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 50,000 patients in Canada are affected by venous thromboembolism each year, with an incidence of approximately 1.3 cases per 1,000 persons annually. Two thirds of these patients present with deep vein thrombosis (DVT). This translates to 1-2 DVTs per year in a typical, individual, Canadian family practice. Approximately one third of patients with DVT also develop symptomatic pulmonary embolism (PE), up to one half will develop 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, 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:

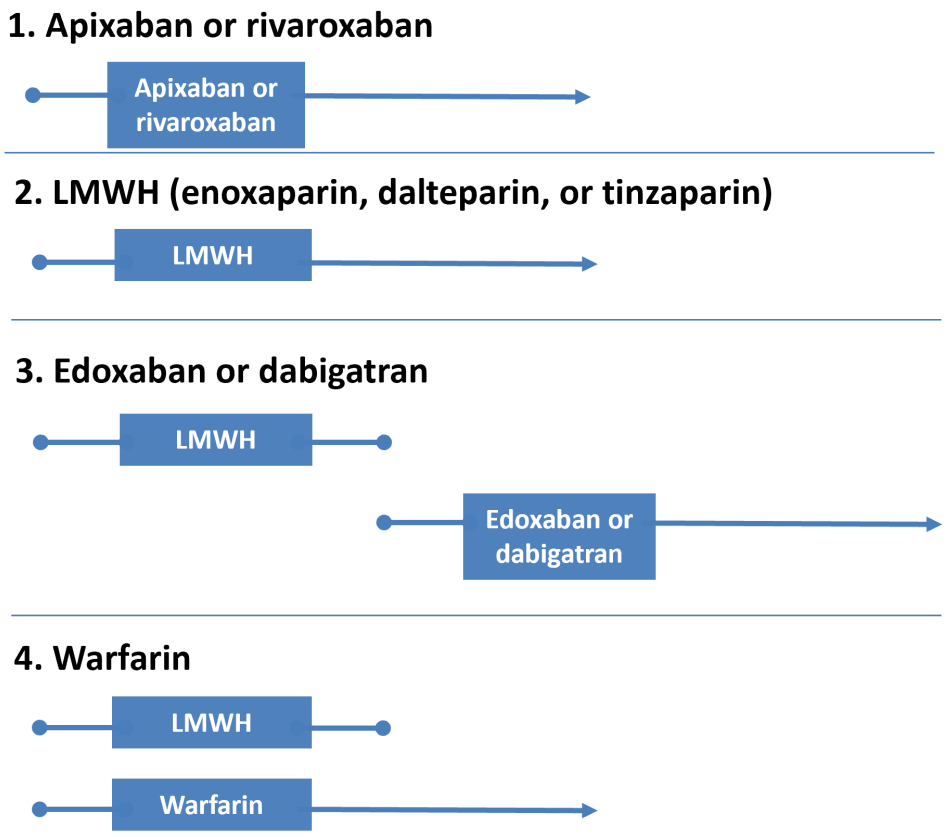
- Unless compression ultrasound (CUS) is rapidly available, patients with moderate-to-high suspicion of DVT (except those with a high risk of bleeding) should start anticoagulant therapy before the diagnosis is confirmed. Imaging confirmation should be obtained as soon as possible.
- Outpatient management is preferred over hospital-based treatment except for patients with limb threatening DVT, patients with high risk of bleeding or patients who have additional indication for hospitalization.
- Initial treatment should have an immediate anticoagulant effect. Therefore, warfarin monotherapy or unfractionated heparin are not appropriate as a initial treatments.
- For patients who cannot be therapeutically anticoagulated due to active bleeding or high bleeding risks such as severe liver disease or significant thrombocytopenia, consultation should be initiated with a thrombosis specialist. Management may include placement of a retrievable inferior vena cava filter (IVC filter) if therapeutic anticoagulation cannot be safely provided in the acute setting **[see Clinical Guide Vena Cava Filter]**.

Anticoagulant Agents and Dosing:

In general, choice of anticoagulation in the acute treatment of DVT should take into consideration patient-specific factors. Guidelines recommend direct oral anticoagulant (DOAC) therapy (apixaban or rivaroxaban) or low molecular weight heparin (LMWH) followed by a DOAC (for dabigatran and edoxaban) over VKA therapy EXCEPT for patients with a diagnosis of antiphospholipid syndrome, drug interactions (concomitant medications metabolized through the CYP3A4 enzyme or P-glycoprotein), conditions that may impair oral absorption, or concurrent indications that require vitain K antagoinst (VKA) use (e.g. mechanical heart valve). DOACs should be used with caution in patients with severe renal impairment and extremes of weight and should be discussed with a thrombosis specialist beforehand.

Other factors that should influence choice of anticoagulant include the requirement for initial parenteral therapy prior to specific DOACs (dabigatran and edoxaban), cost, once daily vs twice daily dosing, and patient preference (see **Figure 1)**.

Figure 1: Options for Initial Anticoagulation for the Treatment of Deep Vein Thrombosis



LMWH is the option to be used as monotherapy for the full duration of treatment in patients with DVT in pregnancy. DOACs are contraindicated during pregnancy and in breastfeeding women, while VKAs are contraindicated during pregnancy except in select circumstances **[**see **Clinical Guides** Pregnancy: Venous Thromboembolism Treatment**]**. LMWH or anti-Xa DOACs (apixaban, rivaroxaban or edoxaban) can be used in patients with active cancer, but some factors require consideration [see **Clinical Guide** Cancer and Thrombosis**]**.

All patients should be treated with anticoagulation for at least 3 months [see **Clinical Guide** Venous Thromboembolism: Duration of Treatment].

Anticoagulants:

DOACs (Direct Oral Anticoagulants) – Apixaban (Eliquis®), Rivaroxaban (Xarelto®), Dabigatran (Pradaxa), Edoxaban (Lixiana®):

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

Of the four DOACs, only apixaban can be considered in the treatment of patients with severe renal dysfunction **[see Clinical Guides for Apixaban (Eliquis®), and Edoxaban (Lixiana®), Rivaroxaban (Xarelto®), and Dabigatran (Pradaxa®)].**

Apixaban (Eliquis®): Apixaban is an oral anticoagulant that works through direct inhibition of clotting factor Xa. Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and should be used with caution in patients with elevated liver enzymes (ALT/AST>2 ULN). Apixaban should also be used with caution in patients with end-stage renal disease (CrCl <15/min or patients undergoing dialysis). For acute venous thromboembolism, 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 long-term treatment beyond 6 months, consideration can be given to reducing the dose to 2.5 mg PO BID for secondary prevention. In end-stage renal disease, doses may vary and should be discussed with a thrombosis specialist beforehand.

Edoxaban (Lixiana®): Edoxaban is an oral anticoagulant that works through direct inhibition of clotting factor Xa. Edoxaban requires a 5- to 10-day initial treatment period with a parenteral anticoagulant (usually LMWH). Edoxaban is usually dosed at 60 mg PO once daily for the duration of treatment. The dose of 30 mg PO once daily is used in patients with CrCl 15-50 mL/min, body weight less than or equal to 60 kg, or concomitant use of P-gp inhibitors (except amiodarone and verapamil). Edoxaban is not recommended for patients with end stage renal disease (CrCl <15mL/min or on dialysis) or in patients with hepatic disease associated with coagulopathy.

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 in patients with CrCl 15-30 mL/min. The large, randomized trials evaluating rivaroxaban in patients with VTE and atrial fibrillation excluded patients with a CrCl <30 mL/min. Use is not recommended in patients with CrCl <15 mL/min. Rivaroxaban is not recommended in patients with significant hepatic disease, and contraindicated in patients with cirrhosis Child-Pugh Class B and C. For patients continuing long-term treatment beyond 6 months, consideration can be given to reducing the dose to 10 mg PO daily for secondary prevention.

Dabigatran (Pradaxa®): Dabigatran is an oral anticoagulant that works through direct inhibition of clotting factor IIa (thrombin). Dabigatran requires a 5- to 10-day initial treatment period with a parenteral anticoagulant (usually LMWH). Dabigatran is dosed at 150 mg PO twice daily for the duration of treatment. The lower dose of dabigatran 110 mg PO twice daily and dose reduction with dabigatran (for extended secondary prevention) has not been studied in venous thromboembolism treatment. Use is contraindicated with CrCl <30 mL/min and should be used with caution in patients with severe hepatic impairment.

LMWH [See Clinical Guide Unfractionated Heparin, Low Molecular Weight Heparin, and Fondaparinux]

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 **[see Clinical Guides Cancer and Thrombosis, and Pregnancy: Venous Thromboembolism Treatment]**. Dosing should be based on patient's actual weight. Doses should be rounded off to the nearest pre-filled syringe to facilitate patient self-administration. 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 effects 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.

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), therapeutic doses of LMWH are generally avoided because of its dependence on renal clearance. According to the monograph, a dose adjustment of enoxaparin to 1 mg/kg once daily is available in those patients. There is limited data available in patients with an estimated CrCl <20 mL/min. However, available evidence suggests no accumulation of tinzaparin in patients with CrCl down to 20 mL/min. Guidelines recommend against testing trough anti-factor Xa levels to monitor for accumulation to guide dose adjustment. Instead, the provider should consider product label-dose adjustments or switching to unfractionated heparin (UFH) due to a lack of high-quality evidence showing a correlation between these levels and bleeding outcomes. Consultation in these cases with a thrombosis expert is recommended.

Unfractionated Heparin (UFH) [See Clinical Guide Unfractionated Heparin, Low molecular weight heparin, and Fondaparinux]

UFH use in the treatment of DVT is limited by a narrow therapeutic range, inter-individual variation in anticoagulant effect, need for laboratory monitoring, the increased risk of HIT and a higher risk of bleeding compared to LMWH. Therefore, the use of UFH should be limited to patients at high risk for bleeding, in whom rapid reversal of the anticoagulant effect may be needed. UFH may also be considered in the following cases: patients with severe renal insufficiency (CrCl <15-20 mL/min or undergoing dialysis) and patients who develop DVT within close time proximity to also receiving thrombolytic therapy.

When 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. When 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; however this SC dosing regimen is contraindicated in patient with creatinine > 200 µmol/L.

Warfarin [See Clinical Guide Warfarin]

Initial treatment with warfarin should be combined with an immediate-acting agent such as LMWH or UFH 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. Frequent monitoring is required until a stable, in-range INR is reached, after which reduced frequency of testing (e.g. every 2-4 weeks) is appropriate. In suitable patients, point of care home INR testing and patient self-adjustment of warfarin therapy can be considered. INR monitoring can sometimes be done by community pharmacists as part of established protocols; ask the patient's pharmacy if this service is available.

Warfarin is associated with many drug and food interactions that affect INR. Alcohol and several 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.

Duration of Therapy:

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:

Extensive proximal lower extremity DVT:

Patients with extensive proximal lower extremity DVT, usually iliofemoral thrombosis, can present with severe symptoms. Anticoagulation still is the core treatment of these DVT. However, more invasive interventions including pharmacomechanical thrombolysis or endovascular intervention such as catheter-directed thrombolysis (CDT) or mechanical thrombectomy could be considered since it rapidly relieves venous obstruction. Two recent trials (ATTRACT, CAVA) did not find a significant difference in PTS rate or in quality of life with the use of catheter-directed thrombolysis (either ultrasound-accelerated or pharmacomechanical), though there may be a role for CDT in select patients with large iliofemoral DVT if done within 14 days of symptom onset. There were more major bleeding events with CDT than with standard therapy. As such, these interventions should generally be reserved for low-risk bleeding patients with severe or limb-threatening DVT, including patients with manifestations like phlegmasia cerulea dolens (severe cyanosis and swelling of the affected leg) or phlegmasia alba dolens (white blanching skin of the affected leg), or patients with severe symptoms who fail anticoagulation alone. The best approach for patients with severe symptoms and extensive proximal lower extremity DVT depends upon the duration and severity of symptoms, patients' comorbidities and of local expertise. As with patients who do not receive interventions, anticoagulation is indicated for at least 3 months.**[See also Clinical Guide Post Thrombotic**

Syndrome]. Inferior vena cava filter is generally not recommended, except if anticoagulation is contraindicated [**see Clinical Guide** Vena Cava Filter].

Upper extremity DVT (UEDVT):

UEDVT are less common than lower extremity DVT, accounting for approximately 5-10% of all venous thromboembolism, and are usually provoked. Effort thrombosis and thoracic outlet syndrome should be considered as secondary causes. **[See Clinical Guide** Central Venous Catheter-Related Deep Vein Thrombosis]. Treatment generally follows the principles for lower extremity DVT. Catheter-directed thrombolysis or mechanical thrombectomy may be considered on a case-by-case basis for patients with extensive and very symptomatic UEDVT.

Isolated distal DVT:

Isolated distal DVT is defined as thrombus involving the deep venous system of the lower limbs distal to the popliteal vein. Many patients with isolated distal DVT resolve without anticoagulant therapy, while others experience propagation of thrombosis and embolization. Thus, treatment varies depending on the estimated risk of thrombus propagation, the presence of other thrombotic risk factors, the risk of bleeding, and patient preference. In patients with isolated distal DVT, it is possible to withhold anticoagulation in favour of serial imaging (repeat ultrasound once a week for two weeks) to assess for proximal extension, which occurs in only 10-15% of patients with isolated distal DVT. This strategy is particularly pertinent for 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. If treatment is initiated, the duration of anticoagulation should be at least 3 months.

Superficial vein thrombosis (SVT):

[See Clinical Guide Superficial Thrombophlebitis, Superficial Vein Thrombosis]

Patients with contraindications to anticoagulation:

[See Clinical Guide Vena Cava Filter]

Pregnancy:

[See Clinical Guide Pregnancy: Venous Thromboembolism Treatment]

Cancer:

[See Clinical Guide Cancer and Thrombosis]

Other Relevant Thrombosis Canada Clinical Guides:

- Apixaban (Eliquis®)
- Cancer and Thrombosis
- Central Venous Catheter-Related Deep Venous 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 Thrombophlebitis, Superficial Vein Thrombosis
- Unfractionated Heparin and Low-molecular-weight Heparin
- Vena Cava Filter
- Venous Thromboembolism: Duration of Treatment
- Warfarin

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