CCPN Acute VTE Tool

VENOUS THROMBOEMBOLISM MANAGEMENT: POCKET REFERENCE

Venous thromboembolism (VTE) including both deep vein thrombosis (DVT) and pulmonary embolus (PE) is associated with significant morbidity and mortality. VTE has an annual incidence rate of 0.1 to 0.3% in the adult population, affecting up to 5% of the population.[1] Approximately one third of patients with an untreated VTE event will suffer a potentially fatal pulmonary embolism (PE). Of those treated, approximately 25-50% will suffer from post-thrombotic syndrome (chronic lower leg edema, pain, pigment changes and skin breakdown) and one third will have a recurrent event within 10 years.[2,3]

The purpose of this pocket reference is to provide clinicians a practical guide for the treatment of acute VTE and prevention of recurrent VTE, with a focus on pharmacologic strategies. This pocket reference is intended only as a general reference to supplement the existing knowledge of healthcare professionals and is NOT a substitute for the sound clinical judgment of the knowledgeable healthcare professional. The authors, editors, or CCPN cannot be held responsible for any harm, direct or indirect, caused as a result of the application of information contained in this resource.

For a complete list of references, please go to: **www.ccpn.ca**

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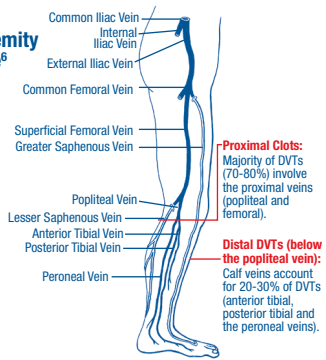
step 1

Determine your patient's likelihood of VTE and confirm diagnosis

VTE has an annual incidence of between 0.1 to almost 0.3% and will affect up to 5% of the population during their lifetime.[1] While DVT may occur anywhere in the venous system, the lower extremities are the most common site for DVT (Figure 1) while the central vasculature in the lungs is the most common site for pulmonary embolism (PE).[4-7]

FIGURE 1: Lower Extremity Vasculature[6]



PE occurs when venous thrombi break off and migrate to the lungs.[8] The likelihood of embolization increases with more proximal clots, while clots located in the distal limb may extend into the proximal circulation and, in turn, embolize to the pulmonary system.

Owing to the consequences of PE, prevention and early detection is fundamental with VTE. This mandates an awareness of the risks as well as the signs and symptoms of VTE. (Table 1).

TABLE 1: Signs/ Symptoms of VTE[9]

DVT*	PE
Leg pain (younger people may report more pain than older persons)	Shortness of breath
Edema / Swelling	Tachypnea
Warmth	Chest pain and rib pain aggravated by breathing (pleuritic)
Dusky discolouration	Tachyarrhythmias (heart rate>100bpm)
Tenderness along the course of venous system	Weak pulse
Dilated surface veins	Cough that may have blood-streaked sputum
	Diaphoresis
	Clammy or bluish coloured skin (lips and face) and oxygen desaturation
	Lightheadedness
	Hypotension
	Signs and symptoms of DVT may be present

* May also occur in upper extremities and symptoms will change in accordance with clot location.

Given the non-specific presentation, the diagnosis of VTE requires patient assessment along with confirmation with objective diagnostic evaluation. Testing for confirmation is guided by the likelihood of the presentation being VTE, and scoring systems are used to assess the likelihood of VTE. Table 2 indicates the Wells score for DVT and table 3 indicates the Wells Score for PE.

TABLE 2: Wells Score for DVT Diagnosis[10]

Clinical Findings	Points
Active cancer or cancer treated within past 6 months	1
Paralysis, paresis or recent orthopedic casting of lower extremity	1
Major surgery or bedridden (> 3 days) within past 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Swelling of the entire leg	1
Calf swelling > 3 cm compared with asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Non-varicose collateral superficial veins	1
Alternative diagnosis more likely than DVT (Baker's cyst, cellulitis, muscle damage, superficial venous thrombosis, post-thrombotic syndrome, inguinal lymphadenopathy, external venous compression)	-2

Score -2-0 indicates low probability of DVT

Score 1-2 indicates moderate probability of DVT

Score 3-8 indicates high probability of DVT

TABLE 3: Wells Score for PE Diagnosis[11]

Clinical Findings	Points
Clinical signs and symptoms of DVT	3
No alternative diagnosis more likely than PE	3
Heart rate >100 beats/min	1.5
Immobilization for > 3 days or surgery within 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1
Malignancy	1

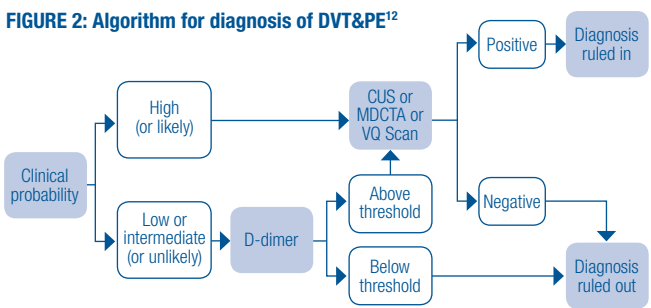
Score 0-1.5 indicates low risk for PE

Score 2-5.5 indicates intermediate risk for PE

Score ≥6 indicates high risk for PE

Diagnostic algorithms for DVT and PE have been developed and validated. An example of a general diagnostic algorithm for VTE is indicated in Figure 2.[12] Further imaging and use of a VQ scan or CT is often employed in the diagnostic algorithm for pulmonary embolism. For specific diagnostic algorithms, refer to www.thrombosiscanada.ca.

FIGURE 2: Algorithm for diagnosis of DVT&PE[12]



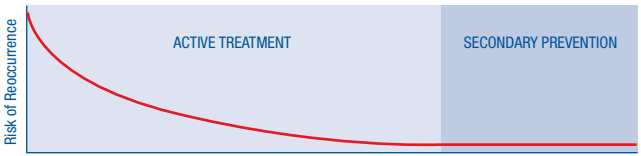
CUS=Compression Ultrasound; MDCTA=Multidetector Computed Tomographic Angiography; VQ scan=Ventilation Perfusion Scan

step 2

Determine treatment options for the Acute and Long-term treatment of VTE

The main goals of acute VTE treatment are to stabilize the existing clot, prevent clot extension or embolization, and ultimately enhance clot dissolution. Long-term goals include the prevention of chronic complications such as post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension associated with clot recurrence/extensive clots. Phases of treatment may be divided into: 1) an early acute phase in which the goal is to prevent clot extension or embolization (first 5-21 days of therapy), 2) a long-term phase (from the end of the acute treatment phase to 3-6 months), and 3) a further extended phase (3-6 months to lifelong) may be considered on a case by case basis for secondary prevention.[12] Figure 3 outlines various phases of care in the treatment of VTE and therapeutic alternatives that may be used, with supporting clinical trials listed.

FIGURE 3: VTE Phases of Care and Clinical Trials[13]



Acute (0-7 or 21 Days) Parenteral/Selected Oral	Long-term (7-21 days to 3-6 months)	Extended (3-6 months to lifelong)
Traditional: Parenteral Anticoagulant + Warfarin	Traditional: Warfarin INR 2.0-3.0	Traditional: Warfarin INR 2.0-3.0
Parenteral Anticoagulant (RECOVER, RECOVER II)	Dabigatran (RE-COVER) Dabigatran (RE-COVER II)	Dabigatran (RE-SONATE) Dabigatran (RE-MEDY)
Rivaroxaban (EINSTEIN – DVT) Rivaroxaban (EINSTEIN – PE)	Rivaroxaban (EINSTEIN – DVT) Rivaroxaban (EINSTEIN – PE)	Rivaroxaban (EINSTEIN – Extension)
Apixaban (AMPLIFY)	Apixaban (AMPLIFY)	Apixaban (AMPLIFY – Extension)

Until recently, the only option for the acute treatment of VTE has been a parenteral anticoagulant in combination with warfarin (the traditional option above). More recently, rivaroxaban, apixaban and dabigatran have been approved by Health Canada (in that order), with specific dosing regimens/strategies unique to this indication. Table 4 highlights clinical trials for the acute treatment of VTE, all non-inferiority by design, comparing a novel oral anticoagulant (NOAC) to standard care of LMWH/UFH plus warfarin. Current guidelines suggest NOACs be preferentially used over warfarin for patients having a DVT of the leg or PE and no cancer.[14]

Table 4 provides inter-trial comparative data. End point definitions along with trial populations differ, and caution must be taken in the interpretation.

TABLE 4: Non-inferiority Acute VTE Trials: NOACs versus Standard Care

	Trial	Study Drug	Comparator	Recurrent VTE + VTE death	Major bleeding
Rivaroxaban Open Label Trial Duration of 3, 6 or 12 months	EINSTEIN DVT[15] N=3449	Rivaroxaban 15mg BID for 21 days, then 20mg daily	Enoxaparin/ warfarin	Non-inferiority 2.1% vs 3.0% HR=0.68 (0.44-1.04; P <0.001)	0.8% vs 1.2% HR=0.65 (0.33-1.30; P=0.21)
	EINSTEIN PE[16] N=4832	Rivaroxaban 15mg BID for 21 days, then 20mg daily	Enoxaparin/ warfarin	Non-inferiority 2.1% vs 1.8% HR=1.12 (0.75-1.68; P=0.003)	Superiority RRR 51% 1.1% vs 2.2% HR=0.49 (0.31-0.79; P=0.003)
Apixaban Double-blind Duration 6 months	AMPLIFY[17] 6 months N=5395	Apixaban 10mg BID x 7d, then 5mg BID	Enoxaparin/ warfarin	Non-inferiority 2.3% vs 2.7% RR=0.84 (0.60-1.18; P<0.001)	Superiority RRR 69% 0.6% vs 1.8% RR=0.31 (0.17-0.55; P<0.001)
Dabigatran Double blind Duration 6 months	RE-COVER[18] N=2564	LMWH or UFH x 5-10 days then Dabigatran 150mg BID	LMWH or UFH/warfarin	Non-inferiority 2.4% vs 2.1% HR=1.10 (0.65-1.84; P<0.001)	1.6% vs 1.9% HR-0.82 (0.45-1.48; P=0.38)
	RE-COVER II[19] N=2589	LMWH or UFH x 5-10 days then Dabigatran 150mg BID	LMWH or UFH/warfarin	Non-inferiority 2.3% vs 2.2% HR=1.08 (0.64-1.80; P<0.0001)	1.2% vs 1.7% HR-0.69 (0.35-1.32; P=NS)

Initial therapy of acute VTE may include parenteral agents as sole therapy based on the severity of clinical presentation or use of other therapies (e.g., thrombolytics). Moreover, parenteral anticoagulants (Table 5) must be used either concomitantly with warfarin until a therapeutic INR is achieved for 2 consecutive days (traditional therapy) or for 5-10 days prior to dabigatran initiation.

TABLE 5: Parenteral Anticoagulants Used in the Acute Treatment of VTE*

	UFH[20]	Dalteparin[21] (Fragmin™)	Enoxaparin[22] (Lovenox™)	Tinzaparin[23] (Innohep™)	Fondaparinux[24] (Arixtra™)
VTE Treatment dose	IV based on aPTT. SC 333 units/kg then 250 units/kg Q12H	200 units/kg SC Q24H Or 100 units/kg SC Q12H	1mg/kg SC Q12H 1.5mg/kg SC Q24H	175 units/kg SC Q24H	weight based: <50kg: 5mg SC daily 50-100kg: 7.5mg SC daily >100kg: 10mg SC daily
Monitoring	Frequent	Not required in most situations			
	aPTT or anti-Xa	Anti- Xa (may need to be calibrated specific to drug)			
Peak Onset	SC:2-4 hrs IV: immediate	4 hours	3 hours	4-6 hours	2 hours
Plasma Half-life	1.5 hours (1-2 hours)	2-2.3 hours	3.5-4.2 hours	1.4 hours	17-21 hours
Use in Renal Dysfunction	Yes	> 30mL/min	>30mL/min	>20mL/min	>30mL/min

UFH=unfractionated heparin; IV=intravenous; SC=sub-cutaneous

* Canadian product monographs for LMWHs recommend capping the dose, regardless of weight. This practice is not adopted by any other country, and Canadian clinicians often dose these agents based on actual body weight.

Oral Agents:

Warfarin (Coumadin®)[25]

Since warfarin has a delayed onset of action, in the setting of acute VTE it must always be initiated with the concomitant use of a parenteral anticoagulant for a minimum of 5 days or until therapeutic anticoagulation (i.e., INR ≥ 2.0) is achieved for 2 consecutive days, whichever is longer.

Initiation doses typically range between 5-10mg daily for one to two consecutive days, followed by an INR assessment on day 2 or 3, with subsequent dosing based on the INR result.

In the initiation phase, INR assessments are typically performed daily (in hospital) or 2-3 times/week (in the community) until some stability with dosing and INR results are achieved, followed by a gradual reduction in testing frequency.[26]

The maintenance phase is achieved once warfarin dosing is constant in the setting of stable INRs, with a weekly warfarin dose established. The clinician must ensure stability of warfarin dosing prior to progressing into the maintenance phase of warfarin.

*Maintenance Dosing Adjustments for INR of 2.0 - 3.0**

INR	Action
< 1.5	Reload† 0 – 2 doses, ↑ weekly dose by 5 – 15%
1.5 – 1.9	Reload† 0 – 1 dose, ↑ weekly dose by 0 – 10%
2.0 – 3.0	No Change
3.1 – 3.5	Hold 0 – 1 dose, ↓ weekly dose by 0 – 10%
3.6 – 4.9	Hold 0 – 2 doses, ↓ weekly dose by 5 – 15%
5.0 – 9.0‡	Hold warfarin, consider Vitamin K_1 1 - 2.5mg PO
> 9‡	Hold warfarin and Vitamin K_1 2.5 – 5mg PO

* Guidelines are to be used as a general framework for dosage adjustment – to be modified as individual needs dictate.
† Reload refers to giving the patient up to twice the daily maintenance dose.
‡ Appropriate in patients with no significant bleeding.

Contraindications:
- Active Bleeding
- *Use with caution in hepatic impairment; monitor INR closely as may potentiate response*

Adverse Effects:
- Bleeding

Drug-Drug Interactions:
Numerous drug interactions are evident with warfarin, and are beyond the scope of this tool. Clinicians should note some of these interactions are delayed, and management of warfarin doses will vary. For a detailed list of drug interactions with management tips, please refer to a published practice tool (cph.sagepub.com/content/144/1/21.full.pdf+html)[27].

Novel Oral Anticoagulants (NOACs)

Rivaroxaban, apixaban and dabigatran all have dosing regimens specific to VTE. Limited data is available for patients with cancer, hence the NOACs are not indicated in this setting. Both clinicians and patients must be aware of the specific dosing regimen (Table 6).

TABLE 6: Dosing Regimens for NOACS in VTE Management[28-30]

	Rivaroxaban (Xarelto®)[28]	Apixaban (Eliquis®)[29]	Dabigatran (Pradaxa®)[30]
Acute Phase	15mg BID x 21 days	10mg BID x 7 days	Parenteral Anticoagulant X 5-10 days
Long-term Maintenance Phase (to complete at least 3 months)	20mg daily	5mg BID	150mg BID (110mg BID)**
Extended‡	20mg daily*	2.5mg BID*††	150mg BID† (110mg BID)**
Transition from parenteral to NOAC	Only done in clinical trials with Dabigatran. Oral agent should be taken when next dose of parenteral is to be administered.		

* Clinical trials compared NOAC against placebo therefore clinical equipoise was assumed for continuation of therapy for the long-term phase.
† Both a placebo (RE-SONATE) and warfarin controlled (RE-MEDY) trial have been completed.
‡ ASA may be an option, offering a 33% relative risk reduction for the prevention of recurrent VTE.
** Although not studied in the acute treatment of VTE, the manufacturer suggests aligning with the atrial fibrillation dosing strategy of 110mg BID for those over the age of 80 years or 75 years of age or greater with a concomitant bleeding risk factor and to consider 110mg BID in those with CrCl between 30 and 50mL/min.
†† In trial, 5mg BID was also studied. The Canadian product monograph only lists 2.5mg BID for the prevention of recurrent VTE.

TABLE 7: Characteristics of NOACs[28-30]

	Rivaroxaban (Xarelto®)[28]	Apixaban (Eliquis®)[29]	Dabigatran (Pradaxa®)[30]
Mechanism of Action	Direct factor Xa inhibitor		Direct thrombin inhibitor
Pharmacokinetics tmax $T_{1/2}$ Elimination	 2-4 hrs 7-11 hrs Renal 33% (active drug)	 3-4 hrs 8.3 hrs Renal 27%	 0.5-2 hrs 12-14 hrs Renal 80%
Administration	Take with food preferably main meal(s) of the day. Can be crushed and administered by NG[31]	Take with or without food. Can be crushed, suspended in water and administered by NG[32]	Do not chew, break or open capsules. Swallow capsule whole with or without food
Contraindications	Active bleeding; Lesions at risk of clinically significant bleeding (e.g., hemorrhagic or ischemic stroke within 6 months [note: for apixaban – recent cerebral infarction], active peptic ulcer disease with recent bleeding)		
	Concomitant treatment with strong inhibitors of both CYP P450 3A4 and P-glycoprotein (e.g., ketoconazole, ritonavir); *strong inducers should also be avoided*		Treatment with strong P-glycoprotein inhibitors or inducers (e.g., ketoconazole, rifampin)
	Use in patients with CrCl<30mL/min is not recommended	Not recommended in patients with CrCl <15mL/min, clinical data are very limited in patients with CrCl 15-24mL/min	CrCl<30mL/min
	Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and with clinically relevant bleeding risk *Use with caution in moderate hepatic impairment*	Not recommended in severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding risk. *Use with caution in mild or moderate hepatic impairment*	Not recommended in patients with hepatic enzymes >3X upper limit of normal
	Not recommended in patients with prosthetic heart valves		Contraindicated in patients with prosthetic heart valves requiring anticoagulation due to valvular status
	Dabigatran is contraindicated in nursing women. *Use in pregnancy is not recommended*		
Laboratory Assessment and Anticoagulation Testing	Monitor CBC at baseline and with any change in health status that may impact hemoglobin, red blood cell count or platelets. Monitor CrCl at baseline and with any change in health status that may impact renal function and appropriateness of dose/continued use.		
	Routine anticoagulant monitoring is not required. The INR and aPTT do not quantitatively correlate with drug levels and should not be used for routine monitoring.		
	Rivaroxaban calibrated anti-Xa levels reflect the pharmacodynamic effect in a dose dependent fashion. In the absence of calibrated anti-Xa levels, PT (Neoplastin® reagent) may be useful to reflect presence of drug.	Rotachrom® Heparin Anti-Xa assay reflects the pharmacodynamic effect of apixaban in a linear, dose-related fashion. In the absence of calibrated anti-Xa levels, PT/INR is not effective for assessing apixaban.	A calibrated TT (Hemoclot assay™) will provide dabigatran levels. In absence of Hemoclot assay availability, a normal TT rules out presence of clinically important dabigatran levels; aPTT may be used to reflect presence of drug, although a minority of patients (<2%) may have a normal aPTT just prior to their next dose while chronically taking dabigatran.[34]

TABLE 7: Characteristics of NOACs[28-30] (continued)

	Rivaroxaban (Xarelto®)[28]	Apixaban (Eliquis®)[29]	Dabigatran (Pradaxa®)[30]
Adverse effects	Bleeding	Bleeding	Dyspepsia, Bleeding
Antidote	For dabigatran only, Idarucizumab (Praxbind™) has conditional NOC for life-threatening or uncontrolled bleeding as well as emergency surgery/urgent procedures.[33] Recommended dose is 5g (administered as 2 consecutive boluses or infusions of the 2.5g vials). Andexanet alpha is currently under study for reversal of anti-Xa inhibitors. Despite limited data, options may include activated prothrombin complex concentrates (PCCs), inactivated PCCs or rFVIIa. For dabigatran only, dialysis may be considered but may not be practical.		
Drug-drug interactions (see detailed table)	Elimination by CYP3A4 and P-glycoprotein (P-gp); concomitant strong inhibitors/inducers of both of these pathways will increase/decrease rivaroxaban and apixaban exposure, respectively.		Dabigatran etexilate is a substrate for the efflux P-gp transporter. Plasma concentrations are affected by strong P-gp inducers and P-gp inhibitors.

TT=Thrombin Time

TABLE 8: Drug-Drug Interactions with NOACs[28,29,30]

Potential ↑ in Rivaroxaban	Potential ↓ in Rivaroxaban
Clarithromycin* Erythromycin* Fluconazole* Ketoconazole, itraconazole, voriconazole, posaconazole‡ Ritonavir‡ Strong inhibitors of both P-glycoprotein and CYP 3A4‡	Carbamazepine¥ Phenobarbital¥ Phenytoin¥ Rifampin¥ St. John's Wort¥ Strong inducers of both P-glycoprotein and CYP 3A4¥

Potential ↑ in Apixaban	Potential ↓ in Apixaban
Diltiazem* Ketoconazole, itraconazole, voriconazole, posaconazole‡ Naproxen* Ritonavir (all HIV protease inhibitors)‡ Strong inhibitors of both P-glycoprotein and CYP 3A4‡	Atenolol* Carbamazepine¥ Phenobarbitol¥ Phenytoin¥ Rifampin¥ St. John's Wort¥ Strong inducers of both P-glycoprotein and CYP 3A4¥

Potential ↑ in Dabigatran	Potential ↓ in Dabigatran
Amiodarone* Clarithromycin* Cyclosporine* Dronedarone¥ Itraconazole* Ketoconazole‡ Nelfinavir* Posaconazole* Quinidine*§ Ritonavir* Saquinavir* Tacrolimus* Tipranavir* Ticagrelor¥ Verapamil*§ Strong P-glycoprotein inhibitors‡	Antacids§ Atorvastatin** Carbamazepine¥ Proton Pump Inhibitors* Phenytoin¥ Rifampin¥ St John's Wort¥ Strong P-glycoprotein inducers‡

* No empiric dosage adjustment required, however use with caution.
§ Recommend to give 2 hours after dabigatran.
‡ Contraindicated.
¥ Caution advised if co-administering, should be avoided.
** No dose adjustment is required.

step 3 Determine your patient's duration of therapy for the Long-term Phase

Clinicians are encouraged to assess the anticipated duration of treatment at the start of therapy. While 3 months is the minimum duration, a risk versus benefit analysis, taking into consideration the patient's wishes is essential in determining duration of therapy (Table 9). The proposed duration of treatment below does not integrate important clinical considerations such as complications (e.g., post thrombotic syndrome, chronic thromboembolic pulmonary hypertension) which may lead to an extension of therapy.

Moreover, a shorter duration of therapy (3 months) may be considered in those with more significant provoking risk factors, such as major surgery, who have a lower expected rate of recurrence. Further, the patient's bleeding risk should be factored when considering duration of therapy. Should long-term therapy be implemented, annual reassessment is recommended.

TABLE 9: Duration of Anticoagulant Treatment*[35]

Category of VTE	Duration of Treatment
VTE Provoked by a transient risk factor†	3 months
First unprovoked VTE‡:	
Low to Moderate Bleed Risk	Suggest extending therapy beyond 3 months
High Bleed Risk	Suggest 3 months of therapy over extending therapy
Second Unprovoked VTE‡	
Low to Moderate Bleed Risk	Suggest extending therapy beyond 3 months
High Bleed Risk	Suggest 3 months of therapy over extended therapy
Provoked Isolated distal DVT	3 months
Cancer associated VTE (regardless of bleed risk)	Minimum of 3-6 months of LMWH and then reassess duration and agent. Continue anticoagulation if active cancer (overt evidence of cancer) or continuing to receive anticancer therapy§

* These decisions are sensitive to patient preference.

† Transient risk factors include surgical and non surgical factors. Nonsurgical provoking factors include pregnancy, estrogen therapy, fracture or plaster casting of lower limb (within 3 months) or hospitalization with confinement to bed (within 3 months), recent lower leg injuries or immobilization or history of prolonged travel (e.g. > 8 hours), within last 6-8 weeks.

‡ Absence of a transient risk factor or active cancer.

§ Current guidelines recommend LMWH therapy over oral anticoagulant options for cancer associated thrombosis.[14] Should an oral anticoagulant be used in cancer associated thrombosis, no preference for either warfarin or a NOAC is given.

step 4 Consider an Extended duration of therapy

The patient's risk of recurrent VTE, major bleeding and personal preferences should all be considered when making a decision to extend anticoagulation therapy beyond 3-6 months. A first unprovoked extensive DVT or PE (with or without complications), a second unprovoked VTE, or active cancers are primary individual risk factors that may warrant extended therapy (Table 10). The benefits of extended therapy need to be weighed against the patient's individual risk of major bleeding (Table 11). Notably, no bleeding risk scales have been validated within the VTE population. Extended therapy should be discontinued once the patient's risk of bleeding exceeds the potential benefit or when a patient chooses to discontinue or alter therapy.

TABLE 10: Likelihood of Clot Recurrence[35,36]

Individual risk factors	Cumulative risk of recurrence*	
	1 year	5 years
PRIMARY FACTORS		
Presence of a reversible provoking risk factor: • Recent surgery • Non-surgical (e.g., estrogen therapy, pregnancy, leg injury, flight of >8 hours)	 1% 5%	 3% 15%
Unprovoked VTE	10%	30%
Active cancer	Unclear: risk estimated at 15% per year but varies according to whether cancer is metastatic, being treated with chemotherapy, or is rapidly progressing. The high mortality rate in this population limits the ability to estimate the long-term risk of recurrence.	
SECONDARY FACTORS		
DVT confined to distal veins (isolated distal or calf DVT)	50% lower risk of recurrence than those with proximal DVT or PE	
VTE was a second or subsequent episode of VTE	50% higher risk of recurrence than those with a first VTE	
OTHER FACTORS	**RR OF RECURRENCE:**	
Negative D-dimer test 1 month after stopping vitamin K antagonist	0.4	
Antiphospholipid antibody	2.0	
Male versus female	1.6	
Hereditary thrombophilia	1.5	
Residual thrombosis in proximal veins	1.5	
Asian ethnicity	0.8	

* Risk of VTE recurrence in patients with proximal DVT or PE. The other factors listed were primarily evaluated in patients with unprovoked VTE.

DVT= deep vein thrombosis; PE= pulmonary embolism; RR=relative risk; VTE=venous thromboembolism

TABLE 11: Risk factors for bleeding with anticoagulant therapy[35]

Risk factors	Risk factors
Advanced age (e.g., >65 years)	Diabetes
Previous bleeding	Anemia
Cancer	Antiplatelet therapy
Metastatic cancer	Poor anticoagulant control
Renal failure	Comorbidity and reduced functional capacity
Liver failure	Recent surgery
Thrombocytopenia	Frequent falls
Previous stroke	Alcohol abuse
	Uncontrolled hypertension

The following trials have assessed the efficacy/safety of an extended duration of antithrombotic therapy (Table 12). Many of these trials compared NOACs to placebo, therefore clinical equipoise for ongoing therapy should be assumed for these patients populations.

TABLE 12: Evidence for Efficacy for the Prevention of Recurrent VTE Treatment (Extended Phase)

Trial and Comparators	Regimen	Population	Primary Efficacy Outcome	Major Bleeding
REMEDY[37] Randomized, double blind trial of dabigatran vs warfarin	Dabigatran 150mg BID vs Warfarin (INR 2-3)	N=2866 with previous symptomatic VTE, already treated with anticoagulant for ≥3 months. Follow up: 6 to 36 months	Recurrent symptomatic VTE or VTE-related death 1.8% vs 1.3% HR 1.44 (CI 0.78-2.64) P=0.01 (non-inferiority)	0.9% vs 1.8% HR 0.52 (CI 0.27-1.02) P=NS
RESONATE[37] Randomized, double blind, placebo controlled trial	Dabigatran 150mg BID vs Placebo	N=1353 with previous symptomatic VTE, already treated with anticoagulant for at least 3 months Follow Up:12 months	Recurrent symptomatic VTE or VTE-related death 0.4% vs 5.6% HR 0.08 (CI 0.02 -0.25) P<0.001 (superiority)	0.3% vs 0 HR not estimable P=NS
AMPLIFY EXT[38] Randomized, double blind, placebo controlled trial	Apixaban 2.5mg BID vs Apixaban 5mg po BID vs Placebo	N=2486 with previous symptomatic VTE patients already treated with 6 -12 months of anticoagulation Follow Up: 12 months	Recurrent symptomatic VTE or VTE-related death (NOTE: this is a secondary endpoint) 1.7% vs 1.7% vs 8.8% P<0.001 for both comparisons (superiority)	0.2% vs 0.1% vs 0.5% P=NS
EINSTEIN EXT[15] Randomized, double blind placebo controlled trial	Rivaroxaban 20mg daily vs Placebo	N=1196 with previous symptomatic VTE already treated with 6-12 months of VKA or rivaroxaban Follow Up: 6 to 12 months	Recurrent VTE 1.3% vs 7.1% HR 0.18 (CI 0.09 – 0.39) P<0.001 (superiority)	0.7% vs 0 HR not available P=0.11

TABLE 12: Evidence for Efficacy for the Prevention of Recurrent VTE Treatment (Extended Phase) (continued)

Trial and Comparators	Regimen	Population	Primary Efficacy Outcome	Major Bleeding
WARFASA[39] Randomized, double blind, placebo controlled trial	ASA 100mg daily vs Placebo	N=403 with 1st episode of symptomatic unprovoked VTE, previously treated for 6-18 months with VKA Follow Up: 2 years	Symptomatic VTE (DVT, fatal or non-fatal PE) 6.6%/year vs 11.2%/year HR 0.58 (CI 0.36- 0.93) P=0.02 (superiority)	0.49% vs 0.51% P=0.97
ASPIRE[40] Randomized, double blind, placebo controlled trial	ASA 100mg daily vs Placebo	N=822 with 1st episode of unprovoked VTE, previously treated with anticoagulation for 6 weeks to 24 months Follow Up: Up to 4 years (median 37.2 months)	Recurrent VTE (Symptomatic DVT or fatal or non-fatal PE)/year 4.8%/year vs 6.5%/year HR 0.74 (CI 0.52-1.05) P=0.09 (superiority)	1.9% vs 1.52% P=NS

step 5 Pertinent information for patients and clinicians

Patients should be well informed of:[28-30,41]

- the appropriate dose and duration of use for each medication in each phase of therapy
- the need for adherence to the dosing regimen as well as the importance of not missing a dose and what to do if a missed dose occurs
  - If a dose of **rivaroxaban** is missed and you are taking 15mg twice daily, take the dose as soon as it is remembered. If you forget to take a dose, you can take two 15mg tablets at the same time to get a total of two tablets (30mg) on one day. On the following day you should carry on taking one 15mg tablet twice daily.
  - If a dose of **apixaban** is missed, the medication should be taken as soon as it is remembered, and then continue with the remaining daily dose that day. Do not take a double dose to make up for a forgotten tablet of apixaban.
  - If a dose of **dabigatran** is missed, take the dose as soon as you remember. If it is almost time for your next dose (less than 6 hours before your next dose), take your next dose when you are supposed to.
- the importance of carrying a wallet card/ medical jewelry stating that they are currently on an anticoagulant
- signs and symptoms of bleeding, along with what to do if bleeding occurs
- signs and symptoms of recurrent DVT or PE, along with what to do if these signs occur
- a plan for therapy reassessment
- take rivaroxaban with food
- need to monitor applicable blood work (CBC, Cr, INR), and potential for drug interactions

steps in care (brief summary)

step 1 Determine your patient's likelihood of VTE and confirm diagnosis

- Assess signs and symptoms of VTE
- Determine probability of patient having a VTE event based on history, physical examination, and risk scoring (e.g., Wells)
- Perform applicable diagnostic testing

step 2 Determine treatment options for the Acute and Long-term treatment of VTE

Phase	Traditional	Apixaban	Dabigatran	Rivaroxaban
Acute	UFH/LMWH + Warfarin	10mg BID x 7 days	Parenteral Anticoagulant X 5-10 days	15mg BID x 21 days
Long-term	Warfarin INR 2.0-3.0	5mg BID	150mg BID (110mg BID)*	20mg daily

* Although not studied in the acute treatment of VTE, the manufacturer suggests aligning with the atrial fibrillation dosing strategy of 110mg BID for those over the age of 80 years or 75 years of age or greater with a concomitant bleeding risk factor and to consider 110mg BID in those with CrCl between 30 and 50mL/min.

step 3 Determine your patient's duration of therapy for the Long-term Phase

Category of VTE	Duration of Treatment
VTE Provoked by a transient risk factor†	3 months
First unprovoked VTE‡:	
Low to Moderate Bleed Risk	Suggest extending therapy beyond 3 months
High Bleed Risk	Suggest 3 months of therapy over extending therapy
Second Unprovoked VTE‡	
Low to Moderate Bleed Risk	Suggest extending therapy beyond 3 months
High Bleed Risk	Suggest 3 months of therapy over extended therapy
Provoked Isolated distal DVT	3 months
Cancer associated VTE (regardless of bleed risk)	Minimum of 3-6 months of LMWH and then reassess duration and agent. Continue anticoagulation if active cancer (overt evidence of cancer) or continuing to receive anticancer therapy

* These decisions are sensitive to patient preference.
† Transient risk factors include surgical and non surgical factors. Nonsurgical provoking factors include pregnancy, estrogen therapy, fracture or plaster casting of lower limb (within 3 months) or hospitalization with confinement to bed (within 3 months), recent lower leg injuries or immobilization or history of prolonged travel (e.g. > 8 hours), within last 6-8 weeks,
‡ Absence of a transient risk factor or active cancer

step 4 Consider an Extended duration of therapy

Determine whether patients should be maintained on extended duration of therapy for secondary prevention. Consider risk of thrombosis recurrence, potential risk reduction with extended anticoagulant therapy, and the patient's individualized risk of bleeding. After discussing these factors with the patient, the patient's preference should be integrated into the treatment plan.

step 5 Pertinent information for patients and clinicians

Factor	Traditional Therapy	Apixaban	Dabigatran	Rivaroxaban
Acute Phase	Parenteral Anticoagulant + Warfarin, INR 2-3	10mg BID x 7 days	Parenteral Anticoagulant x 5-10 days	15mg BID x 21 days with food
Long-term Phase	Warfarin, INR 2-3	5mg BID	150mg BID¥	20mg daily with food
Extended Phase	Warfarin, INR 2-3	2.5mg BID*,**	150mg BID†,¥	20mg daily with food*
Administration	With or without food	With or without food	With or without food	With food‡
Side effect	Bleeding	Bleeding	Dyspepsia, Bleeding	Bleeding
Laboratory Monitoring	INR, Hgb, platelets	CrCl, Hgb	CrCl, Hgb, platelets§	CrCl, Hgb
General Information	• Do not stop your anticoagulant without consulting your healthcare professional • Consult your healthcare professional before taking any new medications • Inform all healthcare providers (dentists, doctors, etc.) you are taking an anticoagulant			

* Clinical trials compared NOAC against placebo therefore clinical equipoise was assumed for continuation of therapy for the extended phase.
† Both a placebo (RE-SONATE) and warfarin controlled ((RE-MEDY) trial have been completed.
‡ AUC decreased by 33% with empty stomach.
** In trial, 5mg BID was also studied. The Canadian product monograph only lists 2.5mg BID for the prevention of recurrent VTE.
§ During run-in phase with heparin.
¥ Although not studied in the acute treatment of VTE, the manufacturer suggests aligning with the atrial fibrillation dosing strategy of 110 mg BID for those over the age of 80 years or 75 years of age or greater with a concomitant bleeding risk factor and to consider 110 mg BID in those with CrCl between 30 and 50 mL/min.

For a complete list of References, go to www.ccpn.ca