

## DEEP VEIN THROMBOSIS (DVT): TREATMENT



Thrombosis Canada  
Thrombose Canada

### OBJECTIVE:

To provide an evidence-based approach to treatment of patients presenting with deep vein thrombosis (DVT).

### BACKGROUND:

An estimated 45,000 patients in Canada are affected by DVT each year, with an incidence of approximately 1-2 cases per 1,000 persons annually. This translates to 2-4 DVTs per year in a typical, individual, Canadian family practice. Approximately one third of patients with DVT also develop symptomatic pulmonary embolism (PE), one third will suffer from post-thrombotic syndrome (PTS) and one third will have a recurrent DVT or PE within 10 years. Rapid diagnosis and treatment of DVT is essential to prevent these complications. Active malignancy, surgery (especially orthopedic), immobilization, and estrogen use/pregnancy are common transient provoking factors. However, up to 50% of first-time DVT is unprovoked (or “idiopathic”).

### MANAGEMENT OF DVT:

#### General measures:

- Unless compression ultrasound (CUS) is rapidly available, patients with moderate-to-high suspicion of DVT (except those with a high risk of bleeding) should start anticoagulant therapy before the diagnosis is confirmed. Imaging confirmation should be obtained as soon as possible.
- Outpatient management is preferred over hospital-based treatment, unless there is an additional indication for hospitalization.
- Initial treatment should have an immediate anticoagulant effect. Therefore, warfarin monotherapy is not appropriate initially.
- For patients who cannot be therapeutically anticoagulated due to active bleeding or high bleeding risks, consultation should be initiated with a hematologist or thrombosis specialist and interventional radiologist regarding placement of an inferior vena cava filter (IVC filter) [see Vena Cava Filter Guide]

#### Anticoagulant Agents and Dosing:

Options for initial anticoagulation include direct acting oral anticoagulant (DOAC) monotherapy (for apixaban and rivaroxaban), unfractionated heparin (UFH) or low molecular weight heparin (LMWH) followed by a DOAC (for dabigatran and edoxaban) or bridging to warfarin, or LMWH monotherapy. Guideline recommendations generally express a preference for DOAC therapy over traditional therapy with LMWH bridging to warfarin. While both strategies are effective, DOACs are more convenient and appear to have lower bleeding risks. All patients should be treated with anticoagulation for at least 3 months [see Venous Thromboembolism: Duration of Treatment guide].

## Anticoagulants:

### **NOACs/DOACs (Non-vitamin K antagonist Oral Anticoagulants/Direct Oral Anticoagulants) – Apixaban (Eliquis®), Rivaroxaban (Xarelto®), Dabigatran (Pradaxa), Edoxaban (Lixiana®):**

Large phase 3 studies have demonstrated the efficacy and safety of these agents for the initial (apixaban and rivaroxaban), acute (all agents) and extended (all agents) treatment of DVT. Four DOACs have been approved in Canada for the treatment of patients with DVT. An initial 5-10 day course of LMWH is required prior to starting dabigatran and edoxaban but not with rivaroxaban and apixaban.

DOACs should not be used in pregnant or breastfeeding women or in those with severe renal dysfunction [see Treatment Guides for Apixaban (Eliquis®), Rivaroxaban (Xarelto®), Dabigatran (Pradaxa®), and Edoxaban (Lixiana®)]. The role DOACs in the treatment of patients with antiphospholipid antibodies and thrombosis remains unclear at this time; trials are currently assessing their efficacy in these patients. Individual product monographs should be consulted for important drug interactions prior to prescribing.

**Apixaban (Eliquis®):** Apixaban is an oral anticoagulant that works through direct inhibition of clotting factor Xa. Apixaban should be used with caution in patients with a creatinine clearance (CrCl) 15-29 mL/min) and is not recommended in those with a CrCl <15 mL/min or undergoing dialysis. The large randomized trials evaluating apixaban in patients with VTE and atrial fibrillation excluded patients with a CrCl <25 mL/min. Apixaban is dosed at 10 mg PO twice daily for the first 7 days, followed by 5 mg PO twice daily for the duration of treatment. For patients continuing on long-term treatment beyond 6 months, consideration can be given to reducing the dose to 2.5 mg PO BID.

**Rivaroxaban (Xarelto®):** Rivaroxaban is an oral anticoagulant that works through direct inhibition of clotting factor Xa. Rivaroxaban is dosed at 15 mg PO twice daily for the first 21 days, followed by 20 mg PO once daily for the duration of treatment. No dosing adjustment is recommended in those with CrCl 15-<50 mL/min, however, caution is recommended for those with CrCl 15-<30 mL/min. Use is not recommended with CrCl <15 mL/min. For patients continuing on long-term treatment beyond 6 months, consideration can be given to reducing the dose to 10 mg PO daily.

**Dabigatran (Pradaxa®):** Dabigatran is an oral anticoagulant that works through direct inhibition of clotting factor IIa (thrombin). Dabigatran requires a 5-10 day initial treatment period with a parenteral anticoagulant (usually a LMWH). Dabigatran is dosed at 150 mg PO twice daily for the duration of treatment. Dose reduction has not been studied in this setting, however, consideration may be given to reducing the dose to 110 mg twice daily in patients 80 years or older and those at higher risk of bleeding (including age at 75 or older with at least one risk factor for bleeding). Use is contraindicated with CrCl <30 mL/min).

**Edoxaban (Lixiana®):** Edoxaban is an oral anticoagulant that works through direct inhibition of clotting factor Xa. Studies excluded patients with CrCl <30 mL/min. Edoxaban requires a 5-10 day initial treatment period with a parenteral anticoagulant (usually a LMWH). Edoxaban is dosed at 60 mg (or 30 mg in those with CrCl 30-50 mL/min or body weight less than or equal to 60 kg or also taking P-gp inhibitors except amiodarone and verapamil) PO once daily for the duration of treatment.

**LMWH** [See Unfractionated Heparin, Low molecular weight heparin, and Fondaparinux guide]

LMWH may be used as initial therapy in conjunction with warfarin for at least the first 5 days and until the international normalized ratio (INR) reaches at least 2.0 for two consecutive days. LMWH may also be used as monotherapy for the full duration of treatment in patients with active cancer and those with DVT in pregnancy. Most patients have little difficulty with self-administration especially if they are coached to do their own first injection. LMWH offers advantages over unfractionated heparin, including more predictable effect allowing fixed-dosing based on body weight and renal function, longer duration of anticoagulant effect enabling once daily treatment, lower risk of heparin-induced thrombocytopenia (HIT), less effect on bone metabolism, and no requirement for routine laboratory monitoring or hospitalization. Dosing should be based on the patient's actual weight. Doses can be rounded off to the nearest pre-filled syringe.

**Dalteparin (Fragmin®):** 200 U/kg SC once daily (preferred) or 100 U/kg SC twice daily (consider in patients >100 kg).

**Enoxaparin (Lovenox®):** 1.5 mg/kg SC once daily or 1 mg/kg SC twice daily.

**Tinzaparin (Innohep®):** 175 U/kg SC once daily.

**Nadroparin (Fraxiparine®):** 171 U/kg SC once daily or 86 U/kg SC twice daily

In patients with **severe renal insufficiency** (CrCl <30 mL/min), LMWH is generally avoided because of its dependence on renal clearance. However, for tinzaparin, available evidence demonstrates no accumulation in patients with CrCl levels down to 20 mL/min. There are limited data available in patients with an estimated CrCl < 20 mL/min. If LMWH is used in patients with severe renal dysfunction, testing anti-factor Xa levels to monitor for accumulation should be considered. Some experts suggest a dose reduction should be considered if the trough anti-Xa level is >0.4 IU/mL; however, good data showing a correlation between these levels and poor clinical outcomes are lacking. Consultation with a hematologist or thrombosis expert is recommended.

**Unfractionated Heparin (UFH)** [See Unfractionated Heparin, Low molecular weight heparin, and Fondaparinux guide]

UFH use in the treatment of DVT is limited by need for hospitalization, a narrow therapeutic range, inter-individual variation in anticoagulant effect, need for laboratory monitoring, and the increased risk of HIT. The use of UFH should be limited to: (1) patients with severe renal insufficiency (CrCl <30 mL/min), in whom LMWHs should generally be avoided; (2) patients at high risk for bleeding, in whom rapid reversal of the anticoagulant effect may be needed; and (3) patients who receive thrombolytic therapy. If used intravenously, UFH should be given with an initial bolus of 5,000 U (or 80 U/kg), followed by an initial UFH infusion of 18-20 U/kg/hr adjusted to achieve a target activated partial thromboplastin time (aPTT) as defined by the local hospital laboratory. Dosing is best guided using standardized nomograms. If used subcutaneously, UFH dosed at 333 units/kg SC for the initial dose and then 250 units/kg SC twice daily is an alternative that does not require aPTT monitoring.

## **Warfarin**

Initial treatment with warfarin should be combined with an immediate-acting agent such as LMWH for at least 5 days and until the INR reaches at least 2.0 for two consecutive days. Initial dosing is best guided by using standardized nomograms; although initial dosing is typically 5 mg once daily, the therapeutic dose is highly variable. The elderly, infirm, and those with a low body-weight typically require a lower dose; initial dosing with 2-3 mg daily should be considered. Conversely, relatively

young, healthy and large patients typically require a higher dose and initial dosing with 7.5-10 mg daily should be considered. Frequent monitoring is required until a stable, in-range INR is reached, after which reduced frequency of testing (e.g. every 2-6 weeks) is appropriate. Warfarin is associated with many drug and food interactions that affect INR. Alcohol and a number of health supplements (e.g. St. John's Wort) can also change the INR. Alterations in concomitant medications and new concurrent illness should prompt more frequent INR testing. Patients should not restrict their intake of foods high in vitamin K, but should be encouraged to maintain a consistent diet. Low intake of vitamin K can be associated with more unstable INR results.

### **ASA (Aspirin®)**

ASA should not be used for initial treatment of VTE and provides less protection than continued anticoagulation (even when anticoagulants are given at prophylactic doses) for extended treatment. Two extended treatment studies of patients with a first unprovoked DVT demonstrated that low-dose ASA provided benefit over placebo for patients having completed 3-18 months of anticoagulation. Combined data from these trials confirmed a statistically significant 32% reduction in recurrent VTE compared to placebo, with no increased risk of clinically relevant bleeding. This is much lower than the 82% reduction with oral anticoagulants. For patients with unprovoked VTE who have completed initial treatment and are averse to long-term anticoagulation, low dose ASA may be considered.

### **DURATION OF THERAPY:** [See Venous Thromboembolism: Duration of Treatment guide]

The duration of treatment should be individualized and based on estimated risks of recurrent thrombosis and bleeding as well as the patient's preferences. In general, at least 3 months of anticoagulation is required for all patients. For more details, see the Clinical Guide: Venous Thromboembolism: Duration of Treatment.

### **SPECIAL CONSIDERATIONS:**

#### **Massive lower extremity DVT:**

Massive DVT is defined as iliofemoral thrombosis with severe symptoms. In such patients not at increased risk of bleeding with symptoms of less than 14 days duration, treatment with pharmacomechanical, catheter-directed thrombolysis (PCDT) should be considered since it rapidly relieves venous obstruction. A recent trial (ATTRACT study) did not find a significant difference in PTS rate with the use of PCDT for DVT, though there may be a role for PCDT in select patients with large iliofemoral DVT. There were, however, more major bleeds with catheter-directed thrombolysis than with standard therapy. Intravenous UFH should be used pre- and post-thrombolytic therapy. As with patients who do not receive PCDT, anticoagulation is indicated following PCDT for at least 3 months. [See also Post-thrombotic Syndrome guide]

#### **Upper extremity DVT (UEDVT):**

Treatment should generally follow the principles for lower extremity DVT. Thrombolysis may be considered on a case-by-case basis for patients with UEDVT with limb compromise. [See Central Venous Catheter-Related Deep Vein Thrombosis guide]. Effort thrombosis and thoracic outlet syndrome should be considered as secondary causes.

**Superficial vein thrombosis (SVT):**

[See Superficial Phlebitis, Superficial Vein Thrombosis clinical guide]

**Isolated distal DVT:**

In patients with an isolated distal DVT, anticoagulation may be withheld in favour of serial imaging to assess for proximal extension, particularly in patients with a high risk of bleeding. Anticoagulation is generally suggested if the patient has severe symptoms, has risk factors for extension at initial assessment (thrombus greater than 5 cm in length, involvement of multiple deep veins, close to the popliteal vein, no reversible risk factor, previous VTE, in-patient, active cancer, or positive D-dimer), is unable or unwilling to return for serial studies, or has progression of the DVT on repeat imaging.

**Patients with contraindications to anticoagulation:**

[See Vena Cava Filter guide].

**Pregnancy:**

[See Pregnancy: Venous Thromboembolism Treatment clinical guide]

**Cancer :**

Although LMWH is often used in patients with cancer and VTE, there are barriers to its long-term use in this patient population. Recent trials comparing anti-factor Xa DOACs, namely edoxaban and rivaroxaban, with LMWH show these agents are reasonable alternatives to LMWH when the risk of gastrointestinal (GI) bleeding is low and in patients with non-GI solid tumour malignancies, provided that drug-drug interactions are not a concern. These studies showed comparable or slightly better efficacy but a 2- to 3-fold higher risk of major or clinical relevant bleeding (particularly upper GI bleeding) with edoxaban or rivaroxaban over LMWH. At present, neither edoxaban nor rivaroxaban have a licenced indication in Canada specifically for use in the cancer patient population. The use of other DOACs (apixaban, dabigatran) is discouraged because evidence of efficacy and safety in comparison with LMWH in this patient population are not yet available. Thorough review of the relative risks and benefits of available anticoagulant options, addition to patient preference and values, is prudent prior to prescribing anticoagulant therapy in patients with cancer-associated thrombosis. Monitoring of renal function, body weight, and drug-drug interactions is essential during treatment with a DOAC. [See Cancer and Thrombosis clinical guide]

**Pediatrics:**

[See Pediatric Thrombosis guide]

**OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**

- Apixaban (Eliquis®)
- Cancer and Thrombosis
- Central Venous Catheter-Related Deep Vein Thrombosis
- Dabigatran (Pradaxa®)

- Deep Vein Thrombosis: Diagnosis
- Edoxaban (Lixiana®)
- Pediatric Thrombosis
- Post Thrombotic Syndrome (PTS)
- Pregnancy: Venous Thromboembolism Treatment
- Pulmonary Embolism: Treatment
- Rivaroxaban (Xarelto®)
- Superficial Phlebitis, Superficial Vein Thrombosis
- Unfractionated Heparin, Low-molecular-weight Heparin, and Fondaparinux
- Vena Cava Filter
- Venous Thromboembolism: Duration of Treatment
- Warfarin

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