Protocol Title: **COVID-19-associated coagulopathy: Safety and efficacy of prophylactic anticoagulation therapy in hospitalized adults with COVID-19**

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1. Background and scientific rationale

Infection with the novel coronavirus SARS-CoV-2, first identified in Wuhan, China in late 2019, has become a global pandemic affecting over 209 countries and territories. The illness caused by SARS-CoV-2 is classified as COVID-19. As of April 8, 2020, the U.S. has by far the largest number of total cases (400,549) with a mortality rate of 3.4%. Higher mortality rates of over 5% have been seen in other countries. Although many patients may have only mild upper respiratory symptoms, some COVID-19 patients become severely ill with respiratory failure with risk of progression to multiple organ failure and development of a systemic coagulopathy with features similar to disseminated intravascular coagulation (DIC).[1] The pathophysiology of COVID-19-associated coagulopathy appears to be complex and multifactorial, involving both cellular and plasmatic elements of the hemostatic system. Development of coagulopathy has been suggested to be a predictor of mortality in patients with COVID-19.[2] The primary treatment of DIC is focused on treating the underlying pathology; which for COVID-19 is currently limited to supportive therapy and experimental therapeutics. Treatment with low-molecular weight heparin (LMWH) in prophylactic doses was associated with better outcomes in severe cases of COVID-19 meeting ISTH criteria for DIC in a retrospective analysis.[1,2] The International Society of Thrombosis and Hemostasis (ISTH) has published an interim guidance document recommending thromboprophylaxis with LMWH for all hospitalized patients with COVID-19.[3] However, it is not known if patients with coagulopathy from COVID-19 benefit from higher levels of prophylactic anticoagulation therapy. Presently no data exist regarding the relative safety or efficacy of intermediate-dose versus low-dose prophylactic LMWH.

This prospective, randomized, open-label, single-center interventional study is designed to compare the safety and efficacy of two LMWH dosing protocols in patients admitted to the University of Iowa Hospitals with COVID-19 who meet the modified ISTH Overt DIC criteria score ≥3. Patients will be randomized to low-dose LMWH (standard of care arm) or intermediate-dose LMWH (intervention arm).

2. Objectives

2.1 The primary objective of the study is to compare all-cause mortality of hospitalized patients with COVID-19 coagulopathy treated with low-dose versus intermediate-dose LMWH at 30 days.

2.2 The secondary objectives are to determine whether the use of low-dose versus intermediate-dose LMWH has an impact on major bleeding, arterial thrombosis, venous thrombosis, ICU admission, or transfusion of blood products.

2.3 The exploratory objectives are to determine the effects of SARS-CoV-2 infection on laboratory coagulation parameters to better understand the mechanism of COVID-19 coagulopathy.

3. Study design

3.1. Design

This is a single center, randomized, open-label study comparing low-dose enoxaparin (40 mg SC daily or 30 mg SC twice daily if BMI ≥40; standard of care arm) versus intermediate-dose enoxaparin (1 mg/kg SC daily or 0.5 mg/kg SC twice daily if BMI≥40; intervention arm) in hospitalized patients with laboratory-confirmed SARS-CoV-2 infection.

3.2. Rationale for enoxaparin dosing

Severe infection with SARS-CoV-2 is commonly complicated with coagulopathy. Prophylactic anticoagulation therapy was associated with decreased mortality in a retrospective analysis of Chinese patients with COVID-19 associated coagulopathy.[2] Pharmacologic thromboprophylaxis is standard of care for patients admitted to the hospital with severe respiratory illness and is recommended by the ISTH guidance document for hospitalized patients with COVID-19.[3] Patients with a BMI ≥ 40 randomized to the standard of care arm will receive low-dose prophylaxis with LMWH but will be adjusted for weight per University of Iowa institutional recommendations.[4] The relative safety and efficacy of low-dose prophylactic LMWH versus higher doses of LMWH is unknown. Due to potential bleeding risks with full therapeutic dose anticoagulation, the intervention arm in this study will be intermediate-dose of LMWH.

4. Selection of subjects

4.1 Inclusion criteria

Subjects must meet all the inclusion criteria to participate in this study.

- Laboratory confirmed SARS-CoV-2 infection
- Age ≥18 years
- Requires hospital admission for further clinical management
- Modified ISTH Overt DIC score ≥ 3

4.2 Exclusion criteria

Subjects meeting any of the exclusion criteria at baseline screening will be excluded.

- Indication for full therapeutic-dose anticoagulation
- Acute venous thromboembolism (deep vein thrombosis or pulmonary embolism) within prior 3 months
- Acute cardiovascular event within prior 3 months
- Acute stroke (ischemic or hemorrhagic) within prior 3 months
- Active major bleeding
- Severe thrombocytopenia (<25,000/mm^3)
- Increased risk of bleeding, as assessed by the investigator
- Acute or chronic renal insufficiency with glomerular filtration rate (GFR) < 30 ml/min calculated by the modified Cockcroft and Gault formula
- Weight < 40 kg or > 150 kg
- Known allergies to ingredients contained in enoxaparin

5. Study procedures and evaluations

5.1 Screening and enrollment

Potentially eligible patients will be identified by a healthcare professional per institutional policy on privacy. The healthcare professional will assess the eligibility of the patient by performing a chart review which will include laboratory results and weight as measured on admission to the hospital. After obtaining verbal consent from the patient to be contacted for the study, a member of the research staff will approach the patient to be part of the study. The research staff will obtain informed consent from the patient/LAR before collecting any data and performing any procedures.

5.2 Trial interventions

As standard of care, hospitalized patients with confirmed COVID-19 will be monitored for coagulopathy. Daily blood tests for platelet count, prothrombin time, D-Dimer, and fibrinogen and weekly thromboelastography will be obtained, and a daily Modified ISTH Overt DIC score will be calculated (Exhibit 1). Only patients meeting all inclusion and exclusion criteria will be asked to participate in the trial. Patients will be randomized to one of two arms:

1) Patients randomized to the **standard of care arm** will receive low-dose enoxaparin (40 mg subcutaneously daily if BMI <40 and 30 mg subcutaneously twice daily if BMI ≥ 40).
2) Patients randomized to the **intervention arm** will receive intermediate-dose enoxaparin (1 mg/kg Subcutaneously daily or 0.5 mg/kg Subcutaneously twice daily if BMI ≥ 40).

5.3 Dose Modifications

1) Enoxaparin will be held if platelets decrease to <25,000/mm^3. Enoxaparin will resume once platelets increase to ≥25,000/ mm^3.
2) Enoxaparin will be held if fibrinogen is <50 mg/dL. Enoxaparin will resume once fibrinogen increases to ≥50 mg/dL.
3) Enoxaparin will be help if glomerular filtration rate (GFR) < 30 ml/min calculated by the modified Cockcroft and Gault formula and resumed once the GFR is ≥30 ml/min.

All participating patients will continue the assigned doses of enoxaparin until hospital discharge or until a clinical event occurs requiring either discontinuation of anticoagulation therapy or full therapeutic dose anticoagulation therapy.

6. Randomization

Randomization to treatment arm will be allocated through a centralized randomization system in a 1:1 ratio for the standard of care versus intervention arms (low-dose versus intermediate-dose enoxaparin, respectively). The randomization process will be initiated by the study personnel who will access the web-based system and enter the patient's unique identifier, confirmation of eligibility and informed consent.

7. Assessment of Scientific Objectives

7.1 Study Outcome Measures

This study will track clinical events of interest

7.1.1 All-cause mortality at 30 days from enrollment date

1) In-hospital mortality will be determined by chart review
2) Out-of-hospital mortality will be determined by chart review or via telephone encounter by a trial investigator

7.1.2 Venous thrombotic events

1) Symptomatic DVT
2) Pelvic DVT or inferior vena cava DVT
3) Superior vena cava thrombosis (SVC syndrome)
4) Pulmonary embolism
5) Cerebral venous thrombosis
6) Retinal vein thrombosis
7) Mesenteric venous thrombosis
8) Adrenal hemorrhage/adrenal vein thrombosis
9) Renal vein thrombosis
10) Line-related venous thrombosis

7.1.3 Arterial thrombotic events

1) Acute limb arterial thrombosis, including arterial limb gangrene
2) Ischemic stroke (defined as any residual neurologic deficits at 24 hours)
3) Transient ischemic attack (defined as no residual deficits at 24 hours)
4) Acute (unstable) coronary syndrome
5) Myocardial infarction
6) Aortic thrombosis
7) Spinal cord infarction
8) Mesenteric artery thrombosis
9) Renal artery thrombosis
10) Hemodialysis graft (or fistula) occlusion

7.1.4 Bleeding events

1) Major Bleeding
    a. Bleeding resulting in a decrease in hemoglobin of 2 g/dL or more over a 24-hour period
    b. Bleeding leading to a transfusion of 2 or more units of packed red blood cells
    c. Bleeding that occurs in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular other than the operative site, intramuscular with compartment syndrome or retroperitoneal)

d. Bleeding that leads to death

2) Minor Bleeding

a. Bleeding event that does not meet any of the criteria required for the event to be classified as a major event

7.1.5 Admission to the intensive-care unit

7.1.6 Acute renal failure

7.1.7 Transfusion of blood products

1) Transfusion of blood products including packed red blood cells, platelets, cryoprecipitate and fresh frozen plasma will be documented and recorded

7.1.8 Laboratory Assessments

1) Daily labs will be obtained including complete blood count with differential, prothrombin time, partial thromboplastin time, D-dimer, fibrinogen, lactate dehydrogenase, C-reactive protein, ferritin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and serum creatinine

2) Thromboelastography (TEG) will be obtained within 24 hours of enrollment and weekly thereafter

3) Blood samples for exploratory laboratory tests will be obtained within 24 hours of enrollment and weekly thereafter. Exploratory tests will include thrombin generation, cell free DNA, and PAI-1.

8. Withdrawal or Termination

Any participant who wishes to withdraw from the study may do so at any time. If a participant chooses to withdraw from the study, no new data about that participant will be collected for study purposes. A participant may also withdraw authorization for the researchers to use his or her data that has already been collected (other than data needed to keep track of the withdrawal, including demographic data), but the participant must do this in writing to the site principal investigator.

The study may be terminated at any time by the Principal Investigator if it is deemed continuation of the protocol will not yield statistically or scientifically useful data.

9. Study Management

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki. Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be

given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form. Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient or the patient's legally acceptable representative, and by the person who conducted the informed consent discussion.

10. Statistical analysis and considerations

The null hypothesis is that intermediate-dose LMWH (intervention arm) will have a mortality rate that is not less than low-dose LMWH (standard of care arm). A sample size of 82 patients to each arm of the study are needed to have 80% power when testing a difference of 20% (40% vs 20% for the two arms). Mean with SD and frequencies for all variables will be reported for each arm. A chi-square test will be conducted to test the mortality difference between the two arms.

Exhibit 1

Modified ISTH Overt DIC Score	
Laboratory Results	**Points**
Platelet Count	
> 100,000/μL	0
< 100,00/μL and ≥50,000 /μL	1
< 50,000 /μL	2
D-Dimer	
No increase, ≤0.50 mcg/mL	0
Moderate increase, >0.50 and <3.00 mcg/mL	2
Strong increase, ≥3.00 mcg/mL	3
Prothrombin time	
Prolonged < 3 sec	0
Prolonged 3 to 5 sec	1
Prolonged ≥ 6 sec	2
Fibrinogen level	
> 100 mg/dL	0
< 100 mg/dL	1
Interpretation of Score	

If≥ 3: compatible with COVID-19-associated coagulopathy
If< 3: not suggestive of COVID-19-associated coagulopathy

References

1. Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine.* 2020.
2. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis.* 2020;18(4):844-847.
3. 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).
4. Lentz SR. Thrombosis in the setting of obesity or inflammatory bowel disease. *Hematology.* 2016;2016(1):180-187.