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 as a lone initial treatment.
- 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. 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:

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 Clinical Guide Venous Thromboembolism: Duration of Treatment].**

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) 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 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 Clinical Guides for Apixaban (Eliquis®), Rivaroxaban (Xarelto®), Dabigatran (Pradaxa®), and Edoxaban (Lixiana®)].**

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. 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. 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- 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. Dose reduction has not been studied in this setting. 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- to 10-day initial treatment period with a parenteral anticoagulant (usually LMWH). Edoxaban is dosed at 60 mg (or 30 mg in those with CrCl 30-50 mL/min, body weight less than or equal to 60 kg, or concomitant use of P-gp inhibitors) PO once daily for the duration of treatment.

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]**. 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 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 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 trough anti-factor Xa levels to monitor for accumulation may 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 bleeding outcomes are lacking. Consultation with a hematologist or 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, 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 develop DVT within close time proximity to also receiving 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 [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. 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®) [See Clinical Guide Acetylsalicylic Acid]

ASA should not be used for initial treatment of VTE. Combined data from two extended treatment studies of patients with a first unprovoked DVT demonstrated that low-dose ASA provided a statistically significant 32% reduction in recurrent VTE over placebo with no increased risk of clinically relevant bleeding for patients having completed 3-18 months of anticoagulation. However, in patients who have completed 6 months of anticoagulation for unprovoked VTE, studies comparing ASA versus therapeutic or low-dose DOAC therapy have shown a higher risk of VTE recurrence with ASA, with no difference in the risk of major bleeding events. As such, in this setting, extended DOAC therapy is generally preferred. For patients with unprovoked VTE who have completed initial treatment and are averse to long-term anticoagulation or have other traditional cardiovascular risk factors, low dose ASA may be considered.

DURATION OF THERAPY: [See Clinical Guide Venous Thromboembolism: Duration of Treatment]

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, including phlegmasia cerulea dolens (severe cyanosis and swelling of the affected leg). In such patients, treatment with pharmacomechanical or catheter-directed thrombolysis (PCDT) within 14 days of symptom onset should be considered since it rapidly relieves venous obstruction. Two recent trials (ATTRACT, CAVA studies) did not find a significant difference in PTS rate 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. There were more major bleeds with CDT than with standard therapy. As such this intervention should generally be reserved for low-risk bleeding patients with severe or limb-threatening DVT. 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 Clinical Guide Post Thrombotic Syndrome]**

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 Clinical Guide Central Venous Catheter-Related Deep Vein Thrombosis]**. Effort thrombosis and thoracic outlet syndrome should be considered as secondary causes.

Superficial vein thrombosis (SVT):
[See Clinical Guide Superficial Phlebitis, Superficial Vein Thrombosis]

Isolated distal DVT:
In patients with an isolated distal DVT, anticoagulation may be withheld in favour of serial imaging to assess for proximal extension, as the majority of distal DVT will not extend proximally. 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, then the duration of anticoagulation should be least 3 months.

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:

- Acetylsalicylic Acid
- Apixaban (Eliquis®)
- Cancer and Thrombosis
- Central Venous Catheter-Related Deep Vein Thrombosis
- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis: Diagnosis
- Edoxaban (Lixiana®)
- 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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delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.