Title: Treating COVID-19 with Anticoagulation based on Kabir Bleeding Risk Score

Running Title: Treating COVID-19 based on Kabir bleeding risk score

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Abstract:

Three large randomized clinical trials named the ATTACC, ACTIV-4a, and REMAP-CAP were terminated early as these trials showed use of therapeutic anticoagulation among non-critical COVID-19 patients increased the probability of survival to hospital discharge as well as reduced the need for cardiovascular or respiratory organ support. These clinical trials also showed when a COVID-19 patient presents with a critical stage, therapeutic anticoagulation does not provide any benefit. The authors also had approx. two thousand five hundred COVID-19 encounters and found that anticoagulation doses can be titrated up or down based on D-Dimer trends and many

patients do not need therapeutic anticoagulation, rather an intermediate dose (Lovenox 0.5mg/kg subQ BID or equivalent) anticoagulation can be sufficient for those who have a higher risk of bleeding. Based on experience, the author developed the Kabir bleeding risk score-based treatment strategies for COVID-19 patients which can be visited by clicking on the following link: [<https://patient.ddrx.com/anticoagulation.php>](https://patient.ddrx.com/anticoagulation.php).

Introduction:

Three largest randomized clinical trials named the ATTACC, ACTIV-4a, and REMAP-CAP were terminated early, and investigators reported on August 4th, 2021, that in noncritically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis [1]. These three clinical trials also reported that among critically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin was not associated with a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than was usual-care pharmacologic thromboprophylaxis [2]. The author also observed the same findings of patients with COVID-19 who were already on anticoagulation, even before the diagnosis of COVID-19, and published that those patients had almost near zero mortality rates [3]. This piece was submitted on August 15th, 2020, in the Journal of Mississippi State Medical Association [3]. These three clinical trials finding validate the author's observation why patients already on anticoagulation with Apixaban (or

Rivaroxaban) were surviving as the patients were non critically ill or even asymptomatic when they were taking anticoagulation orally.

The author treated more than three hundred (300) COVID-19 patients over the last fourteen months (from June 15th, 2020, to August 15th, 2021) on multiple hospital medical floors from three US states (Alabama, Mississippi, and Illinois). The total number of encounters where the author served as a primary attending or consultant were around two thousand five hundred. This author used a variable dose of anticoagulation based on trends of d-dimer and found that intermediate or high dose enoxaparin is associated with better patient outcome and frequently patients do not need therapeutic anticoagulation for survival from COVID-19. The best treatment strategy from the pilot study conducted by the author was starting hospital COVID-19 floor patients on Enoxaparin 0.5 mg/kg subq twice a day (for non-critical patients) and titrating dose up if the patient's condition deteriorates or if d-dimer worsened.

These COVID-19 hospital floor patients provided unique experiences because of their early stages of disease presentation compared to patients admitted in the intensive care units. The author observed COVID-19 patients who presented in the late stages of COVID-19, or those who were directly admitted to the intensive care unit due to intubation or BiPAP requirements, were more likely to have poor outcomes compared to patients presenting at an earlier stage in the COVID hospital floor. Due to poor outcomes with therapeutic anticoagulation in the intensive care unit patients, nationwide intensivists were reluctant to adapt therapeutic anticoagulation in treating COVID-19. The dilemma is mostly rooted in anticoagulation related risk of bleeding and poor

patient outcome. This biased experience of intensive care unit physicians leads to higher deaths among COVID-19 patients since the beginning of the pandemic.

Those patients who were admitted at the hospital medical floor (non-critically ill) have significant mortality benefit with concomitant use of anticoagulation and intravenous steroids. However, those patients who were treated with anticoagulation in the early stage of COVID-19 and later moved from the hospital floor to the intensive care unit have a higher chance of recovery compared to those who did not receive any anticoagulation prior to their critical care unit admission. The reason behind those failures is that anticoagulation does not dissolve microthrombi (blood clots) rather prevents their further growth. Treating patients with anticoagulation only can benefit when capillaries are still open (not clogged due to microthrombi). Bottom line is that those patients present in hospitals needing nasal cannula oxygen or high flow nasal cannula oxygen and or patients with low or moderately high D-Dimer (less than two-fold higher than the upper limit of normal) usually survive with anticoagulation and steroid combination treatments. The author observed that increasing trends of D-Dimer in any patient were inversely proportional to the survival rates and or clinical recovery from COVID-19 and vice versa. There is a dose-effect relationship between the decreasing trends of D-Dimer with the used anticoagulation dose. That means the quicker recovery is directly proportional to the higher dose of anticoagulation used for treating early-stage COVID-19. Hence, D-Dimer can be considered to predict patient outcomes, and healthcare facilities' resources need to tackle COVID-19.

If a state or country's healthcare system is reaching a breaking point it will be too late for getting vaccination to reduce COVID-19 cases as it takes more than four weeks for the vaccination to start working. In such a case, a contingency plan should be to start a nation or state awareness campaign asking patients to come to seek healthcare at urgent care or primary care clinics so that the chance of capturing early noncritical COVID-19 cases is very high. Again, if patients present to the emergency room in a critical stage, there will not be any benefit of therapeutic anticoagulation. Given the clinical trial [X1] findings among noncritical COVID-19 treated with anticoagulation showed reduced use of cardiovascular or respiratory organ support, treating patient at diagnosis with oral therapeutic anticoagulation like Apixaban or Rivaroxaban may reduce need for hospitalization among patient with COVID-19.

Given, all anticoagulant reduces thrombotic risk and at the same time increase the risk of bleeding, the decision to administer an anticoagulant should be based on the assessment of the bleeding risk for the specific patient at a specific point in time. Not all patients need therapeutic anticoagulation to treat COVID-19, a lower dose may be sufficient for those with low D-Dimer level. According to the authors COVID-19 hospitalist experience, the ideal way to decide whether therapeutic anticoagulation is needed or not is to titrate anticoagulation dose based on D-Dimer trends.

The dilemma of using therapeutic anticoagulation versus the treatment of COVID-19 without anticoagulation to prevent bleeding related mortality and morbidity can be solved if anticoagulation is used judiciously. The author developed the Kabir bleeding risk Score based

COVID-19 treatment protocol showed in Table 1. The Kabir bleeding risk calculator can also be visited by clicking the following website: <<https://patient.ddrx.com/anticoagulation.php>>. The author utilized available literature to develop the Kabir bleeding risk calculator [4-6].

Table 1: Developing Kabir risk of bleeding score with anticoagulation based on known risk factors: Treating noncritically ill COVID-19 patients

RISK FACTORS FOR BLEEDING WITH ANTICOAGULATION	LIKELIHOOD
MALE SEX	0.4
OLDER AGE (≥ 80 ; 40 to 80; 18 to 40)	0.75; 0.5; 0;
RACE (ASIAN, HISPANIC, OR AFRICAN AMERICAN, WHITE)	1; 0.5; 0.5; 0;
CURRENTLY TREATED FOR PEPTIC ULCER DISEASE	1
BLEEDING EPISODE WITHIN THE PAST 3 MONTHS	1
PLATELET COUNT $< 50,000$	1
ADMISSION IN ICU OR CCU	0.6
EGFR < 30 ; 30 TO 59; ≥ 60	0.5; 0.4; 0;
INR > 1.5	0.5
ACTIVE CANCER	0.5
HISTORY OF RHEUMATIC DISEASE	0.5

PRESENCE OF CENTRAL VENOUS CATHETER	0.5
PRIOR HISTORY OF STROKE	0.25
PRIOR HISTORY OF GASTROINTESTINAL BLEEDING	0.25
RECENT MYOCARDIAL INFARCTION	0.25
DIABETES MELLITUS TYPE 2	0.25

Recommendation:

If the calculated bleeding score is zero based on Kabir risk score calculator in any patients with COVID-19 or COVID-19 like symptoms, the author suggests starting high dose anticoagulation while titrating anticoagulation dose up or down based on D-Dimer trends (Table 2). However, the author suggests discussion of the risk benefit scenario with patient and family members prior to starting therapeutic anticoagulation among patients with intermediate to high-risk bleeding scores. The author found starting intermediate dose enoxaparin for select patients with high-risk scores is a better strategy than blanket therapeutic anticoagulation in terms of reducing mortality and morbidity related to bleeding associated with anticoagulation.

Table 2: COVID-19 treatment strategy based on Kabir bleeding risk scores.

RISK STRATIFICATION	RECOMMENDATION
LOW RISK (SCORE 0):	Consider starting high-dose anticoagulation for COVID-19 upon diagnosis. For outpatients, consider therapeutic dose DOAC's (i.e. Apixaban); For hospitalized patients consider Enoxaparin 0.5 mg/kg or 1 mg/kg dosing based on the initial level of D-Dimer and adjust dose based on D-Dimer trends.
INTERMEDIATE RISK (BLEEDING SCORE IN BETWEEN 0 - 2):	Consider starting intermediate-dose or high-dose anticoagulation for COVID-19 upon diagnosis. For outpatients, consider Apixaban 5mg PO BID (adjust based on age or eGFR). For hospitalized patients, consider Enoxaparin 0.5 mg/kg subQ BID and adjust the dose up or down based on D-Dimer trends.
HIGH RISK (BLEEDING SCORE > 2):	Consider starting low dose or intermediate-dose anticoagulation for COVID-19 upon diagnosis. For outpatients, consider low dose Apixaban 2.5 mg PO BID. For hospitalized patients, consider Enoxaparin low dose or intermediate dose (40 mg subQ daily or 0.5 mg/kg subQ BID) and adjust the dose up or down based on D-Dimer trends.

Conclusion:

Three clinical trials were terminated early due to the benefit of early initiation of therapeutic anticoagulation among patients with COVID-19. By creating statewide awareness about presenting to seek healthcare when patients are in an early stage of COVID-19, mortality and morbidity can be prevented using therapeutic anticoagulation. However, a reduced dose of therapeutic anticoagulation is suggested if Kabir risk score shows intermediate or high risk. In

such cases, anticoagulation dose can be treated based on trends of D-Dimers which will give an opportunity to further reduce bleeding risk among patients who are treated with anticoagulation.

Conflict of Interest: The author has no conflict of interest to disclose.

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