Anticoagulation management in COVID-19 positive patients

BSTH consensus guideline

Prepared by the Working Group endorsed by the Belgian Society on Thrombosis and Haemostasis (BSTH)

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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]. A French study showed an increased rate of CT-scan detected pulmonary embolism in ICU COVID-19 patients compared to the usual rate encountered in critically ill non-COVID patients. The D-dimer threshold for pulmonary embolism was high (2660 µg/L) [5]. Clinical biology signs of activation of coagulation are also linked to more severe disease and a higher mortality [6]. Several case series also describe an increased risk of arterial thrombosis and of microthrombotic organ damage, including pulmonary intravascular coagulation [7] as well as widespread pulmonary thrombosis [8]. Furthermore, a non-randomized study showed a lower mortality in patients who used thromboprophylaxis as compared to patients who did not receive antithrombotic therapy, in particular in patients with elevated D-dimers.

The American Society of Hematology and the International Society for Thrombosis and Hemostasis recommended to institute venous thromboembolism prophylaxis measures for patients at risk [9]. Nevertheless, the choice and dose of thromboprophylaxis remain controversial.

LMWH is the standard choice for pharmacological thromboprophylaxis in critically ill patients, with the exception of patients with severe renal dysfunction (for whom unfractionated heparin could be considered based on a careful risk/benefit assessment) and patients with a history of heparin-induced thrombocytopenia [10]. In those patients, Fondaparinux is an alternative in patients with prior or suspected HIT, although it is not reimbursed for this indication in Belgium. Direct oral anticoagulants are not reimbursed for primary prophylaxis in medically ill patients in Belgium. Several experimental antivirals used to treat COVID-19 could have interactions because of P-glycoprotein inhibition and/or competition, inhibition or induction of CYP3A4-dependent pathways. Therefore, parenteral LMWH is the agent of choice for thromboprophylaxis in these patients [11]. Although guidelines agree on the choice of thromboprophylaxis, 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 [1,9].

Furthermore, given the high incidence of VTE even despite thromboprophylaxis [12], a clear strategy for the treatment of newly diagnosed VTE in the context of COVID-19 is required. Finally, the optimal management of patients who require therapeutic anticoagulation because of a pre-existing indication (atrial fibrillation, mechanical heart valves, history of venous thrombo-embolism) is unknown.

Aims

The aim of this document is to provide Belgian healthcare workers with recommendations on anticoagulation management in COVID-19 positive patients. These guidelines include recommendations for the prophylaxis and treatment of COVID-related VTE in ambulatory patients and hospitalized patients, as well as recommendations for the use of antithrombotic drugs in patients with prior indication for anticoagulation who develop COVID-19. These recommendations are intended to be easy-to-use guidelines that can be implemented in every Belgian hospital and be used by primary care physicians and gynaecologists. This consensus guideline was established by a working group of experts put together by the Belgian Society on Thrombosis and Haemostasis. These algorithms are based on current knowledge and a limited level of evidence. They are likely to evolve with the knowledge of the disease.

Recommendations

The working group prepared two different schematic algorithms:

1) Anticoagulation management in *hospitalized* COVID-19 patients and *after discharge*
2) Anticoagulation management in *non-hospitalized* COVID-19 patients

The different aspects of these algorithms will be discussed in the document.

Recommendations for anticoagulation management during pregnancy and post-partum period in COVID-19 positive women are not schematically represented but will be discussed in this document.

Anticoagulation management in hospitalized COVID-19 patients and after discharge

The working group stresses that these recommendations should be regarded as guidelines that will be helpful in most patients but that in patients at high risk of bleeding (such as low platelet count, recent major bleeding, dialysis,…) risks and benefits of thromboprophylaxis should be weighed on an individual basis.

At admission

- The working group emphasizes the importance of considering a possible venous thromboembolism (VTE) at diagnosis and during the whole hospitalization period.
- Patients with prior indication for therapeutic anticoagulation should continue to receive therapeutic anticoagulation. Switching to therapeutic LMWH instead of oral anticoagulation (VKA or DOACs) should be considered in the following cases: severely ill patients, patients with gastro-intestinal problems, planned invasive procedures, patients with unstable INRs and/or presence of drug-drug interactions.
- We recommend administering prophylactic anticoagulation of LMWH in patients that have no prior indication for anticoagulation and no VTE at diagnosis.

Anticoagulation regimen in patients with prior indication for anticoagulation

- For patients with a prior indication for therapeutic anticoagulation (for example atrial fibrillation, VTE, mechanical heart valve…), we recommend continuation of anticoagulation in therapeutic doses. If oral anticoagulation is switched to parenteral treatment, we recommend a therapeutic dose of LMWH of 100 IU anti-Xa/kg BID in patients with a high risk of thrombotic complications (mechanical heart valves, recent VTE or high-risk thrombophilia, atrial fibrillation with prior stroke or with high CHADS-VASc score). In patients with lower risk of thrombotic complications (atrial fibrillation with low CHADS-VASc score, secondary prevention of VTE without high-risk thrombophilia,…), either therapeutic doses or high intermediate doses of LMWH could be considered based on the severity of the disease and of the bleeding risk.

Anticoagulation regimen for thromboprophylaxis in hospitalised patients with COVID-19

- For non-ICU patients, a weight-adjusted prophylactic dose is recommended with a minimum of 50 IU anti-Xa/kg/OD, irrespective of renal function.
- For ICU patients, we recommend a high-prophylactic anticoagulation regimen with 50 IU anti-Xa/kg/BID for patients with CrCl >30 mL/min. For patients with CrCl <30mL/min, we suggest to use a reduced dose of 50 IU anti-Xa/kg OD. In the case of severe renal dysfunction (CrCl < 15mL/min), the use of unfractionated heparin should be considered.
- We recommend that therapeutic anticoagulation is restricted to patients with prior indication for therapeutic anticoagulation or patients with confirmed venous thromboembolism (VTE) [13]. Therapeutic anticoagulation in patients with COVID-19 might be associated with improved outcomes in selected very severely ill patients, especially patients under mechanical ventilation, but this has to be put in balance with bleeding risks. Therefore, we recommend to restrict the use of therapeutic anticoagulation in patients without clear indication to clinical trial protocols.
- In patients at high risk of bleeding (such as low platelet count, recent major bleeding, dialysis,…) risks and benefits of thromboprophylaxis should be weighed on an individual basis.

Anticoagulation regimen for treatment of COVID-19-related VTE

- For patients who develop VTE during hospitalisation with COVID-19, we recommend treatment with therapeutic doses of LMWH (100 IU anti-Xa/kg BID). In patients with CrCl <30ml/min, dose-adjusted therapeutic LMWH or tinzaparin should be considered. In patients with CrCl <15ml/min, we recommend the use of unfractionated heparin if there is sufficient local expertise.

D-Dimer

We do not recommend to routinely adapt the anticoagulation regimen based on D-Dimer levels as results may vary according to the assay used. However, increasing D-Dimer levels can be indicative of development of VTE and can guide the decision to perform imaging for VTE.

Screening for VTE

- Systematic screening for VTE in COVID-19 positive patients is not recommended but there should be an increased awareness for the possible development of VTE during hospitalisation (look for clinical signs like swollen leg, hypoxemia non-proportionate to the respiratory status, acute right ventricle failure or dilation, catheter issues...).
- There should be a low threshold to perform imaging in all cases with suspicion of VTE. In the case of strong but unconfirmed diagnosis, therapeutic anticoagulation may be considered especially in the ICU.

Anti-Xa monitoring

We recommend against performing systematic monitoring of anticoagulation with anti-Xa assays as this assay is not routinely available in all hospitals. It is however suggested to perform an anti-Xa assay when suspicion of accumulation of LMWH (and thus increased risk of bleeding) in the following circumstances: patients with extreme body weight (BMI< 18 or BMI >30 kg/m2) or renal insufficiency or in patients with a bleeding diathesis.

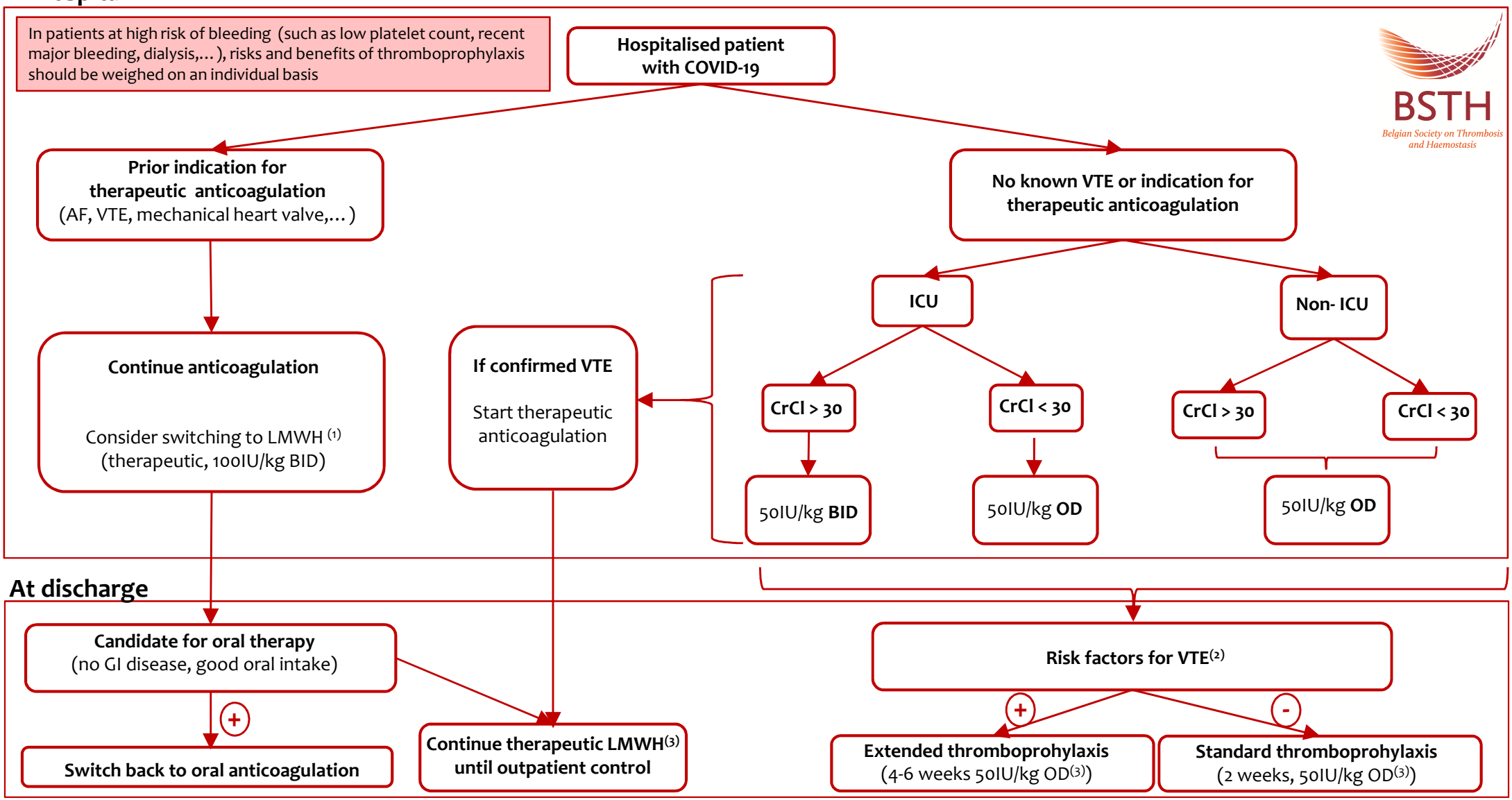
Anticoagulation management at discharge

We recommend continuing anticoagulation after discharge.

- In patients with prior indication for therapeutic anticoagulation, we recommend to switch back to the initial oral anticoagulation medication and regimen unless oral therapy is not feasible.
- In patients who developed a VTE during the hospitalization period, we recommend continuing therapeutic LMWH until outpatient control. Switch to oral therapy, e.g. DOAC, could be considered only in selected patients who are in good general condition and no longer have symptoms of COVID-19. Duration of therapeutic anticoagulation should be at least three months (as usual).
- In patients with no prior indication for therapeutic anticoagulation who received thromboprophylaxis during hospitalisation, we suggest continuing thromboprophylaxis at a weight-adjusted dose of 50 IU anti-Xa/kg/OD for two weeks. If additional risk factors for VTE are present (i.e. ICU stay, known thrombophilia, obesity, smoking, high-dose estrogen use, immobilisation, heart failure, respiratory failure, age >70, active cancer, personal or familial history of VTE and/or major surgery in the last 3 months) we suggest extended thromboprophylaxis for 4 to 6 weeks after discharge.

This continuation of thromboprophylaxis should be discussed according to risk-benefit balance (mobility/bleeding risk and other risk factors).

In order to limit contact with healthcare workers when the patients are back home, it can be considered to switch the LMWH to a direct oral anticoagulant (DOAC), if the patient is eligible and needs therapeutic anticoagulation, has good oral intake and good renal function. If this is not possible, self-administration should be encouraged.



(1) Consider switching to LMWH in following conditions: severely ill patient, GI symptoms, planned invasive procedures, unstable INR and/or presence of drug-drug interactions
(2) ICU stay, known thrombophilia, obesity, immobilisation, heart failure, respiratory failure, age >70, personal or familial history of VTE, active cancer and/or major surgery in the last 3 months
(3) If possible (eligibility, good oral intake,…) consider DOAC treatment or self-administration of LMWH

Anticoagulation management in non-hospitalized COVID-19 patients

The working group stresses that these recommendations should be regarded as guidelines that will be helpful in most patients but that in patients at high risk of bleeding (such as low platelet count, recent major bleeding, dialysis,…) risks and benefits of thromboprophylaxis should be weighed on an individual basis.

General considerations

- If the patient's condition allows it, mobilisation should be encouraged to reduce VTE risk
- Be aware for signs and symptoms of VTE.
- In case of suspected VTE, the patient should be referred for appropriate diagnostic testing. Initiation of therapeutic anticoagulation can be considered if clinical suspicion is high and bleeding risk is low, while awaiting results of diagnostic testing.
- If LMWH has to be administered at home, self-administration should be encouraged in order to avoid contact with healthcare workers

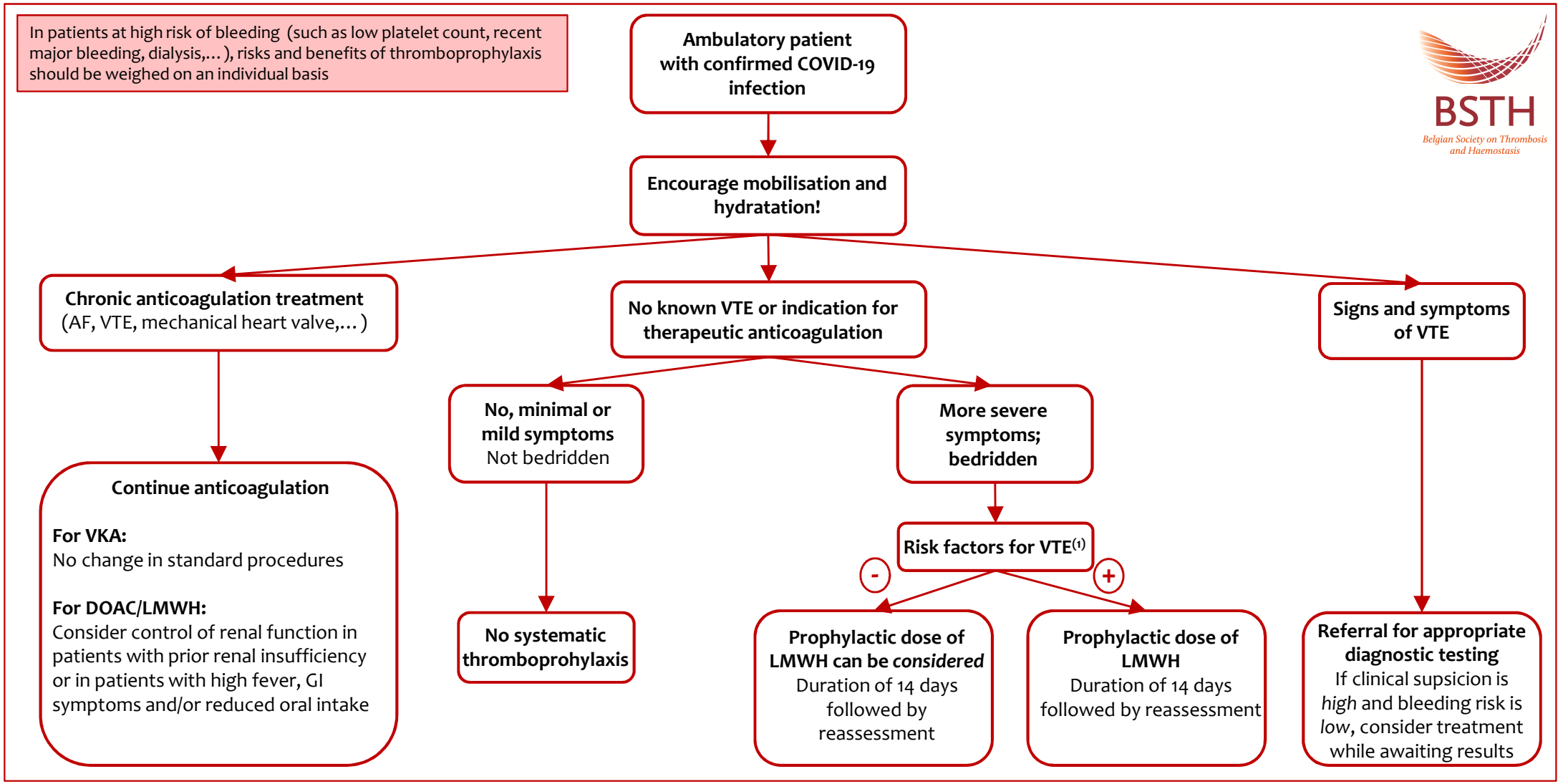
Patients with chronic anticoagulation treatment

- In all cases, anticoagulation therapy should be continued (unless contraindicated).
- In patients under chronic vitamin K-antagonists, we recommend against changing the standard of care, as long as the patient has good oral intake and stable INRs.
- In patients under chronic DOAC or LMWH, control of renal function in patients with prior renal insufficiency or in patients with high fever, gastrointestinal symptoms and/or reduced intake should be considered.

Patients with no known VTE or other indication for therapeutic anticoagulation

- In patients with known SARS-CoV-2 infection who are asymptomatic or mildly symptomatic, we recommend against prophylactic anticoagulation.
- In patients with SARS-CoV-2 infection who are severely ill and who are immobilized (bedridden), we recommend LMWH prophylaxis when additional risk factors for VTE are present: known thrombophilia, personal or familial history of VTE, obesity, pregnancy, heart failure, respiratory failure age >70, active cancer and/or major surgery in the last 3 months.
- In patients with SARS-CoV-2 infection who are severely ill and who are immobilized (bedridden), but who do not have additional risk factors for VTE, LMWH prophylaxis can be considered.
- Duration of the prophylaxis in non-hospitalised patients (if no chronic anticoagulation required) is recommended for 14 days. After 14 days, need for prophylaxis prolongation should be reassessed.

Non-hospitalised patients



(1) Risk factors for VTE: known thrombophilia, obesity, heart failure, respiratory failure, age >70, personal or familial history of VTE, active cancer and/or major surgery in the last 3 months

Anticoagulation management during pregnancy and post-partum period in COVID-19 positive women

The working group stresses that these guidelines do not change the standard anticoagulation management during pregnancy and post-partum. Pregnancy does not change the general recommendations as stated above.

Non-hospitalised women

- In pregnant women with known SARS-CoV-2 infection without severe symptoms, we recommend against thromboprophylaxis if not otherwise indicated.
- In pregnant women with severe COVID-19 symptoms (high fever, immobilization,…), thromboprophylaxis is recommended.

Hospitalised women

- For hospitalised, asymptomatic COVID-19 positive patients, standard obstetric thromboprohylactic risk assessment is recommended (based on current recommendations [14]). This assessment should be repeated if necessary.
- For hospitalised, symptomatic COVID-19 positive patients, we recommend thromboprophylaxis (unless contraindicated).
- If VTE is confirmed, anticoagulant treatment (LMWH during pregnancy) should be continued until 6 weeks postpartum and for a minimum of 3 months [14].
- VTE prophylaxis should be considered in postpartum women with COVID-19, based on individual risk assessment.
- If no antepartum pharmacologic prophylaxis: no postpartum prophylaxis if asymptomatic or mildly symptomatic, uncomplicated delivery and no obstetric indication for postpartum VTE prophylaxis.
- If antepartum prophylaxis because of COVID-19, continue prophylaxis for 14 days. After 14 days, need for anticoagulation should be reassessed according to risk-benefit balance (severity of COVID infection and other risk factors).

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