Penn Medicine recommendations for prophylactic/therapeutic anticoagulation in inpatients with COVID-19

10/26/2021 Update:

1. **<u>Intermediate-intensity prophylaxis</u> continues to be no longer routinely recommended in ICU or sick floor patients based on the results of the INSPIRATION trial (Sadeghipour et al., JAMA 2021).**

2. **Standard intensity prophylaxis is recommended in both ICU and floor patients <u>without</u> suspected or confirmed VTE, <u>but empiric therapeutic anticoagulation with enoxaparin or unfractionated heparin can be considered in high-thrombotic-risk and/or low-bleeding-risk floor patients on a case-by-case basis</u>.** Data from several RCT's comparing standard intensity with therapeutic intensity anticoagulation in floor and ICU patients have either been published or released prior to peer review.

    a. **<u>ACTION trial</u> (only published trial of Factor Xa inhibitors):** Therapeutic anticoagulation (mostly rivaroxaban 20mg daily both in-hospital and for 30 days post-discharge) vs. standard prophylaxis (enoxaparin) in a predominantly non-ICU population: no clear benefits were shown, with a non-significant reduction in venous thromboembolism offset by non-significant increases in mortality and major bleeding and a significant increase in clinically relevant non-major bleeding.
        - <u>Results:</u>

Population	Outcomes (therapeutic versus standard intensity AC)

<u>Population (n = 614)</u>
• 576 (93.8%) "clinically stable"
• 39 (6.2%) "clinically unstable"
	- Primary: Composite of time to death, duration of hospitalization, and duration of supplemental oxygen use through 30 days
	  ○ 34.8% win rate vs. 41.3% win rate [win ratio 0.86 (95% CI: 0.59-1.22)]
	- Composite thrombotic outcome (VTE, MI, CVA, systemic embolism, or major adverse limb event)
	  ○ 7% vs. 10% [RR 0.75 (95% CI: 0.45-1.26)]
	- Venous thromboembolism (VTE)
	  ○ 4% vs. 6% [RR 0.60 (95% CI: 0.29-1.25)]
	- Composite thrombotic outcome or death
	  ○ 15% vs. 14% [RR 1.03 (95% CI: 0.70-1.50)]
	- Death
	  ○ 11% vs. 8% [RR 1.49 (95% CI: 0.90-2.46)]
	- Major bleeding or clinically relevant non-major bleeding
	  ○ 8% vs. 2% [RR 3.64 (95% CI: 1.61-8.27)]
	- Major bleeding
	  ○ 3% vs. 1% [RR 2.45 (95% CI: 0.78-7.73)]
	- Clinically relevant non-major bleeding
	  ○ 5% vs. 1% [RR 5.23 (95% CI: 1.54-17.77)]

Therapeutic AC with riva ineffective

    b. **<u>ACTIV-4a, ATTACC, & REMAP-CAP (aka, Multi-platform Trial) Randomized Controlled Trials</u>: (The ATTACC, ACTIV-4a, and REMAP-CAP Investigators, N Engl J Med. 2021;385(9):777-789 and N Engl J Med 2021; 385(9):790-802):** Therapeutic anticoagulation (mostly enoxaparin) vs. standard prophylaxis in two arms: ICU and non-ICU (moderate illness).
        - <u>Results:</u>

Population	Outcomes (therapeutic versus standard intensity AC)
ICU Patients (n = 1074) Definition: (any of the following) - High flow nasal oxygen - Non-invasive/invasive mechanical ventilation - Vasoactive support	- Primary: No significant improvement in organ support free days (OSFD) ○ Subpopulation analysis indicated significant worsening in OSFDs in patients not on mechanical ventilation at enrollment - No difference in survival - No significant increase in major bleeding: 3.1 % vs 2.4 % (NS) - Trend toward reduced thrombosis: 5.7% vs 10.3%, (p value not reported)
Non-ICU Patients* (n = 2231) *Definition: (≤ 6 L Nasal Cannula)	- Primary: Significant improvement in OSFDs - Significant improvement in survival without organ support: 79.3% vs 75.4% - Significant improvement in survival without thrombosis: 92.0% vs 90.1% - No difference in survival: 92.7% vs 91.8% - No difference in survival without mech. resp. support: 84.2% vs 82.3% - No difference in survival without intubation: 89.1% vs. 87.9% - Major Bleeding: 1.9% vs 0.9%, (OR 1.80, 95% CI: 0.90-3.74) - Major Thrombosis: 1.1 % vs 2.1%, (p value not reported)


Therapeutic Anticoagulation in C


Therapeutic Anticoagulation in I

c. **HEP-COVID Randomized Clinical Trial):** Therapeutic anticoagulation (mostly enoxaparin) vs. standard or intermediate prophylaxis in a mix of ICU and non-ICU (moderate illness) patients. VTE included DVT found by surveillance dopplers.
   - Results:

Population	Outcomes (therapeutic versus standard intensity AC)

Overall population (n = 253)
- 83 (32.8%) ICU patients
- 170 (67.2%) non-ICU patients
	- Primary efficacy outcome (venous/arterial thromboembolism or death):
	  ○ 28.7% vs. 41.9% [RR 0.68 (95% CI: 0.49-0.96)] – significant improvement
	- VTE/ATE
	  ○ 10.9% vs. 29.0% [RR 0.37 (95% CI: 0.21-0.66)] – significant improvement
	- Death
	  ○ 19.4% vs. 25.0% [RR 0.78 (95% CI: 0.49-1.23)]
	- Major bleeding
	  ○ 4.7% vs. 1.6% [RR 2.88 (95% CI: 0.59-14.02)]

ICU population (n = 83)	- Primary efficacy outcome (venous/arterial thromboembolism or death):
	  ○ 51.1% vs.55.3% [RR 0.92 (95% CI: 0.62-1.39)]
	- VTE
	  ○ 11.1% vs. 15.79% [significance not reported]
	- Death
	  ○ 35.6% vs. 39.5% [significance not reported]
	- Major bleeding
	  ○ 8.9% vs. 0.0% [RR 7.62 (95% CI: 0.42-137.03)]

Non-ICU population (n = 170)	- Primary efficacy outcome (venous/arterial thromboembolism or death):
	  ○ 16.7% vs. 36.1% [RR 0.46 (95% CI: 0.27-0.81)] – significant improvement
	- VTE
	  ○ 3.6% vs. 23.3% [signif. not reported, but signif. in per protocol analysis]

	- Death
	  ○ 10.7% vs. 18.6% [significance not reported]
	- Major bleeding
	  ○ 2.4% vs. 2.3% [RR 1.02 (95% CI: 0.15-7.10)]

Therapeutic heparin vs prophyla

d. **RAPID Trial Investigators:** Therapeutic anticoagulation (mostly enoxaparin) vs. standard prophylaxis in a non-ICU (moderate illness) population.

- Results:

Population	Outcomes (therapeutic versus standard intensity AC)

Overall population (n = 465)	- Primary outcome (composite of ICU admission, non-invasive or invasive mechanical ventilation, or death up to 28 days):
	  ○ 16.2% vs. 21.9% [OR 0.69 (95% CI: 0.43-1.10)]
	- All-cause mortality
	  ○ 1.8% vs. 7.6% [OR 0.22 (95% CI: 0.07-0.65)] – significant improvement
	- Invasive mechanical ventilation
	  ○ 4.8% vs. 6.8% [RR 0.70 (95% CI: 0.32-1.55)]
	- Any mechanical ventilation
	  ○ 9.2% vs. 11.0% [RR 0.82 (95% CI: 0.45-1.51)]
	- ICU admission
	  ○ 14.5% vs. 17.7% [RR 0.79 (95% CI: 0.48-1.29)]
	- Death or any mechanical ventilation
	  ○ 10.1% vs. 16.0% [RR 0.59 (95% CI: 0.34-1.02)]
	- Death or ICU admission
	  ○ 15.8% vs. 21.1% [RR 0.70 (95% CI: 0.44-1.13)]
	- Venous thromboembolism
	  ○ 0.9% vs. 2.5% [RR 0.34 (95% CI: 0.07-1.71)]
	- Major bleeding
	  ○ 0.9% vs. 1.7% [RR 0.52 (95% CI: 0.09-2.85)]

Heparin for Moderately Ill Patien

- Summary data:

Outcomes with therapeutic AC in floor COVID-19 patients (statistically significant)	Mortality	Mechanical Ventilation	Organ Support Free Days	ICU admission	VTE	Major bleeding
ACTION (riva)	No diff.	NR	NR	NR	No diff.	No diff.
Multiplatform	No diff.	No diff.	**Improved**	No diff.	NR	No diff.
HEP-COVID	No diff.	No diff.	NR	No diff.	**Improved**	No diff.
RAPID	**Improved**	No diff.	NR	No diff.	No diff.	No diff.

- Conclusions:

- ICU patients did not derive any significant benefit from intermediate-intensity anticoagulant prophylaxis (1 study) or therapeutic-intensity anticoagulation (2 studies) compared with lower-intensity prophylaxis
- Therapeutic doses of DOACs have demonstrated only a non-significant reduction in venous thromboembolism which was offset by non-significant increases in mortality and major bleeding and a significant increase in clinically relevant non-major bleeding in 1 study of mostly non-ICU patients
- Non-ICU patients have received therapeutic enoxaparin/heparin in 3 trials. These trials have shown inconsistent results:
    - The largest study (a multiplatform trial consisting of 3 sub-trials) found significant improvements in organ-support free days and combined endpoints of either survival without organ support or survival without thrombosis. The absolute risk reduction (ARR) in major thrombosis was similar (1%) to the absolute risk increase (ARI) in major bleeding (1%).
    - Two other smaller trials (HEP-COVID published, RAPID pre-published) showed more significant improvements in outcomes.
        - HEP-COVID, in its non-ICU cohort, showed a significant improvement in the combined endpoint of VTE/ATE/death (19.4% ARR) that was driven largely by reductions in VTE (19.7% ARR) though there was a trend to lower mortality as well.
        - RAPID, conversely, found a significant reduction in mortality (5.8% ARR) without demonstrating a significant improvement in VTE nor the composite outcome of ICU admission, non-invasive or invasive mechanical ventilation, or death.
    - The American Society of Hematology has released revised recommendations in October 2021, based upon most of this data excluding HEP-COVID, which reads as follows:
        - **The ASH guideline panel *suggests* using prophylactic-intensity over therapeutic-intensity anticoagulation in patients with COVID-19 related acute illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects).**
    - **<u>Our recommendations, based upon the inconsistent findings among studies, are also to continue to use prophylaxis-intensity anticoagulation for most floor COVID-19 patients, although clinicians can choose to use therapeutic-intensity given only during the course of the hospital stay if they feel their patient is at higher risk for thrombosis and/or lower risk for bleeding; ideally, this risk-benefit analysis should be conducted via shared decision making with their patient.</u>**

I. Pharmacologic prophylaxis/treatment recommendations for inpatients with COVID-19

Table 1. Suggestions for pharmacologic prophylaxis/treatment in hospitalized COVID-19 patients.

Population (location)		Bleeding risk[1]	Recommended pharmacologic prophylaxis/treatment (see Table 2)
Suspected or proven VTE (ICU or medical floor)		Low	Therapeutic-intensity
		High	Unfractionated heparin (UFH) infusion – goal aPTT 60-85 seconds
VTE not suspected	Medical floor	Low	Standard-intensity (or therapeutic-intensity – see below*)
		High	Consider standard-intensity
	Critically ill (ICU)	Low	Standard-intensity (intermediate- and therapeutic-intensity no longer recommended)
		High	Standard-intensity (intermediate-intensity no longer recommended)

* Given inconsistent data from various trials of therapeutic anticoagulation in COVID-19 floor patients, we favor standard-intensity for most floor patients with COVID-19 infection who do not have diagnosed VTE. However, clinicians, optimally in discussion with their patients, can consider therapeutic anticoagulation given only during the course of the hospital stay in patients who they judge to be at lower risk of bleeding and/or higher risk of thrombosis.

- These suggestions are intended to provide guidance to clinicians. They are not intended to substitute for clinical judgment. All decisions require weighing an individual patient's bleeding and thrombotic risk. These revisions reflect incorporating thrombotic risk in critically ill patients from recently published studies and an assessment of events at the 5 Penn Medicine hospitals that revealed an increase in major bleeding in ICU patients receiving therapeutic anticoagulation. We strongly recommend confirmatory testing in any patients with suspected but not confirmed venous thromboembolism (VTE); we also no longer recommend empiric escalation to therapeutic anticoagulation without clinical suspicion of VTE. Combination pharmacologic and mechanical prophylaxis can be considered in select high-VTE-risk ICU patients.
- Any patients undergoing epidural/spinal anesthesia should receive UFH 5000 Q12H or Q8H as thromboprophylaxis. If these patients require therapeutic-intensity dosing, discuss choice of agent with Anesthesia.

1. No validated criteria exist for defining bleeding risk in the above table. Consider bleeding history, clinical exam, platelet count, PT/aPTT, age>65. In general, pharmacologic prophylaxis and treatment should be withheld in patients with active or very recent (within the last 24-48 hours) bleeding.

Table 2. Recommended regimens for pharmacologic prophylaxis/treatment (round enoxaparin to nearest syringe size)

Prophylaxis/treatment intensity	Creatinine Clearance (CrCl) ≥ 30 mL/min	15 ≤ CrCl < 30	CrCl < 15 mL/min OR on renal replacement therapy
Standard-intensity	Enoxaparin 40mg Q24H	Enoxaparin 30mg Q24H OR UFH 5000 Q12H to Q8H	UFH 5000 Q12H to Q8H
Intermediate-intensity	Enoxaparin 0.5 mg/kg Q12H	UFH 7500 Q8H	UFH 7500 Q8H
Therapeutic-intensity	Enoxaparin 1 mg/kg Q12H	Enoxaparin 1 mg/kg Q24H OR UFH infusion – goal aPTT 60-85 seconds	UFH infusion – goal aPTT 60-85 seconds

II. Management of inpatients with COVID-19 who were previously on anticoagulation

Patients admitted on therapeutic anticoagulation:

- Warfarin: continue warfarin if they are not being admitted to an ICU and are not undergoing any procedures
- Direct oral anticoagulants (DOACs), if CrCl ≥ 30 mL/min: change to enoxaparin 1mg/kg every 12 hours, due to frequent need for ICU, with no upper weight limit to enoxaparin use (can resume DOAC once stable for discharge)

III. Post-discharge recommendations for inpatients with COVID-19

Post-discharge considerations:

- **Indication for therapeutic anticoagulation:** continue anticoagulation as per usual recommendations.
- **Received therapeutic anticoagulation for suspected but not confirmed VTE:** complete a 90-day course of anticoagulation for presumed VTE if bleeding risk permits.
- **Received <u>any intensity of prophylaxis</u>:**
    - **We advise <u>against</u> routine use of post-discharge prophylactic anticoagulation**
    - **Post-discharge prophylaxis (for 30 days of prophylactic anticoagulation starting on the day of discharge) may be considered in patients who have been judged to have the following:**
        - **A low bleeding risk <u>AND</u>**
        - **CrCl ≥ 30 mL/min <u>AND</u>**
        - **COVID-19-related symptoms that led to hospital admission with a LOS≥3 days <u>AND</u>**
        - **Significant risk factors for VTE [e.g., IMPROVE VTE Risk Score ≥ 4 – see page 4; OR risk factors like previous VTE, recent major surgery or trauma)**
    - Options include:
        - Rivaroxaban 10mg daily (Cohen AT, et al. NEJM 2013; Spyropoulos AC, et al. NEJM 2018)
        - Enoxaparin 40mg daily (Hull RD, et al. NEJM 2010) – **<u>only FDA-approved as in-hospital prophylaxis</u>**
        - A post-hoc retrospective analysis of the initial rivaroxaban trial (Spyropoulos AC, Clin Appl Thromb Hemost 2019) identified five bleeding risk factors that, had patients with those characteristics been excluded, would have reduced the 35-day major bleeding rate with rivaroxaban from 1.1% to 0.7%
            - Bleeding risk factors:
                - Active cancer
                - Dual antiplatelet therapy
                - History of bronchiectasis/pulmonary cavitation
                - Active gastroduodenal ulcer
                - Any bleeding in the previous 3 months

VTE prophylaxis/treatment recommendations during a hospitalization (prior to discharge)

- D-dimer levels should not be used to influence use of therapeutic anticoagulation in the absence of clinical suspicion for acute arterial or venous thromboembolism
- VTE rates in COVID-19 ICU patients (despite VTE prophylaxis) vary by study, and some studies have identified significant risk of major bleeding in COVID-19 ICU patients:

Study	Patients	Therapeutic AC	VTE rate	Arterial thrombosis	Major Bleeding
Klok (Neth.) Thromb Res 2020	184	9.2%	37% (87% PE)	3.8%	
Helms (France) Intensive Care Med 2020	150	30%	19% (89% PE)	1%	
Lodigiani (Italy) Thromb Res 2020	48	3%	17% (25% PE)	16.6%	
Poissy (France) Circulation 2020	107	Not reported	25% (81% PE)	Not reported	
Middledorp (Neth.) J Thromb Haemost 2020	75	9.3%	28% (52% PE)	Not reported	
Al Samkari (Boston) Blood 2020	144	12.5%	10.4% (7.6% confirmed)	1.4%	5.6%
Maatman (Indianapolis) Crit Care Med 2020	109	6%	28% (16% PE)	5.6%	
Hippensteel (Denver) Br J Haematol 2020	91	32%	26% (21% PE)	Not reported	
Bilaloglu (NYC) JAMA 2020	829	Not reported	13.6% (46% PE)	18.6%	
Penn Medicine data (Unpublished)	443	29.7%	7.6% (53% PE)	4.2%	14.7%
Nopp (meta-analysis) Res Pract Thromb Haemost 2020	2791	Not reported	18.7% (excl. surveillance)	NR	NR

- Laboratory studies of COVID-19 inpatients have consistently demonstrated a profile favoring hypercoagulability: extremely elevated D-dimer, relatively preserved PT/aPTT, elevated fibrinogen, and normal platelets (Zhou F, et al. Lancet 2020).
- **In view of these studies, VTE prophylaxis at minimally standard-intensity is recommended for all non-bleeding inpatients with COVID-19**

Recommendations for intensive care unit (ICU) patients (see "Choice of therapeutic anticoagulation" and "Choice of pharmacologic prophylaxis" sections below for specific medication recommendations):

- In ICU patients at low risk for bleeding, we recommend use of **standard-intensity VTE prophylaxis [therapeutic-intensity and intermediate-intensity no longer recommended given bleeding rates described in COVID-19 ICU patients and negative results from the multi-platform trial (ACTIV-4/ATTACC/REMAP-CAP) and INSPIRATION trials]**
- In ICU patients at high risk for bleeding, we recommend:
    - Use of **intermittent pneumatic compression for all patients PLUS**
    - Strong consideration of use of **standard-intensity pharmacologic prophylaxis as well (intermediate-intensity no longer recommended given bleeding rates described in COVID-19 ICU patients)**
        - Pharmacologic prophylaxis should be withheld if patient is actively bleeding, but should be restarted within 24-48 hours of cessation of bleeding

Recommendations for medical floor patients (see "Choice of therapeutic anticoagulation" and "Choice of pharmacologic prophylaxis" sections below for specific medication recommendations):

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- Medical floor patients at low risk for bleeding should receive **standard-intensity pharmacologic prophylaxis. Preliminary data (unpublished) from two large multi-center randomized trials have been released showing either no benefit (ACTION trial) or possible but uncertain benefit (the multi-platform trial: ACTIV-4/ATTACC/REMAP-CAP) with therapeutic-intensity anticoagulation.**
- Medical floor patients at high risk for bleeding should receive
    - Use of **intermittent pneumatic compression for all patients PLUS**
    - Consideration of use of **standard-intensity pharmacologic prophylaxis**
        - Pharmacologic prophylaxis should be withheld if patient is actively bleeding, but should be restarted within 24-48 hours of cessation of bleeding

Post-discharge VTE prophylaxis/treatment recommendations

- Patient who received prophylactic anticoagulation (regardless of intensity) during hospital stay:
    - **We advise against routine use of post-discharge prophylactic anticoagulation**
    - **More recent data (Roberts L, et al., Blood 2020; Patell R, et al. Blood 2020) have revealed a post-discharge COVID-19-associated VTE rate of only 0.4-0.6% in patients who were largely discharged off of VTE prophylaxis, which is not dissimilar from other medical populations**
    - **Post-discharge prophylaxis (for 30 days of prophylactic anticoagulation starting on the day of discharge) may be considered in patients who have been judged to have the following:**
        - **A low bleeding risk AND**
        - **CrCl ≥ 30 mL/min AND**
        - **COVID-19-related symptoms that led to hospital admission with a LOS≥3 days AND**
        - **Significant risk factors for VTE [e.g., IMPROVE VTE Risk Score ≥ 4; OR risk factors like previous VTE, recent major surgery or trauma)**
            - **IMPROVE VTE Risk Score:**
                - **Previous VTE – 3**
                - **Known thrombophilia – 2**
                - **Current lower limb paralysis – 2**
                - **Current cancer – 2**
                - **Immobilized ≥ 7 days – 1**
                - **ICU/CCU stay – 1**
                - **Age > 60 years – 1**
        - Options include (betrixaban has been withdrawn from the US market):
            - Rivaroxaban 10mg daily (Cohen AT, et al. NEJM 2013; Spyropoulos AC, et al. NEJM 2018)
            - Enoxaparin 40mg daily (Hull RD, et al. NEJM 2010) – **only FDA-approved as in-hospital prophylaxis**
        - Consider consulting a pharmacist to ensure there are no major drug-drug interactions prior to prescribing post-discharge VTE prophylaxis
        - FDA-approved duration for rivaroxaban is 31-39 days inclusive of hospital stay. Additionally, Spyropoulos AC, et al. NEJM 2018, found a reduction in symptomatic VTE without increased major bleeding in patients treated with rivaroxaban for 45 days (beginning at discharge) following hospitalization.
        - There are no established regimens of intermediate-intensity prophylaxis with DOACs so patients who received intermediate-intensity prophylaxis during their stay should generally transition to standard-intensity prophylaxis at discharge.
        - Enoxaparin is only FDA-approved as in-hospital VTE prophylaxis but use of post-discharge enoxaparin prophylaxis has been studied in medical patients and has been associated with reduced rates of symptomatic VTE which was somewhat offset by increased major bleeding.

    - Patients who received therapeutic-intensity anticoagulation during hospital stay

- Patients who were on anticoagulation prior to hospitalization should continue anticoagulation for at least 3 months following discharge or longer if indication persists
- Patients with acute confirmed or suspected VTE who are treated with full dose anticoagulation should complete 3 months of anticoagulation as bleeding risk permits.

Choice of therapeutic anticoagulation

- All admitted COVID-19 patients who are on warfarin at time of admission should remain on warfarin if they are not being admitted to an intensive care unit (ICU) and are not undergoing any procedures
- All admitted COVID-19 patients who are on a therapeutic-intensity dose of a direct oral anticoagulant (DOAC, including dabigatran, rivaroxaban, apixaban, or edoxaban) at time of admission and have a CrCl ≥ 30 mL/min should be transitioned to enoxaparin 1mg/kg every 12 hours (with no upper weight limit to enoxaparin use)
  - This strategy is being pursued due to the frequency with which inpatients with COVID-19 need to transition to an ICU setting and/or undergo procedures
  - DOACs have more drug-drug interactions and generally have longer half-lives than enoxaparin
  - Once an inpatient with COVID-19 is stable for discharge home or is in the recovering phase on a medical floor, DOAC therapy can be resumed provided no drug-drug interactions from COVID-19 treatments preclude their use
- When parenteral therapeutic-intensity anticoagulation is indicated in a patient with no prior h/o HIT, **enoxaparin is preferred to an UFH infusion** when renal function and/or use of epidural/spinal anesthesia permits use, with preferred agent and dosing as follows:
  - CrCl ≥ 30 mL/min: enoxaparin 1mg/kg Q12h (with no upper weight limit to enoxaparin use)
  - 15 ≤ CrCl < 30 mL/min: enoxaparin 1mg/kg Q24h (with no upper weight limit to enoxaparin use) – check anti-Xa level 4 hours after 3rd dose – contact Hematology fellow for approval of testing
  - CrCl < 15 mL/min or on any form of renal replacement therapy: UFH infusion
    - If the baseline aPTT is above the upper limit of normal, consult Hematology to explore reason for APTT prolongation and using anti-Xa levels to adjust dosing
  - History of or newly-diagnosed heparin-induced thrombocytopenia (HIT): consult Hematology and see Heparin-Induced Thrombocytopenia Diagnostic and Treatment Guidelines in Penn Pathways and online formulary

Choice of pharmacologic prophylaxis

- **Standard-intensity prophylaxis:**
  - CrCl ≥ 30 mL/min AND not undergoing epidural/spinal anesthesia: **Enoxaparin 40mg daily**
  - CrCl ≥ 30 mL/min AND history of HIT: **Fondaparinux 2.5mg daily**
  - 15 ≤ CrCl < 30 mL/min: enoxaparin 30mg daily
  - CrCl < 15 OR undergoing epidural/spinal anesthesia: **UFH 5000 Q12H or Q8H**
  - CrCl < 30 AND h/o HIT: consult Hematology for pharmacologic prophylaxis recommendations
  - Higher doses may be required due to the thrombotic risk associated with COVID-19 as well as for patients with elevated body weight
- **Intermediate-intensity prophylaxis (not routinely recommended in COVID-19 inpatients and not to be used if undergoing epidural/spinal anesthesia)**
  - CrCl ≥ 30 mL/min: **Enoxaparin 0.5mg/kg twice daily, rounded to nearest syringe size**
  - CrCl < 30: **UFH 7500 Q8H**
  - **At discharge, patients who received intermediate-intensity prophylaxis should generally be de-escalated to standard-intensity dosing. See page 5 for detailed guidance on selection of agent.**
- **Therapeutic-intensity prophylaxis/treatment: see "Choice of therapeutic anticoagulation" section above**

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