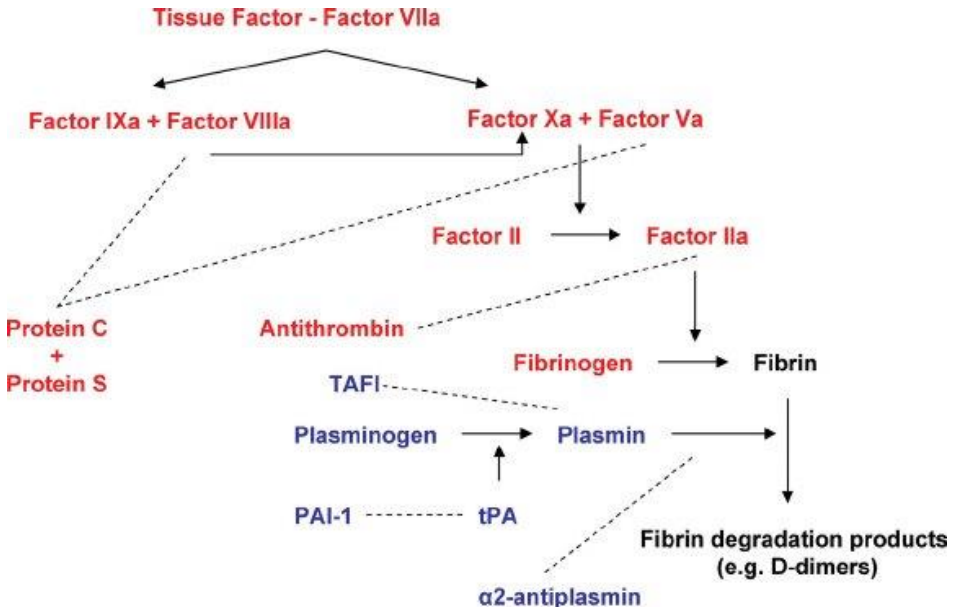
**ON DVT PROPHYLAXIS & D-DIMER IN COVID-19 PATIENTS**

*(Personal communication Dr Sucha Nand, Hematology LUMC, March 28, 2020)*

[[D-dimer: range normal values Hines: 0-0.50 ug/mL FEU (Fibrinogen Equivalent Units)]]

[[D-dimer conversion website: http://unitslab.com/node/83]]

1. D-dimer is an acute phase reactant and goes up in many clinical situations such as infection, trauma, etc. There are studies that use a certain level of positivity to look for DVT/PE, but it is not a well-accepted marker for thromboembolism
2. Patients with viral syndromes frequently develop thrombocytopenia, which may influence the decision to anticoagulated
3. With Covid19 infections Plasminogen Activator Inhibitor-**1** (**PAI-1**) levels could surge. This lowers endogenous TPA levels, causing microthrombi and then promoting both venous and arterial clots. This in fact not only could cause PE, but cardiovascular incidents and even acute renal failure. Interestingly NSAIDs and ACE inhibitors do the same which is possibly why these patient worsen with these agents. .. There is no reason to use ACEi in these patients given the availability of other agents. [See also Hunter M et al. **Is There a Role for Tissue Plasminogen Activator (tPA) as a Novel Treatment for Refractory COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS)?** Journal of Trauma and Acute Care Surgery (in press)]




*Coagulation and fibrinolysis pathways depicted in a simplified manner. Factors involved in coagulation (either stimulatory or inhibitory) are depicted in red; factors involved in fibrinolysis (either stimulatory or inhibitory) are depicted in blue. Black arrows = activation of a next step in the pathway. Dashed lines = inhibitory actions.*

*Upon tissue damage, TF binds Factor VII. The TF-Factor VII complex activates both Factor IX to Factor IXa and X to Xa. The Factor IXa-VIIIa complex also activates Factor X to Xa. The Factor Xa-Va complex activates Factor II to IIa (thrombin). Thrombin facilitates the conversion of fibrinogen into fibrin. Besides its important role in primary hemostasis, vWF binds Factor VIII and thereby decreases Factor VIII clearance. Factors that inhibit fibrin formation include antithrombin, protein C, and protein S. Antithrombin binds and inactivates thrombin and, to a lesser extent, inhibits TF-bound Factor VIIa and Factors Xa and IXa. Protein S is a cofactor to protein C. Activated protein C inactivates Factors Va and VIIIa. Fibrinolysis is initiated by tissue plasminogen activator (tPA), which stimulates the formation of plasmin out of plasminogen. Plasmin in turn dissolves the fibrin complex. Proteins that inhibit fibrinolysis*

*include PAI-1, TAFI, and α2-antiplasmin. PAI-1 inhibits tPA-induced plasmin formation. TAFI is a carboxypeptidase that inhibits fibrinolysis by reducing tPA and plasminogen binding to fibrin. α2-Antiplasmin inhibits plasmin-induced fibrin breakdown (R. van der Pas et al. J Clin Endocrinol Metab, 2012;97:1303-10)*

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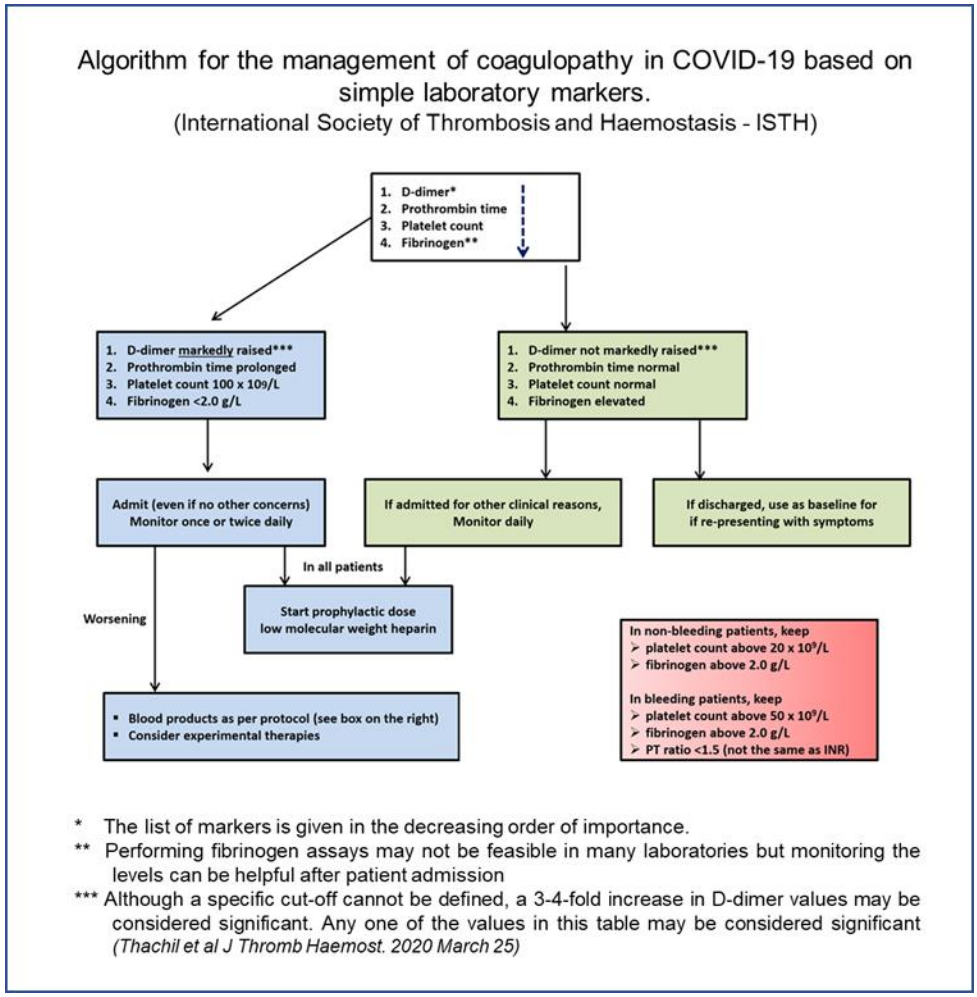
**ISTH interim guidance on recognition and management of coagulopathy in COVID-19**
***(Thachil et al J Thromb Haemost. 2020 March 25. [Epub ahead of print])***

On March 25, 2020, the International Society of Thrombosis and Haemostasis (ISTH) published a "pragmatic statement … to provide a risk stratification at admission for a COVID-19 patient and management of coagulopathy … based on easily available laboratory parameters" *(Thachil et al J Thromb Haemost. 2020 March 25. [Epub ahead of print])*. ISTH recognizes that this is only "an interim guidance … [and that] … this statement will be modified with developing knowledge and therapeutics in managing COVID-19." They recommend measuring "D-dimers, prothrombin time and platelet count (decreasing order of importance) in all patients who present with COVID-19 infection … Any underlying condition (e.g., liver disease) or medication (e.g., anticoagulants) which may alter the parameters should be accounted for while using the algorithm. Low molecular weight heparin (LMWH) should be considered in ALL patients (including non-critically ill) who require hospital admission for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count less than 25 x $10^9$/L; monitoring advised in severe renal impairment; abnormal PT or APTT is not a contraindication)*(Thachil et al J Thromb Haemost. 2020 March 25. [Epub ahead of print]).*

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**Findings of acute pulmonary embolism in COVID-19 patients**
*(Chen et al. Lancet ID 2020 [*https://ssrn.com/abstract=3548771*])*

Retrospective analysis of 25 patients with COVID-19 who had undergone CTPA scans for suspected PE "and other clinical concerns". In the 10 patients with acute PE the median D-dimer level was 11.07 ug/ml (IQR, 7.12-21.66). In the 15 patients without PE the median D-dimer level was 2.44 ug/ml (IQR, 1.68-8.34) ($p< 0.05$). Besides D-dimer levels, there was no difference between PE positive and PE negative patients in terms of $PaCO_2$, $PaO_2$ and $SO_2$. Twenty patients were treated with anticoagulant therapy (LMWH, 0.6mg/kg bid) regardless to the findings of acute PE in CTPA and underwent a follow-up D-dimer test afterwards. D-dimer levels decreased in all patients.

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**Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy**
(Tang N et al. J Thromb Haemost. 2020 March 27. [https://doi.org/10.1111/jth.14817])

**Aim:** To validate the usefulness of "sepsis-induced coagulopathy" (SIC) score and other coagulation parameters (admission PT and D-dimer), in patients with severe COVID-19 – i.e., patients meeting any of the following: respiratory rate ≥30 breaths /min; $SpO_2$≤93% at rest; $PaO_2/FiO_2$ ≤300 mmHg.)

**Design:** Retrospective study of 449 patients of whom 99 received heparin for ≥7 days: 94 patients received LMWH (40-60 mg enoxaparin/day) and 5 patients received UFH (10000-15000 U/day).(The large number of patients not receiving heparin was "due to lack of understanding of this disease, and increasingly used later during this outbreak of COVID-19")

**SIC:** Scoring for the diagnosis of sepsis-induced coagulopathy

| Item | Range | Score |
|---|---|---|
| Platelet count ($x10^9$/L) | ≥150 | 0 |
| | 100-150 | 1 |
| | <100 | 2 |
| | | |
| INR | ≤1.2 | 0 |
| | 1.2-1.4 | 1 |
| | >1.4 | 2 |
| | | |
| SOFA (four items) | 0 | 0 |
| | 1 | 1 |
| | ≥2 | 2 |
| | | |

Diagnosed as sepsis-induced coagulopathy when the total SIC score is ≥4 with PT score **and** platelet score > 2.
Total SOFA is the sum the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, renal SOFA). The score of total SOFA is defined as 2 if the total score exceeded 2.

**Results:** 28-day mortality was positively correlated with D-dimer, PT and age and negatively correlated with platelet count. No difference on 28-day mortality was found between heparin users and nonusers (30.3% vs 29.7%, P=0.910). 28-day mortality of heparin users was lower than nonusers in patients with SIC score ≥4 (40.0% vs 64.2%, P=0.029), or D-dimer > 6-fold of upper limit of normal (32.8% vs 52.4%, P=0.017).

**Conclusions:** Anticoagulant therapy mainly with LMWH appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer.

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**Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia**

*(Cui S et al. J Thromb Haemost April 9, 2020; **https://doi.org/10.1111/jth.14830**)*

**Objectives:** To determine the incidence of VTE in patients with severe COVID-19 pneumonia.

**Methods/Results:** 81 ICU patients with severe COVID-19. Of these 20 (25%) developed VTE. Eight patients with VTE events died. Compared to non-VTE patients, VTE patients were older, had lower lymphocytes counts and higher aPTT and D-dimer levels. D-dimer concentrations above 1.5 μg/mL had high sensitivity (85.0%), specificity (88.5%) and negative predictive value (94.7%) to predict VTE. (In the study, the normal range of D-dimer was 0.0-0.5 μg/mL). After receiving anticoagulant therapy, the level of D-dimer decreased gradually. (Whether D-dimer can monitor the effectiveness of anticoagulants remains to be determined).

**Conclusions:** The incidence of VTE in patients with severe COVID-19 pneumonia is 25% and may be related to poor prognosis. The significant increase of D-dimer in severe COVID-19 pneumonia patients is a good index for identifying high-risk groups of VTE.

**Limitations**: It is unclear what prompted physicians to obtain CTPE and/or lower limb venous dopplers (i.e., screening tests? test obtained according to clinical suspicion?). Retrospective, single-center, small sample study. At the time of publication some patients were still hospitalized, accordingly, their clinical outcome may change.

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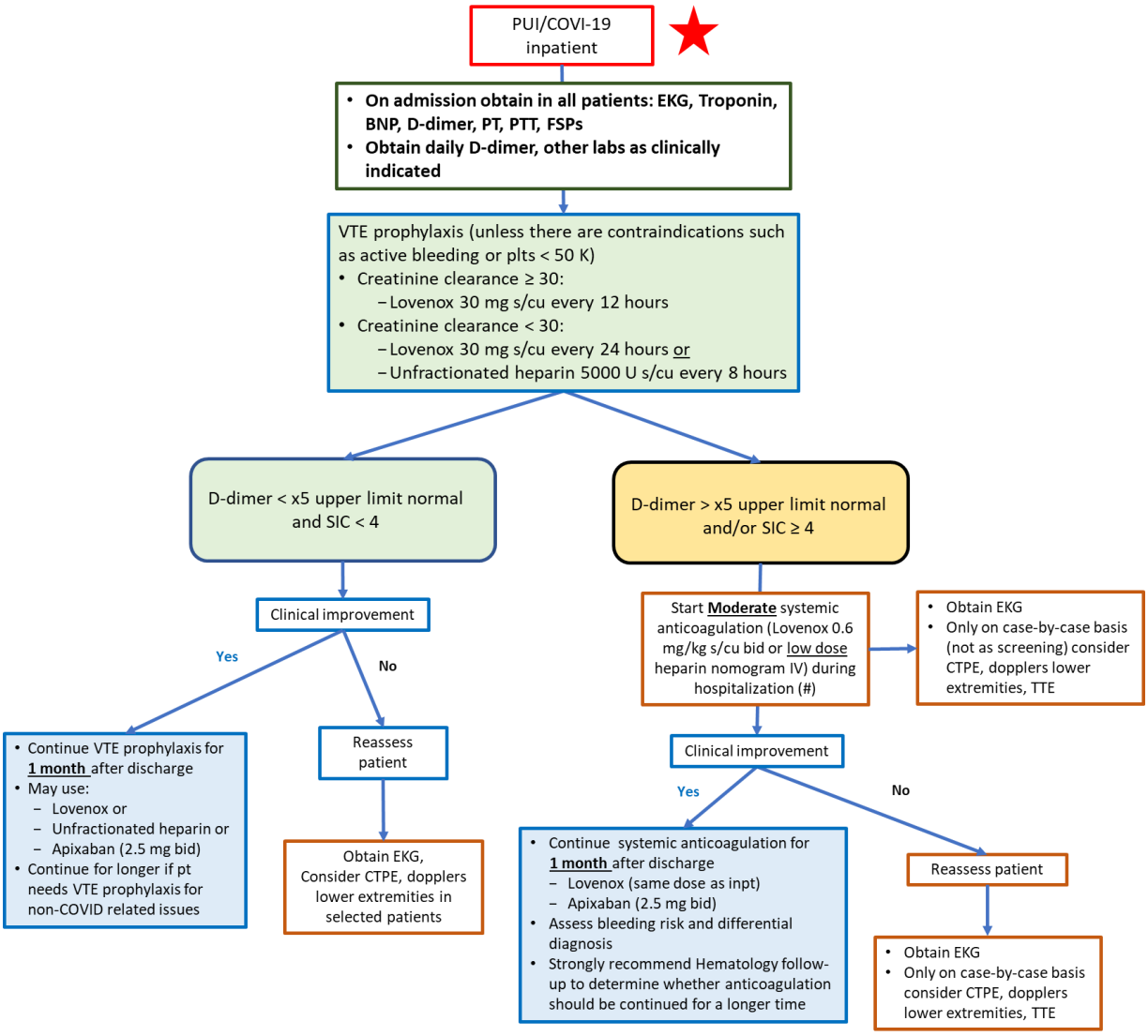
**In summary consider the following:**

- Prophylactic LMWH is recommended for all hospitalized patients in the absence of any contraindications.
- Daily monitoring of coagulation/DIC parameters might be helpful in hospitalized patients, especially in ICU patients.
- For VTE recognition, have a low threshold for ultrasound screening for DVT. (As per other centers doing a CT PE has led to a high incidence of acute renal failure or renal insufficiency exacerbations and could be the precursor to a fatal complication, far worse than prophylactic or even therapeutic anticoagulation (Dr Patrick Stiff; *personal communication 3-28-20*).
- High D Dimer is associated with increased mortality.

# PROPOSED VTE PROPHYLAXIS & TREATMENT IN COVID-19 PATIENTS (April 15, 2020 v4)




★ In COVID-19/PUI patients with documented acute VTE start conventional therapy for acute VTE (same strategies used for non-COVID-19 patients)

**SIC:** Scoring for the diagnosis of sepsis-induced coagulopathy

| Item | Range | Score |
|---|---|---|
| Platelet count ($x10^9/L$) | ≥150 | 0 |
| | 100-150 | 1 |
| | <100 | 2 |
| INR | ≤1.2 | 0 |
| | 1.2-1.4 | 1 |
| | >1.4 | 2 |
| SOFA (four items) | 0 | 0 |
| | 1 | 1 |
| | ≥2 | 2 |

Diagnosed as sepsis-induced coagulopathy when the total SIC score is ≥4 with PT score **and** platelet score > 2.
Total SOFA is the sum the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, renal SOFA). The score of total SOFA is defined as 2 if the total score exceeded 2.

*SIC: sepsis-induced coagulopathy*

*(#) Consider Hematology consultation in pts with BMI > 39, pts with history of HIT, requiring dialysis, and whenever systemic anticoagulation is initiated particularly in patients with thrombocytopenia, liver function abnormalities, DIC, vitamin K deficiency*

*Flow chart based on conversations with University of Milan, University of Genoa, Thachil et al (J Thromb Haemost. 2020 March 25, in press), Tang (J Thromb Haemost. 2020 https://doi.org/10.1111/jth.14817), Chen (Lancet ID 2020 [https://ssrn.com/abstract=3548771]), and suggestions by Dr Sucha Nand, Dr Patrick Stiff, Dr Daulath Singh, Dr Patrick Hagen , Dr Kathleen Phelan – Hem Hines / LUMC)*

**ADDITIONAL CONSIDERATIONS FOR INPATIENT VTE PROPHYLAXIS BASED ON BMI**

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Unless there are contraindications to anticoagulation therapy (e.g., active bleeding, subdural hematoma, DIC, PLT < 50 K)

>>> If d-dimer < x 5 upper limit of normal, recommend:

If Creat Clearance > 30 mL/min/1.73m2:

BMI up to 39: Enoxaparin 30 mg SC every 12 hrs
BMI >39: Enoxaparin 40 mg SC every 12 hrs

If Creat clearance < 30 mL/min/1.73m2:

Unfractionated heparin 5,000 units SC q8hrs

or

BMI up to 39: Enoxaparin 30 mg SC every 24 hrs
BMI >39: Enoxaparin 40 mg SC every 24 hrs

Consider hematology consult if concerned with dosing or patient has history of HIT or requires dialysis.

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>>> If d-dimer > x 5 upper limit of normal, recommend:

If Creat clearance > 30 mL/min/1.73m2:

BMI up to 39: Enoxaparin 0.6 mg/kg SC every 12 hrs
BMI >39: Enoxaparin 0.45 mg/kg SC every 12 hrs (modified from UpToDate bariatric surgery VTE prophylaxis)

If Creat clearance < 30 mL/min/1.73m2:

Low dose Unfractionated Heparin Infusion Nomogram

or

BMI up to 39: Enoxaparin 0.6 mg/kg SC every 24 hrs
BMI >39: Enoxaparin 0.45 mg/kg SC every 24 hrs (modified from UpToDate bariatric surgery VTE prophylaxis)

Consider hematology consult if concerned with dosing or patient has history of HIT or requires dialysis.

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>>> If patient has documented acute VTE proceed with conventional therapy for acute VTE (same strategies used for non-COVID-19 patients)

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## VTE PROPHYLAXIS/TREATMENT AT HOSPITAL DISCHARGE

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**Group #1 (d-dimer <u>never</u> > x5 upper limit of normal while hospitalized) (treat for 1 month post discharge)**

- Creatinine clearance ≥ 30:
  - **Lovenox 30 mg s/cu every 12 hours
  - **Apixaban 2.5 mg every 12 hours
- Creatinine clearance <30:
  - **Lovenox 30 mg s/cu every 24 hours or
  - **Unfractionated heparin 5000 U s/cu every 8 hours
  - ** Apixaban 2.5 mg every 12 hours (for dialysis pts contact Pharmacy for dosing)

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**Group #2 (d-dimer > x5 upper limit of normal while hospitalized but no VTE) (treat for 1 month post discharge)**

- Creatinine clearance ≥ 30:
  - **Lovenox 0.6 mg/kg s/cu every 12 hours
  - **Apixaban 2.5 mg every 12 hours
- Creatinine clearance < 30:
  - **Lovenox 0.6 mg/kg s/cu every 24 hours
  - **Apixaban 2.5 mg every 12 hours (for dialysis pts contact Pharmacy for dosing)

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**Group #3 (documented VTE while hospitalized) (duration of treatment as clinically indicated)**

- Contact inpatient anticoagulation team before discharge
- Creatinine clearance ≥ 30:
  - **Lovenox 1 mg/kg s/cu every 12 hours
  - **Apixaban 5 mg every 12 hours
- Creatinine clearance < 30:
  - **Lovenox 1 mg/kg s/cu every 24 hours
  - **Apixaban 5 mg every 12 hours (for dialysis pts contact Pharmacy for dosing)