VTE TREATMENT

CLINICAL GUIDELINE MARCH 2016

Triad Healthcare Network and Cone Health partners have worked to gather and share evidence based guidelines to improve the everyday management of VTE for adults 18 years and over.

- *See Table 1* below for information on choosing the appropriate anticoagulant
- *See Table 2*, page 2, for information on the duration of anticoagulant therapy
- *See Table 3*, page 2, for general information on the DOACs
- *See Table 4*, page 3, for information on switching anticoagulants

Key Principles

•New studies show that DOACs are as effective as warfarin therapy with reduced risk of bleeding and increased convenience for patients and health-care providers.

Table 1: Factors that may influence Anticoagulant choice for initial and long-term treatment of VTE

Factor	Preferred Anticoagulant	Qualifying Remarks
VTE (DVT; DVT+/-PE; PE)	DOAC	2016 CHEST Guidelines: DOACs are suggested over warfarin for initial and long-term treatment of VTE in patients without cancer. New studies show that DOACs are as effective as warfarin therapy with reduced risk of bleeding and increased convenience for patients and health-care providers.
Cancer	LMWH	LMWH is preferred over UFH for initial therapy (up to 10 days); and LMWH is preferred over VKAs (warfarin) for longer term anticoagulation (typically three to six months) beyond the initial period.
Liver Disease and coagulopathy	LMWH	DOACs contraindicated if INR raised due to liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal Disease and creatinine clearance <30 ml/min	VKA	DOACs and LMWH not studied in patients with ClCR < 30mL/min in clinical trials for VTE. Dosing of DOACs with levels of renal impairment differ with DOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with other DOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of gastrointestinal bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban and edoxaban may be associated with more gastrointestinal bleeding than VKA.
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta.
Isolated Distal DVT without severe symptoms or risk factors	None	Serial imaging of the deep veins for 2 weeks is suggested over anticoagulation. With acute isolated distal DVT of the leg managed with serial imaging, no anticoagulation is recommended if the thrombus does not extend. If the thrombus extends but remains confined to the distal veins or if the thrombus extends into the proximal veins anticoagulation is recommended.
Isolated Distal DVT with severe symptoms	Preferred anticoagulant	Appropriate anticoagulation based on assessment of other factors is suggested over serial imaging of the deep veins.
Thrombolytic therapy use	Unfractionated heparin infusion	Greater experience with its use in patients treated with thrombolytic therapy.
Reversal Agent Needed	VKA, unfractionated heparin, dabigatran	
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
VKA Drug Interactions	DOAC	
Patient factor poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a DOAC because it is less complex.
Limited access to INR monitoring	DOAC	Lack of ability to maintain time in target range (TTR) would be a driver for use of a DOAC.
Frequent procedures	DOAC	For frequent procedures--the use of a DOAC because of their "fast-onset"/"fast-offset" permits the DOAC to be used to within 24-48h of the planned procedure--whereas warfarin must be discontinued typically 5 days prior to procedure. In the appropriate circumstances (MPV's, multiple recurrence of VTE etc. [not in setting of atrial fibrillation]) bridging might still be required with LMWH SQ administration--with additional costs as well as injection requirement--whereas DOACs permit single oral drug approach.
Bariatric Surgery	UFA, LMWH	Due to erratic gastrointestinal absorption following Bariatric Surgery, DOACs are not frequently used.
Cost, coverage, licensing	Varies	Each patient must look at the cost of treatments – including the amount of time needed to visit an anticoagulation clinic each month if they opt for warfarin treatment. Tier 3 agents will have deductibles for Medicare Advantage Plans.

Table 2: Duration of Anticoagulant Therapy	
3 months	**Extended ** The continuing use of treatment should be reassessed at periodic intervals.**
Proximal DVT of the leg or PE provoked by surgery	First VTE that is an unprovoked proximal DVT of the leg or PE and a low or moderate bleeding risk
Proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor	A second unprovoked VTE and a low bleeding risk
Isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor	DVT of the leg or PE and active cancer and not a high bleeding risk
Unprovoked DVT of the leg, isolated distal or proximal, or PE ** Suggest aspirin to prevent recurrent VTE when stopping anticoagulant therapy for unprovoked proximal DVT or PE.	

Table 3: Oral Anticoagulation Medications				
Medication	**Dosage**	**Warnings, Precautions, ADRs, and Drug-Drug Interactions**	**Other special considerations and monitoring**	**Antidote**
dabigatran (Pradaxa) Direct thrombin inhibitor	150 mg twice daily (after 5-10 days of initial parenteral anticoagulant therapy)	**DO NOT USE if:** CrCl < 30 ml/min **ADRs**: dyspepsia, other GI side effects, increased GI bleeds **Drug-Drug Interactions**: antacids, verapamil, amiodarone, clarithromycin, rifampin, St.John's wort, carbamazepine		Idarucizumab (Praxbind)
apixaban (Eliquis) Factor Xa inhibitor	10 mg twice daily for 7 days, followed by 5 mg twice daily	**DO NOT USE in:** severe liver disease, patients on dialysis or if CrCl <30 ml/min **Drug-Drug Interactions**: azole antifungals, HIV protease inhibitors, macrolide antibiotics, carbamazepine, phenytoin, rifampin	Activated charcoal may be useful in managing overdose or accidental ingestion if given within 2-6 hours of use (leading to a more rapid fall in Apixaban blood levels)	*Andexanet alfa (not yet approved)*
rivaroxaban (Xarelto) Factor Xa inhibitor	15 mg twice daily for 21 days, followed by 20 mg once daily	**DO NOT USE in**: liver disease or if CrCl < 30 ml/min **Drug-Drug Interactions**: azole antifungals, carbamazepine, HIV protease inhibitors, macrolide antibiotics, phenytoin, primidone, rifampin, phenobarbital	Once-daily dosing and fewer GI effects may make this the preferred DOAC for some patients Activated charcoal may be useful in managing overdose or accidental ingestion if given within 2-6 hours of use	*Andexanet alfa (not yet approved)*
edoxaban (Savaysa) Factor Xa inhibitor	60 mg once daily (after 5-10 days of initial parenteral anticoagulant therapy) *Dosage adjustment if weight ≤ 60 kg, CrCl 15-50 ml/min, or concomitant therapy with specific P-gp inhibitors: 30 mg once daily*	**DO NOT USE in**: moderate to severe liver disease or if CrCl <15 ml/min **Drug-Drug Interactions**: Specific P-gp inhibitors including verapamil, quinidine; short-term use of azithromycin, clarithromycin, erythromycin, oral itraconazole or ketoconazole	Activated charcoal may be useful in managing overdose or accidental ingestion if given within 2-6 hours of use	*Andexanet alfa (not yet approved)*
warfarin (Coumadin) Vitamin K antagonist	Dose based on current and previous INR	**Interactions**: Many drug-drug and food-drug interactions	Monitoring: INR tests at least every 4 weeks, with frequency based on INR level	Vitamin K, 4F-PCC Consult Pharmacy

Table 4: Procedure for Switching Anticoagulants	
Switch	**Procedure**
Warfarin → DOAC	Stop warfarin Start apixaban and dabigatran when INR <2, rivaroxaban when INR <3 and edoxaban when INR <2.5

Dabigatran → Warfarin	Start warfarin while patient is still taking dabigatran
	Stop dabigatran 1-4 days later, with timing based on patient's CrCl and INR level:
	• **If CrCl >50**: Check INR on day 4 of overlap
	  ○ If INR is ≥2.0, stop dabigatran; repeat INR after 1-2 days of warfarin alone
	  ○ If INR <2.0, consider continuing dabigatran along with warfarin; repeat INR 1-2 days later
	• **If CrCl 31-50**: Stop dabigatran 2 days later and check INR after 2 days of warfarin alone
	• **If CrCl <30**: Stop dabigatran 1 day later and check INR after 3 days of warfarin alone

Apixaban → Warfarin	Start warfarin while patient is still taking apixaban Check INR on day 4 of overlap • If the INR is ≥2.0, stop apixaban and repeat INR after 1-2 days of warfarin alone • If the INR is <2.0, consider continuing apixaban along with warfarin; repeat INR 1-2 days later

Rivaroxaban → Warfarin	Start warfarin while patient is still taking rivaroxaban
	Stop rivaroxaban 2-4 days later, with timing based on patient's CrCl and INR level:
	• **If CrCl >50**: Check INR on day 4 of overlap
	  ○ If INR is ≥2.0, stop rivaroxaban; repeat INR after 1-2 days on warfarin alone
	  ○ If INR Is <2.0, consider continuing rivaroxaban along with warfarin; repeat INR 1-2 days later
	• **CrCl 31-50**: Stop rivaroxaban 3 days later; check INR after patient has received 1-2 days of warfarin only
	• **CrCl <30**: Stop rivaroxaban 2 days later; check INR after patient has received 2 days of warfarin only

Edoxaban → Warfarin	Start warfarin while the patient is still taking edoxaban Reduce current edoxaban dose by 50% • For those taking 60 mg once daily, reduce the dose to 30 mg once daily • For those taking 30 mg once daily, reduce the dose to 15 mg once daily Check INR weekly until INR ≥2.0, stop edoxaban and repeat INR within 1 week of using warfarin alone
Enoxaparin → DOAC	Start dabigatran, apixaban, rivaroxaban or edoxaban 10-12 hours after last enoxaparin dose
DOAC → IV UFH or LMWH	**Dabigatran**: • **If CrCl >30**, start UFH or LMWH 12 hours after last dabigatran dose • **If CrCl ≤30**, consider starting LMWH 24 hours after last dabigatran dose, based on clinical interpretation of the patient's risk of bleeding and thrombosis **Apixaban**: Start UFH or LMWH 12 hours after last apixaban dose **Rivaroxaban**: Start UFH or LMWH 12 hours after last rivaroxaban dose if patient is within the first 21 days of treatment otherwise start UFH or LMWH 24 hours after last rivaroxaban dose **Edoxaban**: Start UFH or LMWH 24 hours after last edoxaban dose

Notes:

- Consider expert opinion or referral to a Coumadin clinic
- For patients with a limited life prognosis (6 months or less) give consideration to discontinuing anticoagulants.

These guidelines apply to common clinical circumstances and may not be appropriate for certain patients and situations. The treating clinician must use judgement in applying guidelines to the care of individual patients.

References:

Kearon C, Akl E, Omelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest.* 2016; 149(2): 315-352.

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