Maine Medical Center
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Clinical Guideline for Anticoagulation in VTE

These clinical guidelines are intended to provide evidence-based recommendations regarding the anticoagulation in patients with DVT and PE. Please note that this guideline should not be used in the setting of massive pulmonary embolism.

These guidelines include unfractionated heparin (UFH), the low molecular weight heparin (LMWH) enoxaparin (Lovenox®), the direct factor Xa inhibitors rivaroxaban (Xarelto®), apixaban (Eliquis®), and fondaparinux (Arixtra®); and the vitamin-K antagonist, warfarin (Coumadin®). Although FDA approved, dabigatran (Pradaxa®) and edoxaban (Savaysa®) require 5 days of bridging with parenteral therapy and therefore are not on the MMC formulary for treatment of VTE.

Therapy Recommendations

See below for specific clinical scenarios that favor one agent over another. Consultation with MMC's anticoagulation pharmacy specialist is also available (pager: 741-7933).

	Recommendation	Grade
Acute treatment	In patients without cancer, initial therapy with DOAC is suggested over warfarin	2B
	In patients without cancer who are not treated with a DOAC, warfarin is suggested over long-term LMWH therapy	2C
	In patients with cancer associated thrombosis, LMWH is suggested over warfarin or DOAC	2C
Duration of treatment	In patients with proximal DVT or PE, treatment should be for 3 months	1B
	In patients with provoked VTE, 3 months of therapy is recommended over shorter or longer durations	1B
	In patients with first unprovoked VTE, 3 months of therapy is recommended over shorter or longer durations	1B
	In patients with first unprovoked VTE who have a low or moderate bleeding risk, indefinite therapy is recommended	2B
	In patients with first unprovoked VTE who have a high bleeding risk, 3 months of therapy is recommended over indefinite therapy	1B
	In patients with second unprovoked VTE, indefinite therapy is recommended over 3 months of therapy	Low bleeding risk: 1B Mod/High bleeding risk: 2B

	In patients with cancer associated VTE, indefinite therapy is recommended over 3 months of therapy	Low bleeding risk: 1B Mod/High bleeding risk: 2B

***Kearon C, et al. CHEST 2016;, doi: 10.1016/j.chest.2015.11.026*[1]**

Medication Pearls:

Formulation	***Agent***	***Treatment Dosing for VTE***	***MMC Specific Exclusion Criteria***
Parenteral	Unfractionated Heparin (High Intensity Protocol)	• Initial bolus 80 units/kg (maximum of 10,000 units) • Infusion start rate 18 units/kg/hour (maximum 2,300 units/hour) • Follow hospital protocol for titration of dose to PTT of 60-80	
	Enoxaparin	Used as a bridge to warfarin† (can be used as monotherapy): Weight ≤ 100 kg: • 1.5 mg/kg subcutaneously every 24 hours (maximum 24 hour dose = 150 mg) Weight > 100 kg (limited data in patients >150 kg): • 1 mg/kg subcutaneously every 12 hours	CL_{Cr} <30 mL/min
	Fondaparinux	Used as a bridge to warfarin†: Weight <50 kg: • 5 mg daily Weight 50-100 kg: • 7.5 mg daily Weight >100 kg: • 10 mg daily	CL_{Cr} <30 mL/min
Oral: **Requires** bridge therapy	Warfarin	Obtain baseline INR prior to warfarin initiation Warfarin naïve patients: • Initiate 5 mg daily protocol Patients who are warfarin sensitive*: • Initiate 2.5 mg daily protocol (as outlined on Agile MD)	
Oral: No bridge therapy	Apixaban	10 mg twice daily for 7 days followed by 5 mg twice daily	CL_{Cr} <30 mL/min OR SCr >2.5 mg/dL
	Rivaroxaban	15 mg twice daily x 21 days, followed by 20 mg daily	CL_{Cr} <30 mL/min

***** Warfarin sensitive patients include: age >70, malnourishment, INR>1.4 without anticoagulation, heart failure, recent major surgery, liver dx, or taking interacting medications

†Bridge therapy for warfarin:

- Use treatment dose of parenteral anticoagulant (UFH, LMWH, or fondaparinux)
- Initiate warfarin on day 1 or 2 of parenteral anticoagulation
- Continue parenteral anticoagulant for 5 days **and** until INR > 2.0 for at least 24 hours

Clinical Pearls[1]

	UFH	LMWH	Fondaparinux	Warfarin	Rivaroxaban	Apixaban
Drug class	Heparin	Heparin	Factor Xa inhibitor	Vitamin K antagonist	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability (%)	100	90	100	>95	80	50
Tmax (hr)	2-4	3-5	3	72-96	2-4	1-3
Half-life (hr)	0.5-1.5	1.5-3	17-21	40	5-9	8-15
Renal Elimination	No	Yes	Yes	No	Yes	Yes
CYP interactions	No	No	No	2C9, 3A4[2], 1A2	3A4[2], 2J2	3A4[2]
p-glycoprotein interactions	No	No	No	No	Yes[2]	Yes[2]
Reversible	Yes	Partial	No	Yes	No	No
Cost[3]	Minimal, requires inpatient treatment					

[1]Dabigatran and edoxaban require 5-10 days of parenteral therapy before therapy can be initiated
[2]Note: if known drug interactions with p-glycoprotein inhibitors/inducers or strong 3A4 inhibitors/inducers exist, warfarin is the preferred agent due to ability to monitor INR
[3]Current cash price at the Pharmacy at Maine Medical Center; 3rd party insurance: Rivaroxaban/Apixaban Tier 2 or 3 co-pay; MaineCare: LWMH/Fondaparinux limited to 7 day supply, DOACs are covered; Manufacturer co-pay cards available for DOACs, contact pharmacy for assistance

	Inhibitor	Inducer
p-glycoprotein (All NOACs)	Amiodarone Dronedarone Macrolide antibiotics Azole antifungals Verapamil Protease Inhibitors	Rifampin Phenytoin Carbemazepime St. John's wort
CYP 3A4 (Rivaroxaban, Apixaban)	Amiodarone Dronedarone Macrolide antibiotics Azole antifungals Verapamil Diltiazem	Rifampin Phenytoin Carbemazepime St. John's wort

Clinical Scenarios

The following list includes several common scenarios where additional guidance in selecting agents may be warranted. This list is not inclusive of all possible scenarios. Consultation with MMC's anticoagulation pharmacy specialist is also available (pager: 741-7933).

- **Obesity:**
  - Weight > 150 kg : UFH bridge to warfarin
  - Weight 100-150 kg : Enoxaparin 1 mg/kg SC q12 hours
    - Twice daily dosing is preferred due to syringe size and pharmacokinetics
  - Fondaparinux also offers weight based dosing
  - Rivaroxaban believed to be effective without dose adjustment[2]; data limited in patients >120 kg

- **Pregnancy/Breastfeeding[3,4]:**
  - LMWH is preferred in pregnancy
    - Enoxaparin 1 mg/kg SC q12 hours
    - Twice daily dosing is preferred due to increased clearance
    - Factor Xa level should be monitored 4 hours after dose
  - Warfarin is contraindicated in pregnancy
  - LMWH may be continued in breast-feeding women[5]
  - Fondaparinux, rivaroxaban, and apixaban have not been formally evaluated in pregnancy[6,7]

- **Renal Insufficiency:**
  - UFH is preferred when CL_{Cr} <30 mL/min[1]
  - Accumulation of drug is possible during treatment with LMWH, fondaparinux, rivaroxaban, or apixaban[6,7]
    - These agents should not be used if CL_{Cr} <30 mL/min

- **Patients with Cancer:**
  - LMWH is preferred agent
    - Enoxaparin 1 mg/kg SC q12h
  - Warfarin therapy is complex in these patients (drug-drug interactions, frequent procedures)
  - Rivaroxaban and apixaban may be considered if LMWH cannot be used. Despite limited data in patients with active cancer, DOACs may be preferred to warfarin given limitations listed above.

- **Concomitant antiplatelet therapy:**
  - **Patients on dual antiplatelet therapy (DAPT):** Therapy with warfarin is preferred
    - Recommend consultation with anticoagulation pharmacy specialist (pager: 741-7933).
  - **Patients on aspirin therapy:** regimen should be evaluated for appropriateness of aspirin therapy as concomitant antiplatelet and anticoagulant therapy increases the risk of bleeding

- **Periprocedural management:**
  - Please see Anticoagulation Reversal

References :

1. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris T, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores CL. Antithrombotic Therapy for VTE Disease: CHEST Guideline, *CHEST* (2016), doi: 10.1016/j.chest.2015.11.026.

2. Kubitza D, Becka M, et al. Body Weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol. 2008 Nov;48(11):1366-7

3. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e691S–e736S.

4. Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1(7):1435–1442

5. Guyatt G, Akl EA, et ca. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb; 141(2 Suppl): 7S-47S.

6. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e44S–e88S.

7. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e24S–e43S.