Full title of the trial: Effectiveness of low molecular weight heparin at increased doses prophylaxis weight-adjusted, compared with lower doses prophylaxis (intermediate or standard), on the onset of venous thromboembolism in coronavirus disease 2019 (COVID-19) hospitalized patients: The randomized multicentric controlled open-label trial «COVI-DOSE»

Title of the trial in easily understood language: Low-molecular-weight heparin to prevent venous thromboembolism in COVID-19 patients: a randomized controlled trial of different doses

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Name of organisation/Sponsor: CHRU de Nancy

Sponsor's protocol code number: 2020PI073

EudraCT Number: 2020-001709-21

Brief Summary:
Worldwide observational studies indicate a significant prothrombogenic effect associated with SARS-CoV-2 infection with a high incidence of venous thromboembolism (VTE), notably life-threatening pulmonary embolism.
According to recommendations for acute medical illnesses, all COVID-19 hospitalized patients should be given VTE prophylaxis such as a low molecular weight heparin (LMWH). A standard prophylactic dose (eg. Enoxaparin 4000IU once daily) could be insufficient in obese patients and VTE has been reported in patients treated with a standard prophylactic dose.
In COVID-19 patients, guidelines from several international societies confirm the existence of an hypercoagulability and the importance of thromboprophylaxis but the "optimal dose is unknown" and comparative studies are needed.
In view of these elements, carrying out a trial comparing various therapeutic strategies for the prevention of VTE in hospitalized patients with COVID-19 constitutes a health emergency.
Thus, we hypothesize that an increased prophylactic dose of weight-adjusted LMWH would be greater than a lower prophylactic dose of LMWH to reduce the risk of life-threatening VTE in hospitalized patients. The benefit-risk balance of this increase dose will be carefully evaluated because of bleeding complications favored by possible renal / hepatic dysfunctions, drug interactions or invasive procedures in COVID-19 patients.
This multicenter randomized (1:1) open-label controlled trial will randomize hospitalized adults with COVID-19 infection to weight-adjusted prophylactic dose vs. lower prophylactic dose of LMWH.

Planned number of subjects to be included: 1000

Medical condition(s) to be investigated: Prevention of thromboembolic events in hospitalised COVID-19 infected patients

Medical condition in easily understood language: Clots prevention (deep vein thrombosis, pulmonary embolism) in hospitalised COVID-19 infected patients

Main objective of the trial : To evaluate the effectiveness, during the hospitalization, of low molecular weight heparin at increased doses prophylaxis weight-adjusted, compared with lower doses prophylaxis (intermediate or standard), on the onset of venous thromboembolism, causing death or not, in coronavirus 19 patients hospitalized in medical care units or intensive care units

Secondary objectives of the trial: To evaluate the effectiveness, during the hospitalization (maximum D28) of a weight-ajusted increased prophylactic dose of low molecular weight heparin, compared with a lower prophylactic dose, on :
1a. Major bleeding,
1b. Major and clinical relevant non-major bleeding,
2. Net clinical benefit corresponding to the association of venous thromboembolism and major bleeding, during hospitalization (maximum D28), and 2 months after inclusion of patient.
3a. Venous thrombosis at other sites than the primary outcome, during hospitalization (maximum D28),
3b. Symptomatic arterial thrombosis, during hospitalization (maximum D28),
4. All-cause mortality during hospitalization (maximum D28) and 2 months after inclusion of patient.
5. Primary outcome in predefined sub-groups (eg. renal function) during hospitalization (max D28),
6. To identify variables associated with the risk of venous thromboembolism during hospitalization (max D28) and 2 months after patient's inclusion.

Principal inclusion criteria:
- Adult
- Having been given an informed consent to participate or consent from relatives in case of vital emergency (patients not able to give a consent)
-Patient admitted at the hospital and presenting with a probable or proven SARS-Cov-2 infection
-SARS-Cov-2 infection confirmed by biology (positive PCR for COVID-19 on a nasophayngeal swab or any other sample) or by a composite criterium associating lung injury on imaging and clinical / biological symptoms suggestive of COVID-19 (eg : dyspnea, cough, fever, biological inflammatory syndrome, lymphopenia, elevated liver enzymes).
- Health Insurance Coverage

Principal exclusion criteria:
-End-stage kidney disease (glomerular filtration rate < 15 mL/min)
- Patients with active hematological malignancy
- Patients treated with dual antiplatelet therapy
-Acute kidney failure KDIGO 3
-Having received at least 3 doses prophylaxis of low molecular weight heparin before the inclusion
-Therapeutic-dose of anticoagulant treatment for more than 24 hours, whatever the route or the drug prescribed for an other indication such as atrial fibrillation, thomboembolic venous disease needing an prolonged treatment, prosthetic heart valves, …
-Iterative catheter-related thrombosis or thrombosis of an extracorporeal membrane oxygenation
- ECMO to be implemented within 24 hours.
-All contraindication to treatment with low molecular weight heparin including those described in paragraph 7.1.2 of the protocol
-High hemorrhagic risk: resistant systolic (> 180 mmHg) or diastolic (> 110 mmHg) hypertension during more than 12 hours or needing an intravenous treatment, recent (< 7j) major bleeding or non-resolved bleeding, coagulopathy (known constitutional deficit or TP<50% or fibrinogen<1.5 g/L), thrombocytopenia < 75 G/L,
- heparin-induced previous thrombocytopenia,
- contraindication to blood-derived products
-Lower limb Venous Doppler ultrasound not feasible (bilateral transfemoral amputation, or severe burns)
- Death expected within 48 hours
- Persons referred in articles L.1121-5 to L.1121-8 and L.1122-2 of the Public Health Code:
    - Pregnant, parturient or breastfeeding woman;
    - Minor person (non-emancipated);
    - Adult person under legal protection (any form of public guardianship).
- Person deprived of liberty for judicial or administrative decision, person under psychiatric care as referred in articles L. 3212-1 and L. 3213-1.

Primary end point: The primary endpoint is the onset of a symptomatic venous thromboembolic event, during the hospitalization stay (and limited to D28 of hospitalization), as defined by a:
- Symptomatic deep venous thrombosis, whatever the site and confirmed by a compression ultrasonography or an abnormal computed tomography angiogram with venous opacification
or
- Symptomatic pulmonary embolism, confirmed by:
• a computed tomography angiogram,
• or a V/Q scan,
• or the presence, in a patient with a recent worsening dyspnea, of a deep venous thrombosis and/or a right ventricular dysfonction diagnosed by a transthoracic echocardiography in an unstable patients unable to benefit from a CT angiogram (2019 European Society of Cardiology Guidelines)
or
- Unexplained death when a pulmonary embolism cannot be excluded.
The primary endpoint is a composite measure of clinical events and/or survival, as recommended by the WHO guidelines on COVID-19 Therapeutic Trial Synopsis (february, 2020).
For each included patient, the onset of each event considered in the composite primary endpoint will be evaluated by a blinded independant endpoint adjudication committee.

Timepoint(s) of evaluation of primary end point:
Between the trial inclusion and the hospitalization discharge (with a limitation of 28 days of hospitalization)

Secondary end point(s):

1a. The onset, during hospitalization (maximum D28), of a major bleeding as defined by the International Society on Thrombosis and Haemostasis:
• Bleeding causing a fall in hemoglobin level ≥ 2 g/dL or needing a transfusion (whole blood or red cells) ≥ 2 units, and/or
• a bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
• fatal bleeding.
1b. The onset, during hospitalization (maximum D28), of a major bleeding and a clinically-relevant non major bleeding as defined by the International Society on Thrombosis and Haemostasis :
• requiring medical intervention by a healthcare professional, and/or
• needing a temporary cessation of the study treatment, and/or
• causing discomfort for the patient such as pain.
The clinically-relevant non major bleeding may be : macroscopic haematuria either spontaneously or for more than 24 hours after an invasive procedure of the urinary tract, gastrointestinal bleeding, hemoptysis, muscle hematoma, spontaneous subcutaneous hematoma > 25 cm2 or provoked subcutaneous hematoma > 100 cm2, multiple source bleeding, hematoma / bleeding from other site.
2. The net clinical benefit defined as composite criterium associating venous thromboembolism and major bleeding during hospitalization (maximum D28) and within 2 months following the patient's inclusion in the trial.
3a. The onset, during hospitalization (maximum D28), of venous thrombosis at other sites than the primary outcome:
• superficial venous thrombosis, and/or
• venous central catheter-related thrombosis/PiCC-line/Midline, and/or
• thombosis of an extracorporeal dialysis circuit (diagnosed by a dysfunction of the circuit), and/or
• thrombosis of an extracorporeal membrane oxygenation (diagnosed by a dysfunction of the circuit)
• deep vein thrombosis in other sites (eg. upper limb, splanchnic vein thrombosis, cerebral thrombophlebitis)
These thromboses must be confirmed by a reference gold standard test according to most recent guidelines.
3b. The onset, during hospitalization (maximum D28), of symptomatic arterial thrombosis, whatever the arterial site:
• stroke, and/or
• acute coronary syndrome, and/or
• acute mesenteric ischemia, and/or
• other arterial thrombosis on other sites (eg. splanchnic arterial or peripheral arteries).
These thromboses must be confirmed by a reference gold standard test according to most recent guidelines.
4. All-cause mortality during hospitalization (maximum D28) and for 2 months after inclusion of the patient in the trial.
5. Same outcome as the primary outcome
6. Variables associated with the occurrence of venous thromboembolism that will be recorded are: age, gender, cardiovascular risk factors, past medical history, treatments, clinical characteristics, laboratory parameters recorded during patient management during hospitalization (maximum D28) and 2 months after inclusion of the patient in the trial.
The occurrence (or not) of the secondary outcomes in each included patient will be reviewed blindly of the randomization arm by an independent adjudication committee.

Timepoint(s) of evaluation of Secondary end point :
1a. et 1b. Between the trial inclusion and the hospitalization discharge (with a limitation of 28 days of hospitalization)
2. During hospitalization (maximum D28) and within 2 months following the patient's inclusion in the trial.
3a. and 3b Between the trial inclusion and the hospitalization discharge (with a limitation of 28 days of hospitalization)
4. During hospitalization (maximum D28) and within 2 months following the patient's inclusion in the trial.
5. Between the trial inclusion and the hospitalization discharge (with a limitation of 28 days of hospitalization)
6. During hospitalization (maximum D28) and within 2 months following the patient's inclusion in the trial.

Scope of the trial : Prophylaxis/ Safety / Efficacy

Trial type and phase : Therapeutic use (Phase IV)