Proposal of the French Society of Vascular Medicine for the prevention, diagnosis and treatment of venous thromboembolic disease in outpatients with COVID-19

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RECOMMENDATIONS

Proposal of the French Society of Vascular Medicine for the prevention, diagnosis and treatment of venous thromboembolic disease in out-patients with COVID 19

Short title: **VTE management in covid outpatients: a proposal from the SFMV**

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The proposal is intended to help physicians treating patients with COVID-19 for the diagnosis, treatment and prevention of venous thromboembolic disease either when leaving the hospital or treated as outpatients.
This document is a synthesis of opinions of a working group from the French Society of Vascular Medicine (SFMV) composed of private practice and hospital-based physicians. This proposal is based on a limited level of evidence. this proposal is likely to evolve with the knowledge of the disease.

COVID-19 and venous thromboembolic disease

In the course of pandemic, cases of venous thromboembolic disease (VTE) associated with SARS-CoV-2 virus infection, associated with severe morbidity and mortality have been reported [1,2]. A Chinese retrospective study of 1008 Wuhan patients reported 25 patients suspect of pulmonary embolism who underwent an angioscan: pulmonary embolism was confirmed in ten patients. D-dimer values were higher in the pulmonary embolism group [3]. A major limitation is the lack of data on the methods used for thromboprophylaxis of these patients.

Other data demonstrate significant biological changes in favour of coagulopathy such as elevated D dimers and a significant inflammatory syndrome [4,5].

Several clinical, pharmacological, and pathophysiological mechanisms as well as the epidemic context of COVID-19 may expose to the risk of thromboembolic disease :

- hypoxemic pulmonary viral infection in its severe form;
- the inflammatory syndrome, which can be very severe and may be in addition to the classic risk factors for venous thromboembolic disease;
- age and a high body mass index (BMI) have been identified as risk factors for mortality;
- a major increase in D-dimers, indicating significant clotting activation is frequent, and also associated with mortality[5] ;
- the proposed treatments against COVID-19 may interact with antithrombotics ;
- the pandemic character changes patient management due to containement and limited availability of medical resources.

Prevention of VTE in medicine and after hospitalization beyond the context of COVID-19

- **<u>Thromboprophylaxis during hospitalization</u>**

Patients hospitalized with an acute medical condition are at risk for VTE. This risk is about 2% at 40 days after hospitalization [6]. The benefit of thromboprophylaxis for 10 +/- 4 days during hospitalization for acute medical conditions was validated in the MEDENOX trial [7]. Thromboprophylaxis is currently recommended in all national and international guides to good practice[8].

The risk factors for patients who are suitable for prophylaxis are well known :

- Age
- Acute infection

- Active cancer
- History of VTE
- Extended immobilization
- Chronic heart failure
- Chronic respiratory failure

- **<u>Extended thromboprophylaxis</u>**

The question of extended thromboprophylaxis in discharged patients may occur if the risk persists. Several trials have tested this venous thromboembolic risk prevention strategy.
In the Exclaim trial, a 32% reduction in the risk of VTE was observed with enoxaparin preventive versus placebo[9]. In the Magellan trial, which evaluated rivaroxaban 10mg during one month, there was a 22% reduction in the risk of venous thromboembolic events and a non-inferiority of rivaroxaban compared to enoxaparin, but with an increased hemorrhagic risk for rivaroxaban[10]. However, the net clinical benefit of these interventions has not been demonstrated in all patients, which is why extended prophylaxis beyond 14 days is not recommended[8].

VTE prophylaxis for COVID-19 in outpatients

Published data dedicated to biological changes in patients with COVID-19 do not provide enough data (thresholds, variations over time) to be incorporated into a risk assessment model of thrombosis and therefore cannot be used.

In the current state of knowledge, it is not allowed to follow the evolution of D dimers in order to decide on thromboprophylaxis.

It is not recommended to systematically perform repeated Doppler ultrasound scans for deep vein thrombosis (DVT) in the absence of clinical signs of VTE.

The thromboembolic risk of COVID patients at home is not known. It might be related to a reduced mobility associated with viral pneumopathy. In addition, there are major known risk factors such as obesity, cancer, a history of VTE or recent surgery. Therefore, the presence of two risk factors, including reduced mobility, can be considered to be the clinical situation that most closely approximates the profile of hospitalized patients for whom evidence validating thromboprophylaxis exists.
this is why, for out-patients COVID patients, experts have chosen this thromboprophylaxis model to be as close as possible to existing published data in non COVID patients.

Thromboprophylaxis may be considered in COVID-19 patients who have, <u>in addition to a significant reduction in mobility, at least one of the following risk factors</u>:

- BMI > 30kg/m^2 ;
- Age > 70 years;
- Active Cancer ;
- Personal history of VTE;
- Major surgery within the last three months;

In these cases, thromboprophylaxis for 7 to 14 days is suggested either with Low Molecular Weight Heparin (LMWH) or Fondaparinux at standard dose (e.g. Dalteparin 5000 IUx1/day or Enoxaparin 4000 IUx1/day or Fondaparinux 2.5mg x1/day) with self-injections if possible to limit the use of a nurse at home and avoid contact.
A high BMI is often present in hospitalized COVID patients. It has been suggested that thromboprophylaxis should be adapted to patient weight in the GIHP/GFHT proposal (https://site.geht.org). These proposals are aimed at hospitalized patients, who often present a more severe form of COVID and may not be adapted to patients at home, whose BMI is probably lower. The experts therefore suggest that thromboprophylaxis should not be adapted to patient weight.

In patients with chronic renal insufficiency, the benefit of thromboprophylaxis at home has to be put in balance with the bleeding risk. In this case, the prescription of a reduced dosage will be decided on an individual basis.

No specific tests will be performed other than platelet count, creatinine and liver tests before prescription of heparin.

After 14 days of thromboprophylaxis, if a significant reduction in mobility AND a major risk factor persists, further duration of thromboprophylaxis will be discussed.

An assessment of bleeding risk should always be performed empirically or by scoring prior to the start of prophylaxis.

Antiplatelet therapy will not be discontinued.

For patients discharged from hospital, the risk varies considerably depending on the type of hospitalization, transfer to follow-up care and the patient's characteristics; it is not possible to suggest systematic thromboprophylaxis, but it should be decided on a case-by-case basis and assessed regularly if necessary.

VTE prophylaxis for suspected COVID-19 in ambulatory patients

Outpatients suspected of having COVID-19 with the VTE risk factors mentioned above may benefit from the same thromboprophylaxis as patients with confirmed COVID-19 : 7 to 14 days and then reassessment to decide whether or not to continue thromboprophylaxis.

Diagnosis of VTE

Outpatient pathway

- **Patient with COVID-19**: precautions are mandatory:
  - For the patient: surgical mask;
  - For the physician: mask (surgical or better FFP2), cap, glasses, gown and overgown, gloves, hydroalcoholic solution;

    - Cleaning of equipment and surfaces in contact with the patient after examination (0.1% bleach);
    - Appointment at the end of the consultation if possible.
- **Patient with COVID-19 symptoms but unknown status :** same precautions.
- **Patient without clinical suspicion of COVID-19**: mask, gloves and disinfection of surfaces.

- **The diagnosis of deep vein thrombosis (DVT) is based on Doppler ultrasound of the lower limbs (US).**

- **The diagnosis of pulmonary embolism (PE) is based on lung CT-scan with injection.**

- **In the presence of clinical signs of VTE, the most appropriate diagnostic test is performed as an emergency measure (within 24 hours).**

- **In case of suspicion of DVT, there is no need to perform D-Dimers on an outpatient, except :**
    - **In case of low or intermediate probability if an ultrasound Doppler cannot be performed within 72 hours.**
    - **Inclusion in a research protocol**

- **A suspicion of PE in an outpatient should result in an emergency angioscan and not a first-line ultrasound Doppler in the epidemic context.**

- **When Superficial Vein Thrombosis (SVT) is suspected, an ultrasound Doppler will be performed except in patient with superficial venous perfusion of the upper limb, without a permanent endovenous device.**

Systematic search for VTE in patients with COVID-19.

- **In ambulatory care, there is no rationale for proposing systematic screening not guided by signs or symptoms even in the case of biological changes, including isolated increase in D Dimers.**

- **The diagnostic sensitivity of repeated compression ultrasound in asymptomatic patients is unknown but probably low.**

- **The risk of contamination of healthcare professionals is a potential factor in the spread of the epidemic and should limit unjustified or routine examinations.**

Treatment of VTE in the case of COVID-19

- **Follow-up of VTE treatment will be done in the usual way, giving priority to teleconsultations when possible.**

- **Treatment will include curative anticoagulation for at least 3 months and routine monitoring will be performed.**

- **The patient will receive the recommended treatment in the absence of contraindications. [11] Consideration should be given to possible interactions with treatments given on a compassionate basis or in clinical studies.**

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