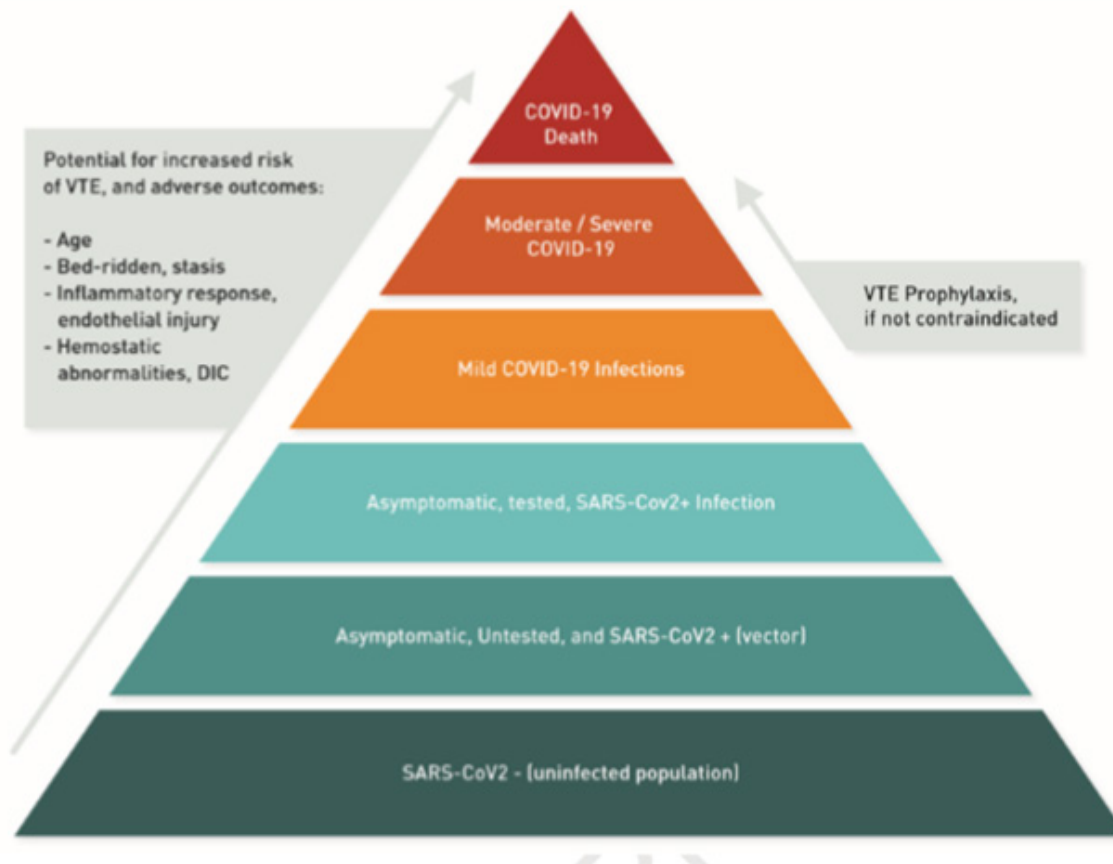


Table 6. Summary of Consensus Recommendation on Antithrombotic Therapy During the COVID-19 Pandemic

Patients with Mild COVID-19 (outpatient)	
	For outpatients with mild COVID-19, increased mobility should be encouraged. Although indiscriminate use of pharmacological VTE prophylaxis should not be pursued, assessment for the risk of VTE and of bleeding is reasonable. Pharmacologic prophylaxis could be considered after risk assessment on an individual case basis for patients who have elevated risk VTE, without high bleeding risk.*
	There is no known risk of developing severe COVID-19 due to taking antithrombotic agents (i.e. antiplatelet agents or anticoagulants). If patients have been taking antithrombotic agents for prior known thrombotic disease, they should continue their antithrombotic agents as recommended.
	For outpatients on vitamin K antagonists who do not have recent stable INRs, and are unable to undergo home or drive-through INR testing, it is reasonable to transition the treatment DOACs if there are no contraindications and no problems with drug availability and affordability. If DOACs are not approved or available, low-molecular weight heparin can be considered as alternative.*
Patients with Moderate or Severe COVID-19 without DIC (hospitalized)	
	Hospitalized patients with COVID-19 should undergo risk stratification for VTE prophylaxis.
	For hospitalized patients with COVID-19 and not in DIC, prophylactic doses of anticoagulation can be administered to prevent VTE.*† If pharmacological prophylaxis is contraindicated, it is reasonable to consider intermittent pneumatic compression.
	For hospitalized patients with COVID-19 and not in DIC, there is insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH.*‡
	Routine screening for VTE (e.g. bilateral lower extremity ultrasound) for hospitalized patients with COVID-19 with elevated D-Dimer (>1,500 ng/mL) cannot be recommended at this point*§
Patients with Moderate or Severe COVID-19 and suspected or confirmed DIC (hospitalized)	
	For patients with moderate or severe COVID-19 and in DIC but without overt bleeding, prophylactic anticoagulation should be administered.*¶§
	For hospitalized patients with COVID-19 with suspected or confirmed DIC, but no overt bleeding, there is insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH.*§
	For patients with moderate or severe COVID-19 on chronic therapeutic anticoagulation, who develop suspected or confirmed DIC without overt bleeding, it is reasonable to consider the indication for anticoagulation and weigh with risk of bleeding when making clinical decisions regarding dose adjustments or discontinuation. The majority of authors of this manuscript recommended reducing the intensity of anticoagulation in this clinical circumstance, unless the risk of thrombosis considered to be exceedingly high.
	For patients with moderate or severe COVID-19 and an indication for dual antiplatelet therapy (e.g. percutaneous coronary intervention within the past 3 months or recent myocardial infarction) and with suspected or confirmed DIC without overt bleeding, in the absence of evidence, decisions for antiplatelet therapy need to be individualized. In general, it is reasonable to continue dual antiplatelet therapy if platelet count >50,000, reduce to single antiplatelet therapy if 25,000-platelet count <50,000, and discontinue if platelets <25,000. However, these guidelines may be revised upward or downward depending on the individualized relative risk of thrombotic complications vs. bleeding.
	For patients who were admitted and are now being discharged for COVID-19, routine screening for VTE risk is reasonable for consideration of pharmacological prophylaxis for up to 45 days post-discharge. Pharmacological prophylaxis should be considered if there is elevated risk for thrombotic events, without high bleeding risk.*#
	Ambulation and physical activity should be encouraged.
Patients with COVID-19 presenting with ACS	
	For presentations concerning for STEMI and COVID-19, clinicians should weigh the risks and severity of STEMI presentation with that of potential COVID-19 severity in the patient, as well as risk of COVID-19 to the individual clinicians and to the healthcare system at large. Decisions for primary percutaneous coronary intervention or fibrinolytic therapy should be informed by this assessment.*
Patients without COVID-19 who have previously-known thrombotic disease	
	There is no known risk of developing severe COVID-19 due to taking antithrombotic agents. Patients should continue their antithrombotic agents as recommended.
	To minimize risks associated with healthcare worker and patient in-person interactions, follow-up with e-visits and telemedicine is preferable in most cases.
Patients without COVID-19 who develop new thrombotic disease	
	To minimize risks associated with healthcare worker and patient in-person interactions, in-home treatment or early discharge should be prioritized.
	To minimize risks associated with healthcare worker and patient in-person interactions, follow-up with e-visits and telemedicine is preferable in most cases.
Patients without COVID-19 but with co-morbid conditions (e.g. prior VTE, active cancer, major cardiopulmonary disease), who are homebound during the pandemic	
	Recommendations include increased mobility, and risk assessment for the risk of VTE and risk of bleeding is reasonable. Administration of pharmacologic prophylaxis could be considered after risk assessment on an individual case basis for patients who have elevated risk for thrombotic events, without high bleeding risk.
*Indicates recommendations as reached by consensus of at least 66% of authors determined via Delphi method. †Although high-quality data are lacking, some panel members (55%) considered it reasonable to use intermittent pneumatic compression in patients with severe COVID-19, in addition to pharmacological prophylaxis. Specific areas of concern included limited data on use in the prone position as well as potential high incidence of preexisting asymptomatic DVT. ‡If VTE prophylaxis is considered, enoxaparin 40mg daily or similar LMWH regimen (e.g. dalteparin 5000U daily) can be administered. Subcutaneous heparin (5000U twice to three times per day) can be considered for patients with renal dysfunction (i.e. creatinine clearance <30 mL/min). §While the majority of the writing group did make this recommendation, 31.6% of the group were in favor of intermediate-dose anticoagulation [e.g. enoxaparin 1mg/kg/day, or enoxaparin 40mg BID, or UFH with target aPTT of 50-70] and 5.2% considered therapeutic anticoagulation. &The majority of the investigators recommended against routine VTE screening (68%); however, the remaining members of the group (32%) recommended to consider such testing. §The majority of the investigators recommended prophylactic anticoagulation (54%). A minority of investigators (29.7%) voted for intermediate-dose parenteral anticoagulation in this setting, and 16.2% considered therapeutic anticoagulation. While the majority of investigators voted to reduce the intensity of anticoagulation if the indication were not acute (62%), this survey question did not meet prespecified cut-off of 66%. #The majority of the writing group recommended prophylaxis with DOACs (51%) and minority (24%) recommended LMWH, if available and appropriate. ACS: acute coronary syndrome; DOAC: direct oral anticoagulant, LMWH, low-molecular weight heparin; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin; VTE, venous thromboembolism.	

Table 10 – International guidance on prophylaxis for pregnant patients with COVID-19

Sociedad Española de Trombosis y Hemostasia[16, 21]

Infection by SARS-CoV-2 in pregnant women should be considered as one more risk factor for VTE.

GENERAL RECOMMENDATIONS FOR THE PREGNANT PATIENT FOR THROMBOSIS PREVENTION

1. Adequate hydration.
2. Encourage walking around the home.
3. Do flexo-extension exercises and circular movements with the feet several times a day.
4. Avoid prolonged standing or sitting and avoid crossing your legs.
5. Perform gentle exercise, such as pilates for pregnant women or yoga.
6. In case of doubts, appearance of symptoms or worsening, contact the health center, the area obstetrician or obstetrics on-call team.

RECOMMENDATIONS FOR ASSESSMENT OF THE PREGNANT / POST PARTUM PATIENT FOR THROMBOSIS (see tables below)

1. Assessment of risk factors for thrombosis during pregnancy and the puerperium.
2. Recommend adequate hydration
3. Recommend home mobilization.
4. Patient seen in emergency department by clinic suggestive of COVID-19, joint evaluation emergency physician and obstetrician considering the need for thromboprophylaxis.
5. The dose of LMWH will be prophylactic adjusted to the weight. In case of D-dimer values >3000, notify hematology to adjust the dose.
6. The obstetrics service will contact the patient to inform her of the test result and telephone follow-up of the patient.
7. Indicate to the patient that, in case of doubts, appearance of symptoms or worsening, contact with your health center, your obstetrician, or the on-call team of obstetricians.

These tables are taken from both the SETH guidance on 29th April together with the guidance on the 15th of April.

Table SETH Recommendation for pregnant women

Pregnant	Symptoms			
COVID-19	none	Mild at home	Moderate (bedbound at home)	Pneumonia / admitted
Positive	LMWH prophylactic dose (table D) adjusted to weight for 2 weeks.		LMWH prophylactic dose adjusted to weight for 2 weeks and up to 7 days after resolution.	LMWH prophylactic dose adjusted to weight. At home after hospitalization: continue prophylaxis 1 month. Evaluate in 3rd quarter prolong until delivery + 6 weeks postpartum.
Suspected symptoms by	Act as if positive. If the test has been carried out, wait for the result and act accordingly. Explain to the patient that, in case of worsening, to contact the health center, obstetrician, or the on-call team at obstetrics.			The same as if positive above.
Suspected contact with positive patient, symptoms by no	If the test has been performed, wait for the result and act on it. Re-evaluate every 48-72 hr. Explain to the patient that, if symptoms appear, to contact the health center, obstetrician, or the on-call team at obstetrics. Advise about symptoms and give recommendations for home isolation.			
Negative	Adequate hydration and promote mobilization Evaluate risk factors for thrombosis in pregnancy.			

For risk factors of VTE see tables F and G (below).

Table D. LMWH prophylactic dose

Dosis Profilácticas	Función renal	
	Aclaramiento de creatinina >30 mL/min	Aclaramiento de creatinina <30 mL/min
Enoxaparina	< 80 Kg: 40 mg / 24h s.c. 80 – 100 Kg: 60 mg / 24h s.c. > 100 Kg: 40 mg / 12h s.c.	< 80 Kg: 20 mg / 24h s.c. > 80 Kg: 40 mg / 24h s.c.
Tinzaparina	< 60 Kg: 3500 UI/ 24h s.c. > 60 Kg: 4500 UI / 24h s.c.	< 60 Kg: 3500 UI / 24h s.c. > 60 Kg: 4500 UI / 24h s.c.
Bemiparina	3500 UI/24h s.c.	2.500 UI/24h s.c.
Nadroparina	0,3 ml / 24h s.c.	---
Dalteparina	5000 UI / 24h s.c.	---

Table SETH Recommendation for post-partum women

Post-partum	Symptoms			
COVID-19	none	Mild at home	Moderate (bedbound at home)	Pneumonia admitted /
Positive	If no other risk factors: LMWH prophylactic dose adjusted to weight for 2 weeks. If risk factors are present consider continuing prophylaxis for 6 weeks.		LMWH prophylactic dose adjusted to weight for 2 weeks and up to 7 days after resolution.	LMWH prophylactic dose adjusted to weight; continue prophylaxis 6 weeks.
Suspected symptoms	by	Act as if positive. If the test has been carried out, wait for the result and act accordingly. Explain to the patient that, in case of worsening, to contact the health center, obstetrician, or the on-call team at obstetrics.		The same as if positive above.

Suspected by contact with positive patient, no symptoms	If the test has been performed, wait for the result and act on it. Re-evaluate every 48-72 hr. Advise about symptoms and give recommendations for home isolation. Advise the patient to contact her health centre if symptoms appear, the obstetrician or the on-call team of obstetricians.
Negative	Adequate hydration and promote mobilization Evaluate risk factors for thrombosis in pregnancy. If risk factors < 2: Early hydration and mobilization If risk factors ≥ 2: LMWH weight-adjusted prophylactic dose 2 weeks.

See table H and I for risk factors (below).

Table F. MAJOR THROMBOTIC RISK FACTORS IN PREGNANCY (RCOG 2015)

- Hospital admission - Cancer - Heart or lung disease - Systemic Lupus Erythematosus
- Inflammatory diseases (intestinal or polyarthropathy) - Nephrotic syndrome - Diabetes mellitus type I with nephropathy - Drepanocytosis - Parenteral drug use - Surgical procedure intercurrent - Severe ovarian hyperstimulation syndrome (OHS), only in first Quarter

Table G. MINOR THROMBOTIC RISK FACTORS IN PREGNANCY (RCOG 2015)

- BMI > 30kg/m² at the beginning of pregnancy
- Age > 35 years
- Parity ≥ 3
- Smoking >10 cigarettes/day
- Severe Varicose Syndrome
- Current preeclampsia
- Immobilization ≥ 3 days
- Family history of VTE by unidentifiable FR or in relation to estrogens in first degree relative
- Multiple gestation
- Assisted reproductive techniques (IVF)
- Dehydration/Hyperemesis gravidarum
- Systemic infection
- Long-term trips (≥4 hours)

Table H. MAJOR THROMBOTIC RISK FACTORS IN THE PUERPERIUM (RCOG 2015).

- BMI ≥40kg/m²
- Re-admission or hospital admission (≥3 days) in postpartum
- Any surgical procedure in the post-surgery period (except repair immediate perineum)
- Cancer
- Heart or lung disease
- Systemic Lupus Erythematosus
- Inflammatory diseases (intestinal or polyarthropathy)
- Nephrotic syndrome
- Diabetes mellitus type I with nephropathy
- Drepanocytosis
- Parenteral drug use
- Intrapartum Cesarean section

Table I. MINOR THROMBOTIC RISK FACTORS IN THE PUERPERIUM (RCOG 2015)

- | |
|--|
| <ul style="list-style-type: none">- BMI > 30kg/m²- Age > 35 years- Parity ≥ 3- Elective Cesarean section- Smoking >10 cigarettes/day- Severe Varicose Syndrome- Family history of VTE by unidentifiable FR or in relation to estrogens in first degree relative- Low risk thrombophilia- Multiple gestation- Intrauterine dead fetus- Prolonged labor- Systemic infection- Immobilization ≥ 3 days (paraplegia, long-distance travel)- Current preeclampsia- Postpartum hemorrhage (loss of >1L or blood transfusion) |
|--|
-

Gestion du risque thromboembolique chez les femmes enceintes COVID-19 + ou suspectes



Une majoration du risque thrombotique semble présente chez les patient(e)s infecté(e)s par le SARCoV-2 (COVID-19). Dans ce contexte, le CARO et le CNGOF proposent la stratégie d'évaluation et de prise en charge suivante (en date du 15 avril 2020)

FACTEURS DE RISQUE DE THROMBOSE EN PRÉ-PARTUM CHEZ LA FEMME ENCEINTE COVID-19 +

FDR majeurs	- ATCD personnels thromboemboliques - Thrombophilie asymptomatique à haut risque - Σ^d des antiphospholipides symptomatique - O₂thérapie > 4 L/min ou ONHD ou ventilation artificielle
FDR mineurs	- Obésité (IMC > 30) ou poids > 120 kg - Immobilisation prolongée et complète - O₂thérapie ≤ 3 L/min

Risque faible	- Aucun FDR
Risque modéré	- 1 à 2 FDR mineurs combinés
Risque élevé	- FDR majeur(s) ou ≥ 3 FDR mineurs

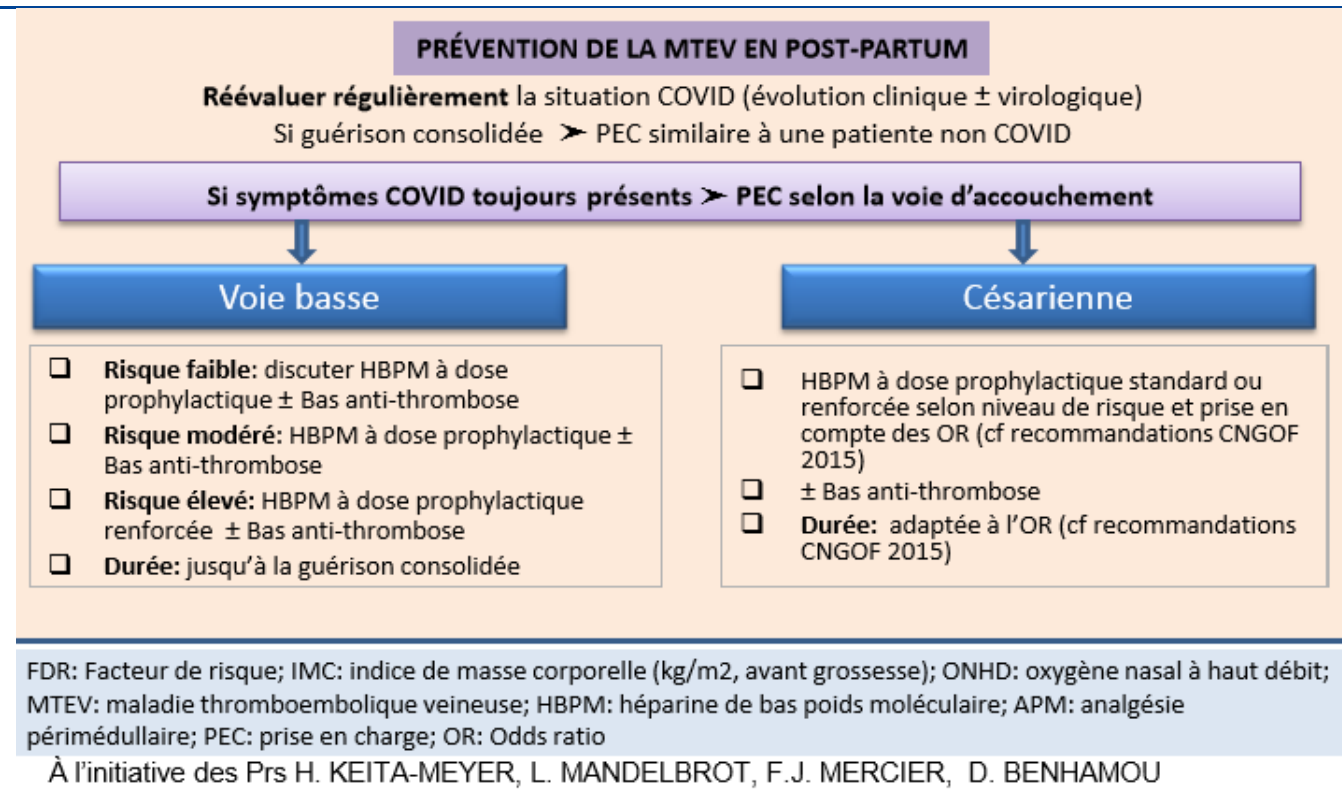
PRÉVENTION DE LA MTEV EN PRÉ-PARTUM

- **Risque faible:** Pas de prophylaxie
 - **Risque modéré:** HBPM à dose prophylactique standard (ex: enoxaparine 4000 UI /24h SC)
 - **Risque élevé:** HBPM à dose prophylactique renforcée (ex: enoxaparine 4000 UI /12h SC ou 6000 UI/12h SC si poids > 120 kg)*
 - **Durée:** jusqu'à la guérison
 - **Ne pas débiter la prophylaxie si accouchement imminent (avis obstétrical)**
- * HBPM à dose prophylactique renforcée, surveiller l'activité anti-Xa 4 heures après la 3ème injection, puis régulièrement en cas d'insuffisance rénale, pour rechercher un surdosage (valeur seuil variable selon l'HBPM) exposant à un risque hémorragique plus élevé.



Prendre en compte les modalités de la prophylaxie par HBPM pour la gestion de l'accouchement et réalisation de l'APM

For the post-partum :



Bikdeli et al. [1]

Consideration for risk of VTE in pregnant patients with COVID-19 deserves further attention. The risk of VTE is increased during pregnancy and the postpartum period. Although limited data are available, pregnant women admitted to hospital with COVID-19 infection are likely to be at an increased risk of VTE. It is reasonable to assess the risk of VTE and to consider pharmacological thromboprophylaxis, especially if they have other VTE risk factors. Weight-adjusted prophylactic dosing of anticoagulation is an interesting topic that requires additional investigation.

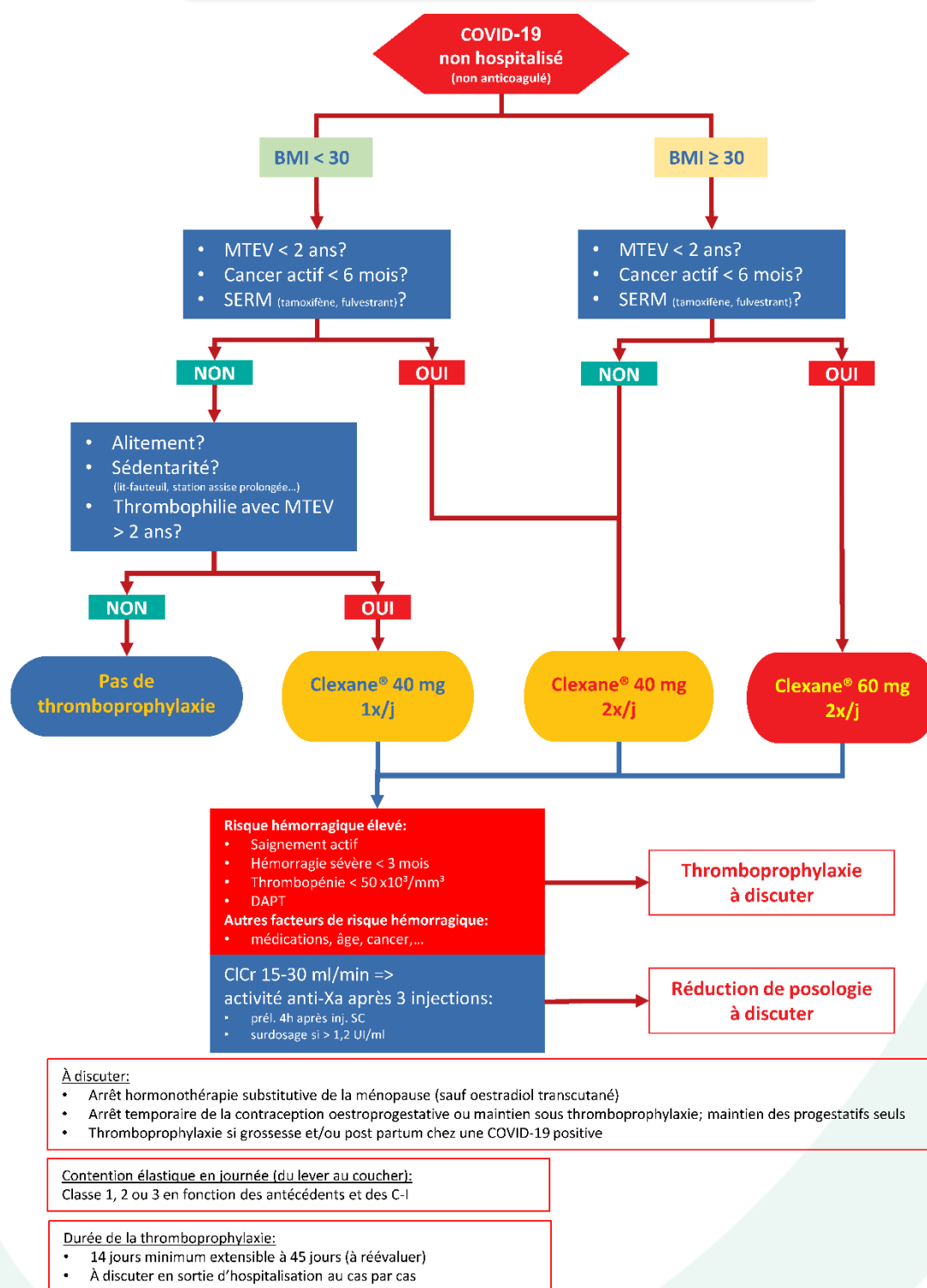
APPENDIX 2. OLD VERSION OF ALGORITHMS BELGIAN SOCIETY OF THROMBOSIS AND HAEMOSTASIS

Belgian Society of Thrombosis and Haemostasis

Recommendations for the management of coagulopathies associated with COVID-19. Below are the old algorithms as published on April 14th 2020 on the website. Currently the old versions are no longer available and have been replaced by the new algorithms on <https://bsth.be/professionals>.

Thromboprophylaxie et anticoagulation du patient COVID-19 non hospitalisé

P. Péters
M. Sprynger
C. Oury
P. Lancellotti



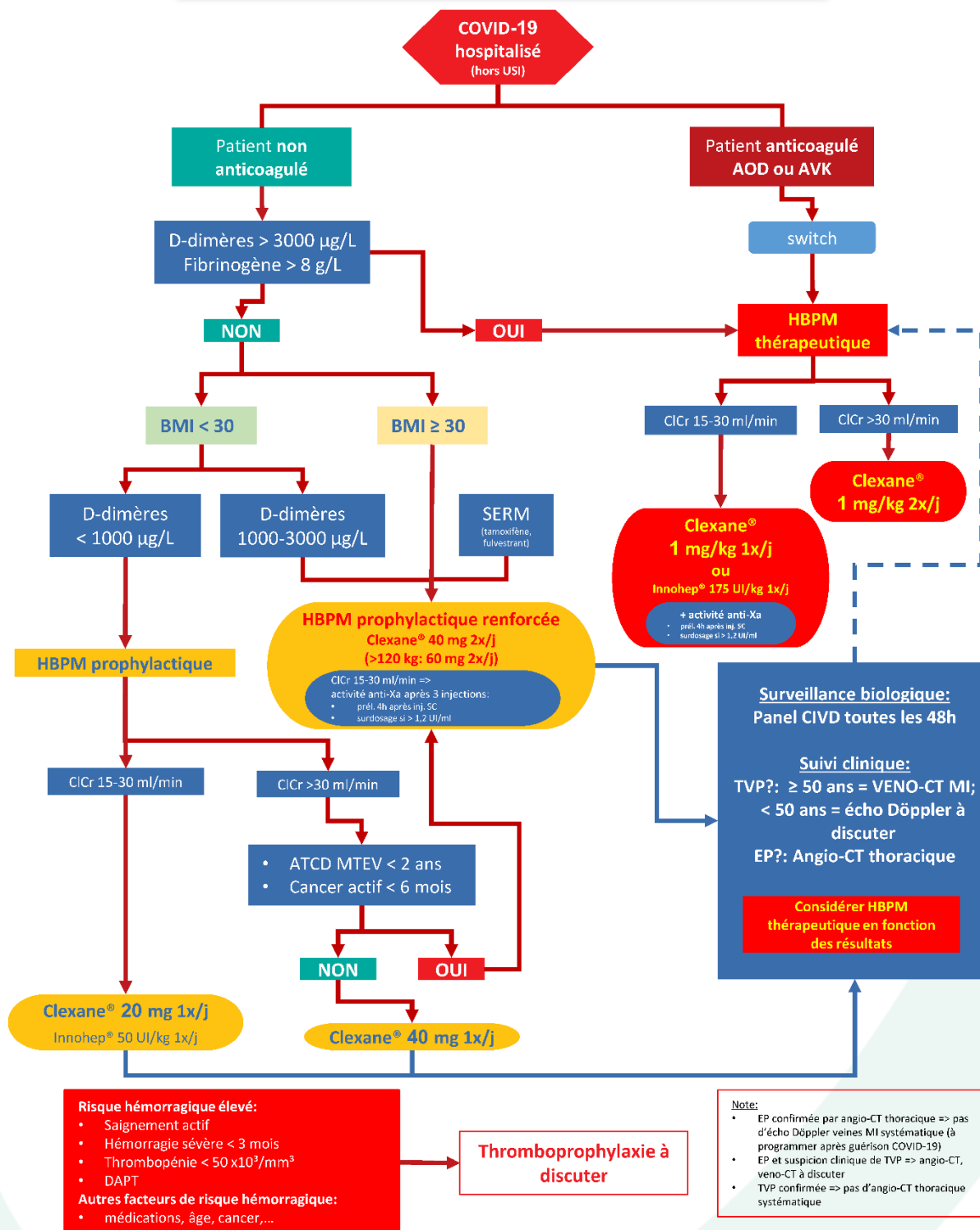
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Légende: BMI, body mass index (kg/m²); MTEV, maladie thromboembolique veineuse; ClCr, clairance de créatinine; DAPT, bithérapie antiplaquettaire

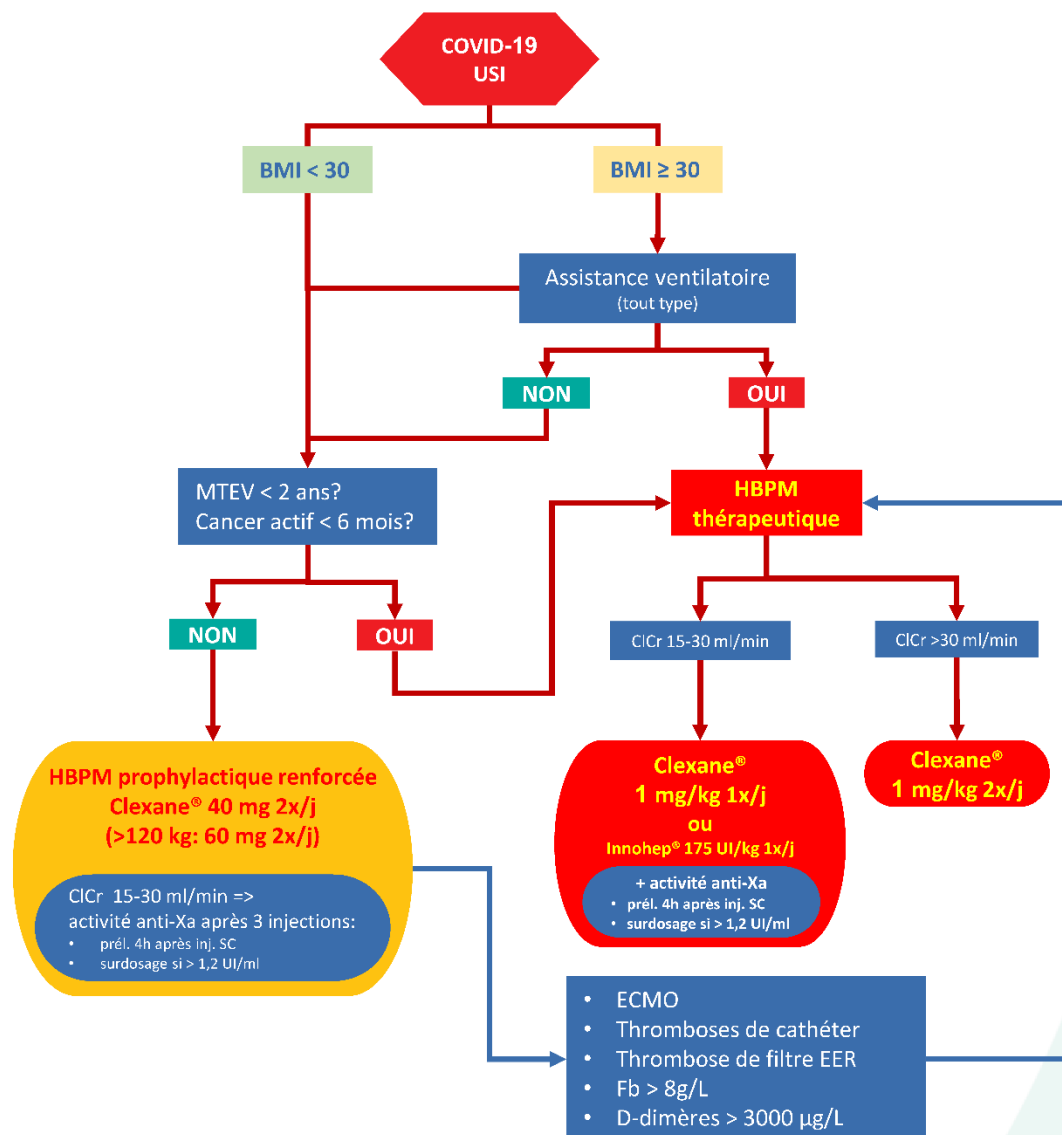
Consensus d'experts soumis à révision régulière vu le faible niveau de recommandations et l'évolution rapide des données – 15/04/2020

Thromboprophylaxie et anticoagulation du patient COVID-19 hospitalisé (hors USI)



Thromboprophylaxie et anticoagulation du patient COVID-19 hospitalisé en USI

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DANS TOUS LES CAS

Surveillance biologique:

Panel CIVD toutes les 24-48h

Cas sévère: considérer SFM, AT (+/- FII, FV)

Suivi clinique:

TVP?: ≥ 50 ans = VENO-CT MI; < 50 ans = écho Doppler à discuter

EP?: Angio-CT thoracique

Contact:

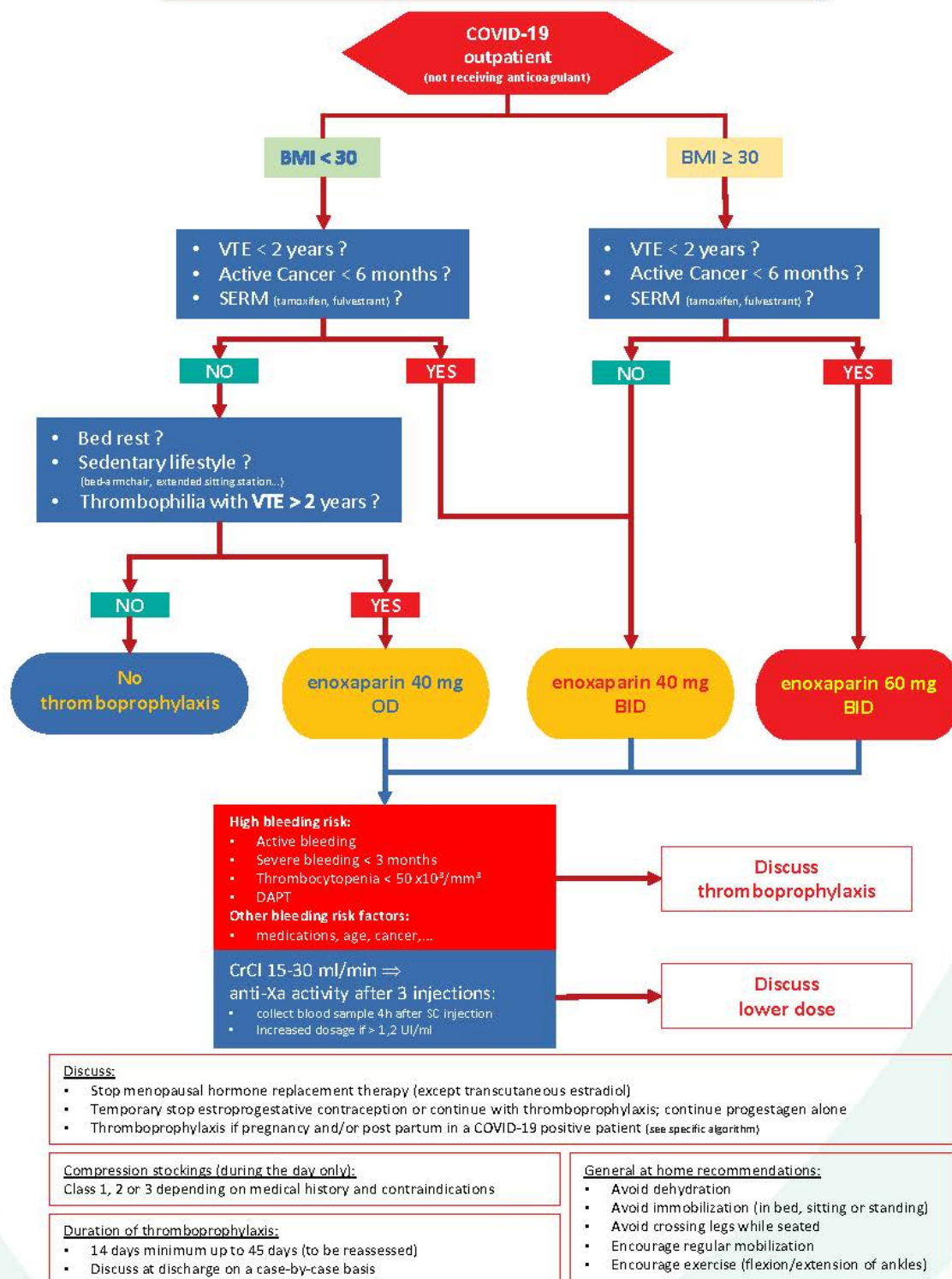
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Légende: BMI, body mass index (kg/m²); MTEV, maladie thromboembolique veineuse; HBPM, héparine de bas poids moléculaire; CICr, clairance de créatinine; EER, épuration extra rénale; SFM, monomères solubles de fibrine; AT, antithrombine; FII, facteur II; FV, facteur V; TVP, thrombose veineuse profonde; EP, embolie pulmonaire

Consensus d'experts soumis à révision régulière vu le faible niveau de recommandations et l'évolution rapide des données – 15/04/2020

Thromboprophylaxis and anticoagulation of COVID-19 outpatient

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Contact:

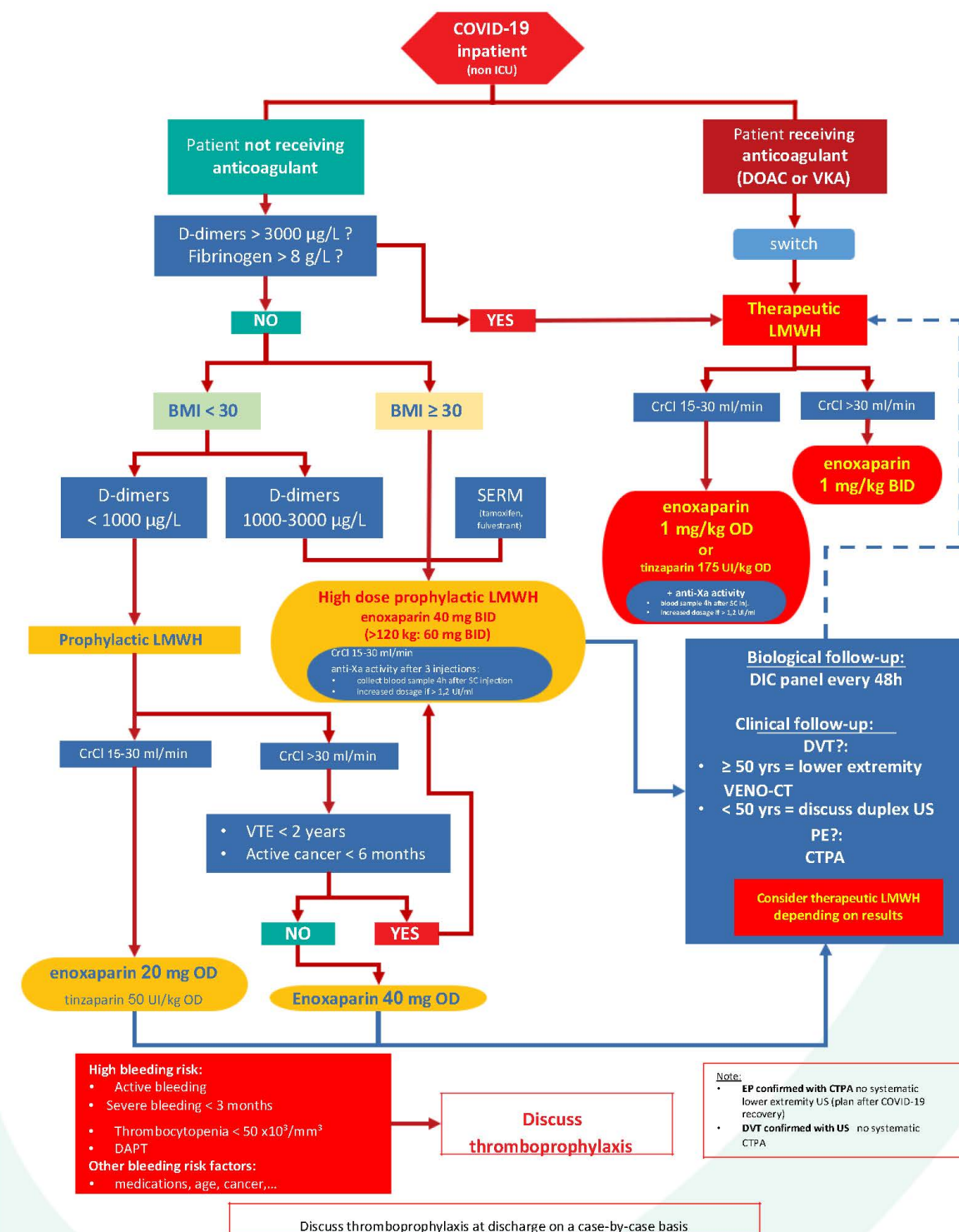
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Legend: BMI, body mass index (kg/m²); VTE, venous thromboembolism; CrCl, creatinin clearance; DAPT, dual antiplatelet therapy

Expert consensus may be subject to revision due to lack of recommendations and regular availability of new data – 20/04/2020

Thromboprophylaxis and anticoagulation of COVID-19 inpatient (non ICU)

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M. Sprynger
C. Oury P.
Lancellotti

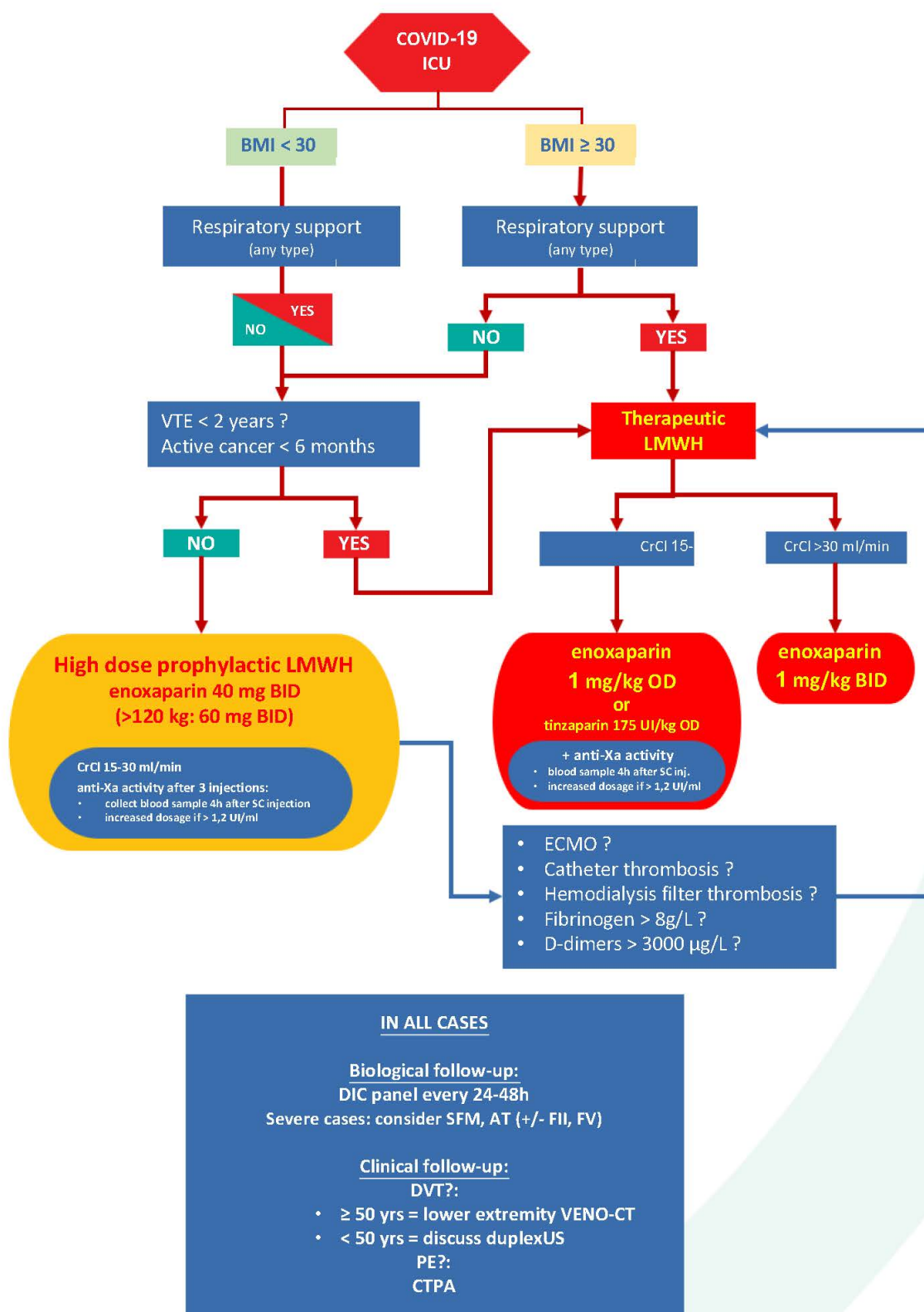


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Legend: BMI, body mass index (kg/m^2); VTE, venous thromboembolism; LMWH, low molecular weight heparin; CrCl, creatinin clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; DAPT, dual antiplatelet therapy

Thromboprophylaxis and anticoagulation of COVID-19 patient in ICU

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Legend: BMI, body mass index (kg/m²); VTE, venous thromboembolism; LMWH, low molecular weight heparin; CrCl, creatinin clearance; SFM, soluble fibrin monomers; AT, antithrombin; FII, factor II; FV, factor V; DVT, deep vein thrombosis; PE, pulmonary embolism

Expert consensus may be subject to revision due to lack of recommendations and regular availability of new data – 20/04/2020

APPENDIX 3. ANTITHROMBOTIC THERAPIES FOR COVID-19 DISEASE

RAPID RESPONSE **ESP** Evidence Synthesis Program

Antithrombotic Therapies for COVID-19 Disease



QUESTIONS

1. In patients with COVID-19, what is the incidence of thromboembolism?
2. In patients with COVID-19 disease, do antithrombotic therapies improve outcomes?



RATIONALE AND BACKGROUND

Infection with the novel coronavirus SARS-CoV-2, which causes the disease COVID-19, can lead to profound inflammation and a prothrombotic state characterized by elevations in D-dimer, fibrin/fibrinogen degradation products, and fibrinogen.^{1,2} These lab abnormalities have been proposed as markers of severe disease and worse prognosis.^{1,3} Although the co-occurrence of inflammation and hypercoagulability in sepsis⁴ has previously been recognized, including during the Severe Acute Respiratory Syndrome (SARS) epidemic⁵ of 2002–2003, clinicians and researchers studying COVID-19 are asking whether the incidence of venous and arterial thromboembolism is higher in COVID-19 than with other sources of infection^{6,7} and whether COVID-19 patients would benefit from antithrombotic therapies. Clinical scenarios in which antithrombotic therapies for COVID-19 patients have been proposed include extending prophylactic dosing of unfractionated heparin (UFH) or low molecular-weight heparin (LMWH) once patients discharge home, using higher doses of thromboprophylaxis for hospitalized patients,^{7,8} and empiric use of therapeutic anticoagulation and thrombolytics as a compassionate salvage approach when critically ill patients appear to be clinically deteriorating.⁹ The role of antithrombotic therapies in the latter scenario is based on speculation that patients with COVID-19 may worsen due to deposition of fibrin in the airspaces and lung parenchyma in addition to fibrin-platelet microthrombi in the pulmonary vasculature.⁹ Of note, broader use of Vitamin K antagonists and direct oral anticoagulants (DOACs) in COVID-19 treatment has generated less interest due to potential drug-drug interactions with antiviral therapies.^{2,10}



CURRENT GUIDANCE

1. The WHO recommends prophylactic dose heparin or LMWH in adults and adolescents with severe COVID-19 disease except if contraindicated¹¹; this guidance is referenced by the CDC¹² and DoD.¹³ Similarly, the International Society of Thrombosis and Haemostasis (ISTH) recommends considering prophylactic dose LMWH for all hospitalized patients with COVID-19 unless contraindicated.¹⁴ (See Table 1.)
2. The Italian Society on Thrombosis and Haemostasis¹⁰ suggests intermediate dosing thromboprophylaxis and extended thromboprophylaxis post-discharge for patients at higher risk of venous thromboembolism (VTE) and recommends against empiric use of therapeutic dose UFH and LMWH.
3. Previously published guidelines from the American Society of Hematology (ASH) recommend thromboprophylaxis for acutely and critically ill hospitalized patients with LMWH, UFH, or fondaparinux.¹⁵ This guidance is based on a large number of systematic reviews and primary studies of thromboprophylaxis in hospitalized patients as well as a trial of fondaparinux compared to no anticoagulation. ASH does not recommend extended thromboprophylaxis post-hospital discharge, which has been found to have a narrow risk benefit ratio even in patients at higher risk for VTE based on systematic reviews.¹⁶
4. In the past, other agents have been proposed to mediate the prothrombotic state in sepsis including antithrombin, thrombomodulin, recombinant activated protein C, and heparin.⁴ 2016 SCC¹⁷ guidelines recommend against the use of antithrombin based on a trial showing lack of benefit and increased bleeding risk. 2016 SCC guidelines make no recommendation regarding thrombomodulin or heparin.



NEW EVIDENCE (COVID-19 STUDIES)

Studies of hypercoagulability and COVID-19 are limited to case reports and case series and are inadequate to estimate the incidence of thromboembolism in COVID-19 disease. (See Table 2.) Similarly, few studies have examined the effect of antithrombotic therapies on clinical outcomes in hospitalized patients with COVID-19. (See Table 2.) A single-center retrospective study of 449 hospitalized patients with COVID-19 in China found that patients with more-severe disease had a mortality benefit with prophylactic dose heparin or LMWH¹⁸, which is already the standard of care in many regions. A case series of 3 critically ill COVID-19 patients who received tissue plasminogen activator (tPA) +/- heparin¹⁹ is too small, with variable direction of results, incomplete descriptions of clinical decision-making, and inconsistent reporting of clinical outcomes, to draw conclusions regarding this treatment strategy.



SUMMARY

New evidence on thromboembolism in COVID-19 does not warrant a change in current guidance on thromboprophylaxis among acutely and critically ill hospitalized patients. To date, the incidence of thromboembolism among patients with COVID-19 remains largely unknown. Evidence is limited to case reports and case series with methodological limitations including inadequate follow-up, which may have biased results towards underreporting of thromboembolism. Two studies have been published on antithrombotic therapies and clinical outcomes in patients with COVID-19. Several studies are planned to further evaluate the incidence of thromboembolism in COVID-19 and potential therapeutics. (See Table 3.) Of note, no trials comparing prophylactic dosing strategies of UFH and LMWH have been registered on clinicaltrials.gov, although hematology experts have called for this type of trial.^{6,7,10}



QUESTION 1: IN PATIENTS WITH COVID-19, WHAT IS THE INCIDENCE OF THROMBOEMBOLISM?



Cui 2020²⁰

Design: Single-center, retrospective series of 81 hospitalized (ICU only) COVID-19 patients at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology in China

Patients: 81 patients with COVID-19 pneumonia admitted to intensive care (8 died). At baseline, 25% of patients (20/81) had hypertension, 10% (8/81) had diabetes, 12% (10/81) had coronary artery disease, and 43% (35/81) smoked.

Treatment: All patients received antiviral and supportive treatment for COVID-19 infection after diagnosis. No patients received anticoagulation for thromboprophylaxis.

Results: 25% of patients (20/81) were diagnosed with lower extremity venous thrombosis (DVT). Compared to patients without DVT, diagnosis of DVT was associated with older age (68.4 ± 0.1 vs. 57.1 ± 14.3 years; $p < 0.001$), degree of lymphopenia (0.8 ± 0.4 vs. $1.3 \pm 0.6 \times 10^9/L$; $p < 0.001$), increased aPTT (39.9 ± 6.4 vs. 35.6 ± 4.5 seconds; $p = 0.001$), and elevated D-dimer (5.2 ± 3.0 vs. $0.8 \pm 1.2 \mu g/mL$).

Major Strengths and Weaknesses

- Potential differences in baseline characteristics between patients who developed thromboembolism and those who did not, such as co-morbid tobacco use, were not reported and could have biased results.
- Length of follow-up is poorly characterized and inadequate to evaluate outcomes. 11% of patients (9/81) remained hospitalized at the time of reporting results and it is possible that some of these patients developed DVT later during their hospital course.
- The study does not include other forms of venous thromboembolism, such as pulmonary embolism (PE), which could have led to falsely low rates of venous thromboembolism.

Bottom Line

This study demonstrates that patients with COVID-19 who are critically ill are at risk of VTE but otherwise does little to improve understanding of thromboembolism incidence in COVID-19. Importantly, no patients in this study received thromboprophylaxis, and therefore results have limited applicability to settings and regions in which thromboprophylaxis is standard of care in acute and critically ill patients.



Klok 2020²¹

Design: Multi-center, retrospective series of 184 hospitalized (ICU only) COVID-19 patients at Leiden University Medical Center, Erasmus University Medical Center, and Amphia Hospital Breda in the Netherlands

Patients: 184 patients diagnosed with novel coronavirus pneumonia admitted to the ICU (23 died). 9.2% of patients (17/184) were on therapeutic anticoagulation at admission (indications not reported), 2.7% (5/184) had active malignancy, and 13% (23/184) received renal replacement therapy during the study period.

Treatment: All patients received at least standard doses of thromboprophylaxis, although dose intensity varied depending on institution (all used nadroparin 2850 IU QDAY at lowest range up to 5700 IU BID at highest range). All patients >100 kg received at least nadroparin 5700 IU QDAY.

RAPID RESPONSE ESP

Evidence Synthesis Program

Results: The observed cumulative incidence of a composite outcome consisting of acute PE, DVT, ischemic stroke, myocardial infarction or systemic arterial embolism was 31% (95% CI 2-41%). 14% of patients (25/184) had CT-confirmed PE, 1.6% (3/184) had ultrasound-confirmed venous thromboembolic event (including DVT), and 1.6% (3/184) had ischemic stroke (classified as arterial thrombotic event). Age (adjusted hazard ratio (aHR) 1.05/per year, 95% CI 1.004-1.01) and coagulopathy, defined as spontaneous prolongation of the prothrombin time >3 s or activated partial thromboplastin time >5 s (aHR 4.1, 95% CI 1.9-9.1), were independent predictors of thrombotic complications.

Major Strengths and Weaknesses

- Potential differences in baseline characteristics between patients who developed thromboembolism and those who did not, such as active malignancy, were not reported and could have biased results.
- Length of follow-up is inadequate to evaluate outcomes. 76% of patients (139/184) remained in the ICU at the end of the observation period and it is possible that some of these patients developed VTE later during their hospital course.
- All of the patients received at least a "standard" dose of thromboprophylaxis with nadroparin, but the actual dose varied among the 3 institutions and dosing protocols changed at 2 hospitals during the observation period.

Bottom Line

This study demonstrates that patients with COVID-19 who are critically ill can develop thromboembolism despite standard use of thromboprophylaxis. However, due to inadequate follow-up, the study likely underestimates incidence of thromboembolism. Results may also be biased due to potential confounding with baseline co-morbidities and anticoagulation use.



Chen 2020²²

Design: Single-center, retrospective series of 25 hospitalized COVID-19 patients at Central Hospital of Wuhan in Wuhan, China

Patients: 25 patients with a diagnosis of COVID-19 pneumonia [15/25 with a positive real time reverse-transcription-polymerase chain-reaction (RT-PCR) test; 10/25 with a negative in RT-PCR test diagnosed with COVID-19 clinically] who underwent CT scan due to suspicion for acute PE or other clinical concerns.

Treatment: 20/25 patients were treated with LMWH (0.6 mg/kg Q12H) regardless of findings of acute pulmonary embolism on CTA.

Results: 40% of patients (10/25) met criteria for acute pulmonary embolism; 2 of these patients died, 5 were discharged, and 3 remained hospitalized. One patient was found to have a lower extremity DVT via ultrasound despite being negative for acute pulmonary embolism on CT scan. Patients with acute PE had significantly higher D-dimer compared to those without PE (median 11.07 µg/mL vs. 2.44 µg/mL; p=0.003), but other lab values were not statistically significantly different.

Major Strengths and Weaknesses

- The study does not indicate how 25 patients were selected from the larger cohort of hospitalized 1008 patients with COVID-19 pneumonia between January and February 2020, which could have introduced selection bias.
- The study does not specify why some patients were treated with LMWH and others were not or whether patients received LMWH before or after PE diagnosis, which could have biased results and makes them difficult to interpret.

Bottom Line

In this sample of 25 patients with COVID-19 who underwent CT scans partially due to clinical suspicion for, 40% had positive findings of acute PE. Because the study does not report how patients were selected for inclusion, it is possible that other patients in the larger cohort of 1008 hospitalized patients had CT scans and/or were diagnosed with PE. Thus, no conclusions can be drawn regarding the incidence of VTE.

We also identified a case report²³ and cases series²⁴ describing pulmonary embolism in a total of 3 COVID-19 patients.



QUESTION 2: IN PATIENTS WITH SEVERE COVID-19 DISEASE, DOES ANTITHROMBOTIC TREATMENT IMPROVE OUTCOMES?



Tang 2020¹⁸

Design: Single-center, retrospective series of 449 hospitalized patients with severe COVID-19 at Tongji Hospital in Wuhan, China

Patients: 449 adults with severe COVID-19 as defined by National Health Commission of China (any of the following: RR $\geq$ 30, PaO₂ $\leq$ 93%, PaO₂/FiO₂ $\leq$ 300 mmHg.) Patients with a bleeding diathesis, age $<$ 18, hospital stay $<$ 7 days, or unknown coagulation parameters and medications were excluded.

Treatment: The anticoagulant treatment group received thromboprophylaxis for $\geq$ 7 days, either UFH (10,000-15,000 U/day) or LMWH (40-60 mg enoxaparin/day).

Results: 22% of patients (99/449) received thromboprophylaxis. Of these patients, 94 received LMWH and 5 patients received UFH. 28-day mortality was 29.8% (134 patients) overall, with no difference between the 2 groups. Subgroup analysis found lower mortality with heparin treatment in patients who had sepsis-induced coagulopathy (SIC) scores $\geq$ 4 (40.0% vs 64.2%, P=0.029) and D-dimer $\geq$ 3.0 ug/ml (6-fold upper limit of normal) (32.8% vs 52.4%, P=0.017).

Major Strengths and Weaknesses

- Results may be biased due to potential confounders such as baseline co-morbidities and other treatments received for COVID-19 disease. No information is available regarding why certain patients received thromboprophylaxis and others did not or why UFH or LMWH were used.
- The study states that bleeding events were "unusual and commonly mild" but does not provide more detail regarding adverse events associated with thromboprophylaxis.

Bottom Line

This study suggests that patients with higher SIC scores (indicating sepsis-induced coagulopathy) had a mortality benefit with thromboprophylaxis. However, results have limited applicability to settings and regions in which thromboprophylaxis is already standard of care in acute and critically ill patients.



Wang 2020¹⁹

Design: Case series of 3 COVID-19 patients in the US

Patients: 3 critically ill, mechanically ventilated patients with COVID-19 and acute respiratory distress syndrome (ARDS)

Treatment: tPA (Alteplase) 25 mg IV over 2 hours, followed by 25mg tPA over subsequent 22 hours, then transitioned to a heparin infusion with a PTT goal of 60-80

Results:

- Patient 1 was a 75-year-old male who had a PaO₂/FiO₂ (or P/F ratio, a measure of ARDS severity with a lower number representing more severe disease) between 140 to 240 prior to tPA, which improved to 408 partway through the infusion, then worsened to 136 one hour after tPA was transitioned to heparin. The patient continued to have multiple organ failure and died 3 days later.
- Patient 2 was a 59-year-old female requiring intubation and IV tPA was given 4 days later. Four hours after completion of tPA her prone P/F ratio was stable at 135, with some improvement at 12-hours post-tPA to 150. Her supine P/F ratio was 135, improved from 90 three days earlier.
- Patient 3 was a 49-year-old male on a heparin drip for suspicion of venous thromboembolism. His P/F ratio improved 3 hours following tPA (125 from 72-90). 33 hours post-tPA, his P/F ratio declined to 71, thus requiring proning.

Major Strengths and Weaknesses

- Clinical outcomes including mortality are not reported for 2/3 patients.
- There was no consistency of the timing of P/F measurements, nor criteria for when tPA or therapeutic heparin would be started or stopped. Also, use of thromboprophylaxis is not reported.
- Adverse events associated with tPA, such as bleeding, are not reported.
- Authors are subject to conflict of interest as many have industry support or investments.

Bottom Line

The study is too small, with variable direction of results and inconsistent reporting of clinical outcomes, to draw any conclusions regarding thrombolytic therapy for patients with severe COVID-19 disease.



Table 1. Current Guidance

Source	Recommendation	Date Published	Date Accessed
Guidance specific to COVID-19			
World Health Organization ¹¹	Use pharmacological prophylaxis (LMWH [preferred if available] or heparin 5000 units subcutaneously twice daily) in adolescents and adults without contraindications. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices).	3-13-2020	4-12-2020
International Society of Thrombosis and Haemostasis ²⁵	Consider prophylactic dose LMWH in all patients (including non-critically ill) who require hospital admission for COVID-19 infection, in the absence of any contraindications	3-25-2020	4-12-2020
Centers for Disease Control and Prevention ¹²	No specific comment on anticoagulation in COVID-19 patients; refers to WHO guidance	4-3-2020	4-12-2020
Department of Defense	No specific comment on anticoagulation in COVID-19 patients; refers to WHO guidance	3-23-2020	4-12-2020
Infectious Disease Society of America ⁸	No specific comment on anticoagulation in COVID-19 patients	4-11-2020	4-12-2020
The Italian Society on Thrombosis and Haemostasis ¹⁰	- Use LMWH, UFH, or fondaparinux at doses indicated for prophylaxis of VTE in all COVID-19 hospitalised patients; patients with anticoagulant contraindications should be treated with limb compression. - Thromboprophylaxis should be administered for the entire hospital stay and maintained at home for 7-14 days after hospital discharge or in the pre-hospital phase, in case of pre-existing or persisting VTE risk factors. - The use of intermediate-dose LMWH (i.e., enoxaparin 4,000 IU subcutaneously every 12 hours) can be considered on an individual basis in patients with multiple risk factors for VTE. - Use of therapeutic doses of UFH or LMWH is not recommended as a standard treatment.	4-8-2020	4-14-2020
Guidance published prior to COVID-19			
American Society of Hematology ¹⁵	Use UFH, LMWH, or fondaparinux rather than nonparenteral anticoagulant in acutely ill medical patients and UFH or LMWH in critically ill medical patients.	11-2018	4-12-2020
Society of Critical Care Medicine ¹⁷	Recommend against the use of antithrombin for the treatment of sepsis and septic shock. No recommendation regarding the use of thrombomodulin or heparin for the treatment of sepsis or septic shock.	03-2020	4-12-2020


Table 2. Published/released studies of VTE incidence among COVID-19 patients and antithrombotic therapy

Author/ Year	Location/Setting (ie, hospital, country)	Dates	Number of Cases	Patient Characteristics (ie, age, gender)	Outcomes Assessed
Question 1: In patients with COVID-19, what is the incidence of thromboembolism?					
Cui 2020	ICU of Union Hospital, Tonji Medical College, Huazhong University of Science and Technology in China	January 30 – March 22, 2020	n=81	• Age (mean): 59.9 years • Gender (% Male): 46% • Comorbidities (%): ◦ Hypertension: 25% ◦ Diabetes: 10% ◦ Coronary artery disease: 12% ◦ Smoking: 43%	• Development of ultrasound-confirmed lower extremity venous thrombosis
Klok 2020	ICUs at Leiden University Medical Center, Erasmus University Medical Center, Amphibia Hospital Breda in the Netherlands	March 7 – April 5, 2020	n=184	• Age (mean): 64 years • Gender (% male): 76% • Active cancer (%): 2.7% • Coagulopathy* during admission (%): 38% • Therapeutic anticoagulation at admission (%): 9.2% • Renal replacement therapy during admission (%): 13%	• Composite of thromboembolic phenomena (acute pulmonary embolism, deep vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism)
Chen 2020	Central Hospital of Wuhan in Wuhan, China	January 2020 – February 2020	n=25	• Age (median): 65 years • Gender (% male): 60% • Comorbidities (%): ◦ Hypertension: 40% ◦ Diabetes: 20% ◦ Cardiovascular disease: 16% ◦ Smoking: 24% ◦ Prior DVT: 4%	• CT-proven acute pulmonary embolism • D-dimer, lymphopenia, CRP, B-type BNP, CMP
Danzi 2020 ²³	European hospital (details not reported)	NR	n=1	75 year-old woman; past medical history not reported	• Diagnosis of PE • Treatment with LMWH
Xie 2020 ²⁴	Wuhan, China	NR	n=2	57 year-old man and 70 year-old man; past medical history not reported	• Diagnosis of PE
Question 2: In patients with COVID-19 disease, do antithrombotic therapies improve outcomes?					
Tang 2020	Tongji Hospital in Wuhan, China	January 1 – February 13, 2020	n=449	• Age (mean): 65 years • Gender (% male): 60% • Comorbidities (%): ◦ Hypertension: 40% ◦ Diabetes: 21% ◦ Cardiovascular disease: 9.1%	• 28-day mortality • Sepsis-induced coagulopathy (SIC) score and D-dimer result
Wang 2020	US hospital (details not reported)	NR	n=3	Case 1: 75 year old man with hypertension, hyperlipidemia, type 2 diabetes mellitus, and coronary artery disease Case 2: 59 year old female with hypertension Case 3: 49 year old male with no known medical history	• Use of tPA +/- heparin

*Coagulopathy: spontaneous prolongation of prothrombin time (PT) > 3 seconds or activated partial thromboplastin time (APTT) > 5 seconds



Table 3. Ongoing/planned clinical trials on thromboembolism in COVID-19 disease and treatment

Agent	Sponsor	Title	ClinicalTrials.gov Identifier	Study Type	Primary Outcome	Secondary Outcome(s)
NA	Jessa Hospital	COVID-19 and Deep Venous Thrombosis: a Cross-sectional Study	NCT04338932 ²⁶	Observational	Prevalence and possible risk factors for DVT in ICU	None
Aspirin 75 mg, Clopidogrel 75 mg, Rivaroxaban 2.5 mg, Atorvastatin 40 mg, Omeprazole 20 mg	Imperial College London	Preventing Cardiac Complication of COVID-19 Disease With Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial.	NCT04333407 ²⁷	Interventional	All-cause mortality at 30 days after admission	Absolute change in serum troponin from admission to peak value, discharge rate, intubation rate.
Defibrotide	IRCCS San Raffaele Scientific Institute	Use of Defibrotide to Reduce Progression of Acute Respiratory Failure Rate in Patients With COVID-19 Pneumonia	NCT04335201 ²⁸	Interventional	Eval progression to acute respiratory failure.	Adverse events, duration of hospitalization, systemic inflammation, overall survival
Tissue Plasminogen Activator (tPA) ²⁹	Beth Israel Deaconess Medical Center	NR	Not registered	Interventional	NR	NR

REFERENCES

1. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020;16:16.
2. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic. *J Am Coll Cardiol*. 2020.
3. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847.
4. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent J-L. Sepsis and septic shock. *Nature Reviews Disease Primers*. 2016;2(1):16045.
5. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *J Pathol*. 2003;200(3):282-289.
6. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *Journal of Thrombosis and Thrombolysis*. 2020.
7. Hunt J. Webinar: Thrombosis, Thromboprophylaxis & Coagulopathy in COVID- 19 Infections. 2020; <https://academy.isth.org/isth/2020/covid-19/291581/marcel.levi.26.beverley.jane.hunt.webinar.thrombosis.thromboprophylaxis.26.html?f=menu%3D8%2ABrowseby%3D8%2Asortby%3D2%2Alabel%3D19794>. Accessed April 13, 2020.
8. H; Mustafa R; Sultan S; Falck-Ytter BAMRSALLBLC-CCVEGRMWOHJSSM. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. 2020; <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>. Accessed April 13, 2020.
9. Moore HB, C; Moore, C; et al. Is There a Role for Tissue Plasminogen Activator (tPA) as a Novel Treatment for Refractory COVID-19 Associated Acute Respiratory Distress Syndrome(ARDS)? *Journal of Trauma and Acute Care Surgery*. 2020.
10. Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus*. 2020;08:08.
11. *Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. WHO/2019-nCoV/clinical/2020.4*. World Health Organization;2020.
12. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). 2020; <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>. Accessed April 13, 2020.
13. Matos; Chung K. DoD COVID-19 PRACTICE MANAGEMENT GUIDE: Clinical Management of COVID-19. 2020; <https://asprtracie.hhs.gov/technical-resources/resource/7899/dod-covid-19-practice-management-guide-clinical-management-of-covid-19>. Accessed April 13, 2020.
14. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020.
15. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Advances*. 2018;2(22):3198-3225.
16. Tao DL, Bien JY, DeLoughery TG, Shatzel JJ. Extended thromboprophylaxis with direct oral anticoagulants for medical patients: a systematic review and meta-analysis. *Blood*. 2017;129(5):653-655.
17. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Medicine*. 2017;43(3):304-377.

18. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* 2020;27:27.
19. Wang J, Hajizadeh N, Moore EE, et al. Tissue Plasminogen Activator (tPA) Treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): A Case Series. *J Thromb Haemost.* 2020.
20. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis.* n/a(n/a).
21. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020.
22. Chen J, Wang, Xiang, Zhang, Shutong, Liu, Bin, Wu, Xiaoqing, Wang, Yanfang, Wang, Xiaoqi, Yang, Ming, Sun, Jianqing, Xie, Yuanliang. Findings of Acute Pulmonary Embolism in COVID-19 Patients. 2020; Available at SSRN: <https://ssrn.com/abstract=3548771>. Accessed April 13, 2020.
23. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *European Heart Journal.* 2020.
24. Xie Y, Wang X, Yang P, Zhang S. COVID-19 Complicated by Acute Pulmonary Embolism. *Radiology: Cardiothoracic Imaging.* 2020;2(2):e200067.
25. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *Journal of Thrombosis and Haemostasis.* n/a(n/a).
26. Björn SH, J. COVID-19 and Deep Venous Thrombosis. 2020; <https://clinicaltrials.gov/ct2/show/NCT04338932?term=NCT04338932&draw=2&rank=1>. Accessed April 13, 2020.
27. Preventing Cardiac Complication of COVID-19 Disease With Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial. (C-19-ACS). ClinicalTrials.gov Identifier: NCT04333407. 2020; <https://clinicaltrials.gov/ct2/show/NCT04333407?term=NCT04333407&draw=2&rank=1>. Accessed April 13, 2020.
28. Fabio C. Defibrotide in COVID-19 Pneumonia (DEFI-VID19). ClinicalTrials.gov Identifier: NCT04335201. 2020; <https://clinicaltrials.gov/ct2/show/NCT04335201?term=NCT04335201&draw=2&rank=1>. Accessed April 13, 2020.
29. Stephenson K. tPA-COVID-19. 2020; <https://collaborate.hms.harvard.edu/display/covid19/tPA+Study>. Accessed April 13, 2020.

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Suggested updates or corrections can be sent to: esp.cc@va.gov

APPENDIX 4. INTERACTIONS ANTITHROMBOTICS AND ANTI-COVID-19 MEDICATION

Vivas et al table of drug interactions

	Hidroxicloroquina	Cloroquina	Azitromicina	Lopinavir/ritonavir	Darunavir/cobicistat	Remdesivir	Favipiravir	Metilprednisolona	Interferón	Tocilizumab
Ácido acetilsalicílico										
Clopidogrel				**	**					
Prasugrel										
Ticagrelor				*	*					
Acenocumaryl			*	*	*			*		
Warfarina			*	*	*			*		
Dabigatran	*	*		*	*					
Rivaroxabán				*	*					
Apixabán				*	*					
Edoxabán	*	*		*	*					
Heparinas										
Cangrelor										
Abciximab										
Tirofiban										
Eptifibatida										

From Vivas et al.[20] *Use in combination may increase the concentration of the antithrombotic drug, thus increasing the bleeding risk. **Use in combination may reduce the concentration of the antithrombotic drug, thereby increasing the risk of thrombosis.

Bikdeli et al. Tables of drug interactions

Table 3. Potential Drug Interactions Between Antiplatelet Agents* and Investigational Therapies for COVID-19					
Investigational COVID-19 Therapies	Mechanism of Action of COVID-19 Therapy	P2Y ₁₂ Platelet Receptor Inhibitors			Phosphodiesterase III Inhibitor
		Clopidogrel ^{1,2}	Prasugrel ²	Ticagrelor ^{3,4}	Cilostazol
Lopinavir/Ritonavir	Lopinavir is a protease inhibitor; Ritonavir inhibits CYP3A4 metabolism increasing lopinavir levels	CYP 3A4 Inhibition (minor pathway): Reduction in clopidogrel active metabolite. Do not co-administer or if available utilize P2Y ₁₂ platelet function assays for monitoring.† With limited clinical data, prasugrel may be considered as alternative, if no contraindications	CYP3A4 Inhibition: Decreased active metabolite but maintained platelet inhibition. Can administer with caution.	CYP3A4 Inhibition: Increased effects of ticagrelor. Do not co-administer or if available utilize P2Y ₁₂ monitoring or consider dose-reduced ticagrelor*	CYP3A4 Inhibition: Recommend decreasing dose to maximum of 50 mg BID.
Remdesivir	Nucleotide-analog inhibitor of RNA-dependent RNA polymerases	Reported inducer of CYP3A4 (minor pathway): No dose adjustment recommended.	Reported inducer of CYP3A4 (major pathway): No dose adjustment recommended.	Reported inducer of CYP3A4 (major pathway): No dose adjustment recommended.	Reported inducer of CYP3A4 (major pathway): No dose adjustment recommended.
Tocilizumab	Inhibits IL-6 receptor; may potentially mitigate cytokine release syndrome symptoms in severely ill patients	Reported increase in expression of 2C19 (major pathway) and 1A2, 2B6, and 3A4 (minor pathways): No dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway) and 2C9 and 2C19 (minor pathway): No dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway): No dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway): No dose adjustment recommended.
Sarilumab	Binds specifically to both soluble and membrane-bound IL-6Rs (sIL-6Rα and mIL-6Rα) and has been shown to inhibit IL-6-mediated signaling; may potentially mitigate cytokine release syndrome symptoms in severely ill patients	Reported increase in expression of 3A4 (minor pathways): No dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway): No dose adjustment recommended.	Reported increase in expression of CYP3A4 (major pathway): No dose adjustment recommended.	Reported increase in expression of 3A4 (major pathway): No dose adjustment recommended.
Other drugs being studied to treat COVID-19 include azithromycin, bevacizumab, chloroquine/hydroxychloroquine, ecilizumab, fingolimod, interferon, losartan, methylprednisolone, pirfenidone, and ribavirin. Drug-drug interactions between these medications and antiplatelet agents have yet to be identified. *Cangrelor, aspirin, dipyridamole, and glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban, abciximab) are not known to interact with investigational therapies for COVID-19. †Monitoring of P2Y ₁₂ levels can be assessed through the VerifyNow assay, or others. Evaluation of effect of protease inhibitors on P2Y ₁₂ inhibitors has not been extensively studied. Dose reduction recommendations for P2Y ₁₂ inhibitors or P2Y ₁₂ platelet function assay monitoring is not commonly practiced.					

APPENDIX 5. REFERENCES

1. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164881/>. Journal of the American College of Cardiology. 2020 2020/04/17/. doi: <https://doi.org/10.1016/j.jacc.2020.04.031>.
2. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis.n/a(n/a). doi: 10.1111/jth.14830.
3. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis Research. 2020 2020/04/10/. doi: <https://doi.org/10.1016/j.thromres.2020.04.013>.
4. Llitjos J-F, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. Journal of Thrombosis and Haemostasis.n/a(n/a). doi: 10.1111/jth.14869.
5. Leonard-Lorant I, Delabranche X, Severac F, et al. Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels. Radiology.0(0):201561. doi: 10.1148/radiol.2020201561. PubMed PMID: 32324102.
6. American Society of Hematology. COVID-19 and VTE/Anticoagulation: Frequently Asked Questions. <https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation>. April 17th 2020.
7. Testa S, Prandoni P, Paoletti O, et al. Direct oral anticoagulant plasma levels striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents. The Cremona experience. Journal of Thrombosis and Haemostasis.n/a(n/a). doi: 10.1111/jth.14871.
8. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of thrombosis and haemostasis : JTH. 2020 Apr;18(4):844-847. doi: 10.1111/jth.14768. PubMed PMID: 32073213; PubMed Central PMCID: PMC7166509. eng.
9. Sciensano. Behandeling van gehospitaliseerde patiënten: INTERIM CLINICAL GUIDANCE FOR ADULTS WITH SUSPECTED OR CONFIRMED COVID-19 IN BELGIUM, version 7. <https://covid-19.sciensano.be/nl/covid-19-procedures>. April 7th 2020.
10. Tao D, Maldonado E, Mackey K, et al. Antithrombotic therapies for COVID-19 disease. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-199; 2020. <http://covid19reviews.org/Antithrombotic>. April 20th 2020.
11. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. <https://onlinelibrary.wiley.com/doi/10.1111/jth.14810>. Journal of Thrombosis and Haemostasis. 2020;18(5):1023-1026. doi: 10.1111/jth.14810.
12. Hunt B, Retter A, McClintock C. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. <https://www.portailvasculaire.fr/documents-covid19> March 25th 2020.

13. Société Française d'Anesthésie et de Réanimation (SFAR). Traitement anticoagulant pour la prévention du risque thrombotique chez un patient hospitalisé avec Covid-19 et surveillance de l'hémostase. <https://sfar.org/traitement-anticoagulant-pour-la-prevention-du-risque-thrombotique-chez-un-patient-hospitalise-avec-covid-19-et-surveillance-de-lhemostase/>. April 3th 2020.
14. BCFI. COVID-19 en coagulopathie: wat met ambulante patiënten? <https://www.bcfi.be/nl/gows/3366>. April 30th 2020.
15. Société Française de Médecine Vasculaire. Propositions de la Société Française de Médecine Vasculaire pour la prévention, le diagnostic et le traitement de la maladie thromboembolique veineuse des patients avec COVID 09 non hospitalisés. https://www.portailvasculaire.fr/sites/default/files/docs/sfmv_propositions_mtev_covid-19_texte.pdf <https://www.portailvasculaire.fr/documents-covid19>.
16. La Sociedad Española de Trombosis y Hemostasia (SETH). Recomendaciones sobre profylaxis ETV en el embarazo y puerperio durante la pandemia COVID-19. Recommendations on prophylaxis of thromboembolic disease (VTE) in pregnancy and postpartum during COVID-19 pandemic. <https://www.covid-19.seth.es/wp-content/uploads/2020/04/Recomendaciones-sobre-profilaxis-ETV-en-embarazo-y-puterperio-COVID-19.pdf>. April 15th 2020.
17. CARO et CNGOG. Gestion du risque thromboembolique chez les femmes enceintes COVID-19 + ou suspectes. <http://caro-club.univ-lyon1.fr/>. April 15th 2020.
18. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. https://www.esicm.org/wp-content/uploads/2020/04/863_author_proof.pdf. April 15th 2020.
19. Casini A, Alberio L, Angelillo-Scherrer A, et al. Thromboprophylaxis and laboratory monitoring for in-hospital patients with COVID-19 - a Swiss consensus statement by the Working Party Hemostasis. Swiss medical weekly. 2020 Apr 6;150:w20247. doi: 10.4414/smw.2020.20247. PubMed PMID: 32277760; eng.
20. Vivas D, Roldán V, Esteve-Pastor MA, et al. Recomendaciones sobre el tratamiento antitrombótico durante la pandemia COVID-19. Posicionamiento del Grupo de Trabajo de Trombosis Cardiovascular de la Sociedad Española de Cardiología. Revista Española de Cardiología. 2020 2020/04/22/. doi: <https://doi.org/10.1016/j.recesp.2020.04.006>.
21. La Sociedad Española de Trombosis y Hemostasia (SETH). Recomendaciones de tromboprofilaxis y tratamiento antitrombótico en pacientes con COVID-19. Recommendations for thromboprophylaxis and antithrombotic treatment in patients with COVID-19. <https://www.covid-19.seth.es/recomendaciones-de-tromboprofilaxis-y-tratamiento-antitrombotico-en-pacientes-con-covid-19/>. April 29th 2020.
22. American college of cardiology. Thrombosis and COVID-19: FAQs For Current Practice. <https://www.acc.org/latest-in-cardiology/articles/2020/04/17/14/42/thrombosis-and-coronavirus-disease-2019-covid-19-faqs-for-current-practice>. April 22th 2020.
23. Song JC, Wang G, Zhang W, et al. Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19. Military Medical Research. 2020 Apr 20;7(1):19. doi: 10.1186/s40779-020-00247-7. PubMed PMID: 32307014; PubMed Central PMCID: PMCPMC7167301. eng.

Colophon

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