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Review Article

A Multicentric, Randomized, Double Dummy Study to Evaluate Therapeutic Dose Efficacy of Enoxaparin Versus Apixaban in Hospitalize Double Blind, D Covid-19 Patients

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Abstract

SARS-Co-2 is a novel human infectious single-stranded enveloped RNA virus. Patients will present with fever, cough, fatigue and pneumonia of varying severity. CDC report dated July 4, 2020 showed > 6.5 million cases globally, in more than 180 countries. Fatal outcomes are in > 65 years patients. 31% of the patients have increased risk of thromboembolic phenomenon (TE), 50% with poor prognosis if has elevated D-Dimmer, 13 - 69% develops venous thrombosis. This study planned to assess the therapeutic doses of enoxaparin versus apixaban in hospitalized patients with COVID-19 result in reduction of in arterial or venous thromboembolic events on top of institutional COVID-19 therapy as primary goal. In secondary goals, we will compare the survival rate, time to event, time to ICU admission, time to discharge, and safety between the two groups.

Keywords: *SARS-Co-2; Thromboembolic Phenomenon (TE); COVID-19*

Background and Rationale for the Trial

- SARS-CoV-2 is a novel human infectious single-stranded enveloped RNA virus and patients presents with fever, cough, fatigue, and pneumonia of varying severity [2,5-7,14].
- CDC report dated Jul 4, 2020, >6.5 million cases globally >180 countries, >380,000 deaths [2].
- Individuals of all ages are at risk for infection and severe disease. Fatal disease is highest in people aged ≥65 years and in nursing homes [2,5,7].

Clinical progression of COVID-19 [10]

- Thirty one% patients with COVID-19 are at increased risk of thromboembolic (TE) phenomenon [4].
- Elevated D-dimer levels are associated with poor prognosis in 50% patients [13].
- According to CDC 13-69% critically ill COVID-19 patients develop venous thromboembolic (VTE), with standard pharmacologic prophylaxis [2,9,12].

- This study is planned to assess the therapeutic doses of enoxaparin vs apixaban:
    - Enoxaparin is a parenteral (LMWH) with proven safety and efficacy indicated for prophylaxis and treatment of acute DVT [11].
    - Apixaban, an oral (factor Xa inhibitor) with proven safety and efficacy is indicated for reduction of risk of stroke and systemic embolism [1].

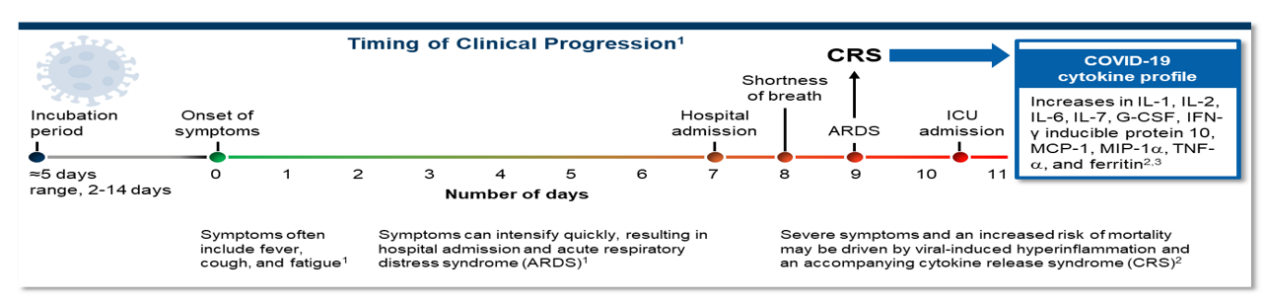

Figure 1: *Team 7 assignment 5 presentation Jul-2020.*

Study Aims

- The primary goal of the study is to determine if therapeutic doses of enoxaparin and apixaban administered to hospitalized patients with COVID19 result in reduction of arterial or venous thromboembolic events on top of institutional COVID19 therapy.
- Secondary goal of the study to assess if therapeutic doses of enoxaparin and apixaban improve the survival rate.
- Secondary goal:
    - Compare survival rate between the two treatment groups.
    - Compare time to ICU admission between the two treatment groups.
    - Compare time to discharge between the two treatment groups.
    - Compare the safety between the two treatment groups.

Study Design

Design: Multicentric, randomized (1:1), double-blind, double-dummy, two-arm parallel design study in hospitalized confirmed COVID-19 patients on top of institutional COVID-19 therapy.

Treatment duration: 14 days or during hospitalization.

Each patient will undergo screening visit, randomization, treatment period of 14 days or during inpatient stay, and a follow-up period 30 and 90 days. During the course of the study efficacy and safety will be assessed.

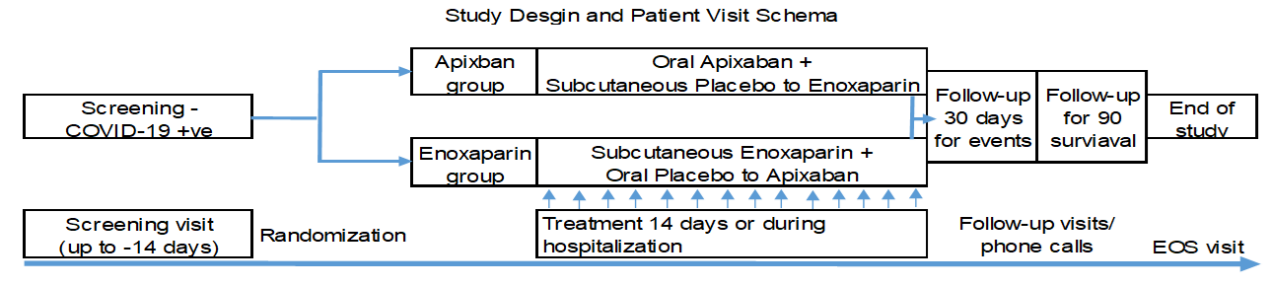

Figure 2

Key inclusion criteria

- Adults ≥ 18 years old willing and able to provide written informed consent prior to performing study procedures.
- COVID-19 positive patient confirmed by polymerase chain reaction (PCR) test.
- Hospitalized with elevated D-dimer levels (> 2 µg/mL).

Key exclusion criteria

- Known allergy to low molecular weight heparin or oral anticoagulant agent.
- Pregnant and nursing women.
- Key medical illnesses:
    - Acute ischemic stroke.
    - Active evidence of bleeding.
    - Recent major surgery or trauma (6 - 12 weeks).
    - Liver disease.
    - Renal failure (Creatinine clearance < 20 mL/min or on dialysis).
    - Thrombocytopenia (< 50,000 platelets/L).
- Participation in any other clinical trial of an experimental treatment for COVID-19 within 30 days or 5 half-life of screening visit.

Study treatments

- **Enoxaparin treatment group**
    - Enoxaparin subcutaneous injection therapeutic dose - 1 mg/kg BID:

        - Dose adjustment will be based on renal function.
    - Placebo to Apixaban 0 mg BID orally.
- **Apixaban treatment group**
    - Apixaban 5 mg BID orally:
        - Dose adjustment will be based on renal function.
    - Placebo to Enoxaparin subcutaneous injection BID.
- The study treatment is administered on top of the institutional COVID-19 therapy.
- Duration of treatment will be up to 14 days or during hospitalization whichever is longer.

Primary and secondary endpoints

- **Primary**
    - Any thromboembolic events (arterial or venous) within 30 days after entering the study:
        - Thromboembolic events is incidental event(s) of asymptomatic or symptomatic deep vein thrombosis (DVT) or symptomatic pulmonary embolism (PE) or fatal PE or stroke or myocardial infraction (MI) or ischemic complications of unstable angina and non Q-wave MI or acute ST-segment elevation MI or percutaneous coronary intervention (PCI).
- **Secondary**
    - Time to event death (90 days survival analysis).
    - Time to ICU admission (as applicable).
    - Time to discharge.
    - Safety assessment include (not limited) adverse events, incidence of major/clinically relevant bleeding, laboratory parameters.

Sample size and power calculation

- H0: $|t1 - t2| \geq d$.
- Ha: $|t1 - t2| < d$.
- Assuming a risk reduction of 60% for both groups, based on what has been shown in studies using pharmacologic prophylaxis for VTE [15], we determine P = 0.6 for both groups.
- Power of the study 90%, with diference between treatment groups (d) of 10%.
- Based on the table, our sample size is estimated as 414 per group are expected to complete the study.

- Therefore, a total of 850 patients will be enrolled.

For equivalence study

*P**	*P**	*d*	*N**
0.9	0.9	0.1	155
0.9	0.9	0.2	39
0.6	0.6	0.1	414
0.6	0.6	0.2	103
0.9	0.85	0.1	746
0.9	0.8	0.2	215

Table 1: *Sample size calculations for α= 0.05, ß = 0.10 [3].*
**N is the sample size for each group treatment.*

Statistical analysis plan

- Summary statistics will presented by treatment for demographic and baseline characteristics.
- Chi-square tests for bivariate analysis will be used to compare the occurrence of the outcome (thromboembolic event) between the two groups.
- The Kaplan-Meier method will be used to estimate time to event,
    - Log-rank test will be used to compare the time course among treatment groups.

Cox-proportional hazards regression for multivariate analysis.

Limitations and Conclusion

- The institutional conventional COVID-19 therapy varies and is not defined here.
- Includes patients > 65 years with co-morbid conditions.
- The trial is a head on comparison of anticoagulant therapy - generally prescribed as preventive (prophylactic) therapy, whereas in this trial we are using therapeutic dose and therefore not able to compare with placebo or institutional conventional CO-VID-19 therapy.
- Hospitalization is driven by institutional guidelines.

Bibliography

1. Bristol-Myers Squibb Company ELIQUIS: Highlights of prescribing information (2019).
2. Centers for Disease Control and Prevention (2020).
3. Christensen E. "Methodology of superiority vs. equivalence trials and non-inferiority trials". *The Journal of Hepatology* 46.5 (2007): 947-954.

4. Cohen AT., *et al*. "Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial". *British Medical Journal* 332.7537 (2006): 325-329.

5. European Centre for Disease Prevention and Control (2020).

6. Garg S., *et al*. "Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1–30, 2020". *Morbidity and Mortality Weekly Report* 69 (2020): 458-464.

7. Guo YR., *et al*. "The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status". *Military Medical Research* 7.1 (2020): 11.

8. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet". *Lancet* 395.10223 (2020): 497-506.

9. Klok FA., *et al*. "Incidence of thrombotic complications in critically ill ICU patients with COVID19". *Thrombosis Research* (2020).

10. Mehta P., *et al*. "COVID-19: consider cytokine storm syndromes and immunosuppression". *Lancet* 395.10229 (2020): 1033-1034.

11. Sanofi-Aventis U.S. LLC, Lovenox: Highlights of prescribing information (2020).

12. Tang N., *et al*. "Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy (2020).

13. Yu B., *et al*. "Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis". *The Journal of Thrombosis and Thrombolysis* (2020).

14. Zhu N., *et al*. "A Novel Coronavirus from Patients with Pneumonia in China, 2019". *The New England Journal of Medicine* 382.8 (2020): 727-733.

15. Aryal MR., *et al*. "Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world". *Blood Advances* 3.15 (2019): 2381-2387.

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