It has become increasingly clear that a large percentage of patients with COVID-19, particularly those that become critically ill, develop a prothrombotic state\(^1\)

**ALL COVID-19 positive and PUI patients should receive pharmacologic VTE prophylaxis unless contraindicated**

(e.g., PLT <25-30K, active bleeding, fibrinogen < 0.5 g/L)

- NIH COVID-19 Treatment Guidelines Panel
- WHO
- International Society for Thrombosis and Haemostasis
- American Society of Hematology
COVID-19 Thromboprophylaxis – INPATIENT MANAGEMENT UPDATE

STANDARD PROPHYLAXIS: D-dimer < 2000
- CrCl ≥ 30 ml/min: enoxaparin 40 mg subcutaneous daily
- CrCl < 30 ml/min: heparin 5000 units subcutaneous TID

INTERMEDIATE THROMBOPROPHYLAXIS: D-dimer ≥ 2000
- CrCl ≥ 30 ml/min: enoxaparin 0.5 mg/kg subcutaneous BID
- CrCl < 30 ml/min: heparin 7500 units subcutaneous TID

EMPIRIC TREATMENT DOSING ANTICOAGULATION: Consider for high suspicion of VTE
- In non-ICU level patients, there is not enough preliminary evidence to recommend for or against treatment dose anticoagulation for VTE prophylaxis
- In ICU level patients preliminary evidence suggests against use of empiric treatment anticoagulation for VTE prophylaxis outside of a high suspicion of VTE
  - full dose anticoagulation
    - CrCl ≥ 30 ml/min: enoxaparin 1 mg/kg subcutaneous BID
    - CrCl < 30 ml/min: heparin infusion
ABBREVIATED EVIDENCE TO DATE

• Because of the severity of coagulopathy in critically ill COVID-19 patients and reports of high rates of VTE despite routine prophylaxis, a more aggressive anticoagulation strategy using intermediate prophylaxis or therapeutic dosages of anticoagulation for prophylaxis continues to be studied.

• Several retrospective studies suggest that high-intensity prophylactic anticoagulation or therapeutic anticoagulation may be associated with lower mortality compared with standard VTE prophylaxis is severe COVID-19 patients.

• Elevated D-dimer levels is a common finding in patients with COVID-19. An elevated D-dimer on admission is associated with poor prognosis:
  - An elevated D-dimer does not currently warrant routine investigation for acute VTE in absence of clinical manifestations or other supporting information.
  - A retrospective review in China suggests that thromboprophylaxis therapy is associated with decreased mortality in severe COVID-19 patients with D-Dimer > 6x ULN.
  - In a retrospective review of 106 French COVID-19 positive patients who underwent a CT angiogram, 30% were positive for acute PE. This paper indicates a D-dimer positive predictive value of >2660.
ABBREVIATED EVIDENCE TO DATE

• There is still conflicting evidence regarding the best dosing strategy for VTE prophylaxis in hospitalized COVID-19 patients

  - A meta-analysis by the American Society of Hematology found no difference in risk of VTE and mortality between patients treated with prophylactic dose anticoagulation and those treated with higher doses of anticoagulation; critically ill patients who received intermediate- or therapeutic-dose anticoagulation had lower odds of PE (OR 0.09) but higher odds of major bleeding (OR 3.84)\textsuperscript{16}

  - The INSPIRATION RCT published in JAMA 3/2021 showed no difference in the composite endpoint of venous or arterial thrombosis, ECMO, or mortality within 30 days between standard & intermediate dose prophylaxis in patients in the ICU\textsuperscript{17}
    • VTE event rate was lower than presented in other literature
    • “Standard” prophylaxis was adjusted to enoxaparin 40mg BID for weight >120 kg or BMI > 35 kg/m\textsuperscript{2}

  - Results from the multicenter, adaptive platform trials (REMAP-CAP, ACIV-4, and ATTACC) comparing “usual care” versus therapeutic anticoagulation are still pending
    • Full dose anticoagulation in ICU patients was stopped for futility
    • Full dose anticoagulation in NON-ICU patients was stopped for superiority (organ support-free days)
COVID-19 patients are at increased risk of DVT/VTE. DVT prophylaxis is strongly recommended. D-Dimer is elevated in COVID-19 patients. D-Dimer can be utilized to guide thromboprophylaxis dosing.

- Chemoprophylaxis with enoxaparin is preferred if there are NO contraindications
  - If CrCl is < 30ml/min consider heparin
- Contraindications: PLTs < 30, patient already on therapeutic anticoagulation, or significant active bleeding.
- SCDs are acceptable when chemoprophylaxis is contraindicated, however they likely increase nursing care/exposures.

STANDARD prophylaxis: D-dimer less than 2000

INTERMEDIATE prophylaxis: D-dimer greater than or equal to 2000

EMPERIC TREATMENT: consider for high suspicion of VTE
- In non-ICU level patients, there is not enough preliminary evidence to recommend for or against treatment dose anticoagulation for VTE prophylaxis.
- In ICU level patients evidence suggests against use of empiric treatment anticoagulation for VTE prophylaxis outside of a high suspicion of VTE.

D-Dimer greater than or equal to 2000 consider ultrasound to rule out VTE

Extended post-hospitalization VTE prophylaxis should be considered on discharge in high risk patients.

High risk patients:
- patients with D-Dimer greater than or equal to 2000
- Immobility, or ICU level care during admission or prior VTE history, or hormone use, or BMI greater than 30, or history of cancer AND
- No/low bleeding risk (consider e HAS-BLED score)

Options: enoxaparin 40mg daily, rivaroxaban (Xarelto) 10mg daily, apixaban (Eliquis) 2.5mg BID

**Pharmacologic Prophylaxis**

- Standard VTE prophylaxis for D-dimer less than 2000
- Intermediate dosing VTE prophylaxis for D-dimer greater than or equal to 2000
- Empiric treatment
- VTE Prophylaxis is not indicated or contraindicated

Defaults to enoxaparin option when selected

Options to open either enoxaparin treatment or heparin infusion order sets when selected
COVID-19 Thromboprophylaxis - POST-HOSPITALIZATION MANAGEMENT

- Extended post-hospital VTE prophylaxis should be considered in high-risk patients.
  - While no data specific to COVID-19 exists, experience from the MAGELLAN\textsuperscript{11}, APEX\textsuperscript{12}, and MARINER\textsuperscript{13} studies suggest that in individuals who are at high risk, post-discharge thromboprophylaxis may be beneficial if bleeding risk can be minimized.

- High-risk patients:
  - D-dimer > 2000 AND
  - Immobility, ICU level care, prior VTE history, hormone use, BMI > 30, history of cancer AND
  - No bleeding risk or low bleeding risk (consider HAS-BLED score)

- Continue prophylactic anticoagulation for 2 weeks after symptom resolution AND able to get LE duplex U/S. U/S should be completed prior to discharge.

- Medication selection should be based on patient coverage
  - Enoxaparin (Lovenox) 40 mg subcutaneous daily
  - Rivaroxaban (Xarelto) 10 mg daily
  - Apixaban (Eliquis) 2.5 mg BID

- For prolonged post-ICU stay, clinical judgement of risk/benefit should be used when making the decision to continue prophylactic anticoagulation on discharge.
COVID-19 Thromboembolic treatment - POST-HOSPITALIZATION MANAGEMENT

- confirmed VTE (or unconfirmed and treating)
  - continue full dose anticoagulation for 3 months then reassess (unchanged process for a provoked DVT)
  - Medication selection based on patient coverage
    - Rivaroxaban (Xarelto) 15 mg BID for 21 days followed by 20 mg daily
    - Apixaban (Eliquis) 10 mg BID for 7 days followed by 5 mg BID
    - Enoxaparin (Lovenox) 1mg/kg subcutaneous BID (*not-preferred*)
REFERENCES

15. Should DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at intermediate-intensity or therapeutic-intensity vs prophylactic intensity be used for patients with COVID-19 related critical illness who do not have suspected or confirmed VTE. EID's and Guidelines (gradepro.org)