DEEP VEIN THROMBOSIS: TREATMENT

Thrombosis Canada
Thrombose Canada

TARGET AUDIENCE: All Canadian health care professionals.

OBJECTIVE:

To provide an evidenced-based approach to treatment of patients presenting with deep vein thrombosis.

ABBREVIATIONS:

ASA	acetyl salicylic acid
CrCl	creatinine clearance
DVT	deep vein thrombosis
HIT	heparin induced thrombocytopenia
INR	international normalized ratio
LMWH	low-molecular-weight heparin
PE	pulmonary embolism
SC	subcutaneously
SVT	superficial vein thrombosis
UEDVT	upper extremity deep vein thrombosis
UFH	unfractionated heparin
US	ultrasound
VTE	venous thromboembolism

BACKGROUND:

An estimated 45,000 patients in Canada are affected by deep vein thrombosis (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, where these cases commonly present. Approximately one third of untreated DVT result in potentially fatal pulmonary embolism (PE), one third will suffer from post-thrombotic syndrome manifest with chronic lower leg edema, pain, pigment changes and skin breakdown and one third will have a recurrent event within 10 years. Rapid diagnosis and treatment of DVT is essential to prevent these complications. Active malignancy (see Cancer and Thrombosis guide), surgery (especially orthopedic; see Thromboprophylaxis: Orthopedic Surgery guide), immobilization > 8 hours, and estrogen use/pregnancy (see Thromboprophylaxis: Pregnancy guide) are transient provoking factors. Up to 50% of first-time DVT is unprovoked (or idiopathic).

DIAGNOSIS OF DVT:

See DVT: Diagnosis guide.

MANAGEMENT:

General measures:

a) Unless ultrasound (US) is rapidly available, patients with moderate to high suspicion of DVT, unless they have a high risk of bleeding, should start therapy before the diagnosis is confirmed.

b) Outpatient management is generally preferred over hospital-based treatment.

c) Initial treatment chosen should have an immediate anticoagulant effect. Warfarin monotherapy is not appropriate initially.

d) Compression stockings should be worn in patients with symptoms of post-thrombotic syndrome.

Pharmacologic Therapy

The following agents may be used for the treatment of DVT:

Low-molecular-weight Heparin (LMWH)

LMWH may be used as initial therapy in conjunction with warfarin for the first 5 days and until the international normalized ratio (INR) reaches at least 2.0, or may be used as monotherapy for the full duration of treatment. Consideration can be given to decreasing the dose by 25% after one month in patients with a good response. It is the preferred long-term treatment for cancer patients. Most patients have little difficulty with self-administration. LMWH offers advantages over unfractionated heparin (UFH), including better bioavailability when administered subcutaneously (SC), longer duration of anticoagulant effect enabling once daily treatment, lower risk of heparin-induced thrombocytopenia (HIT), predictable anticoagulant effect allowing fixed-dosing based on body weight and renal function, less effect on bone metabolism and no requirement for routine laboratory monitoring.

AGENTS AND DOSING:

Dalteparin (Fragmin®): 200 U/kg SC daily or 100 U/kg SC twice daily (once daily dosing preferred).

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

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

For patients with severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min), clinical data on the use of LMWH for the treatment of PE are limited and LMWHs should be avoided. If used, the dose of LMWH should be reduced by approximately 50% and monitoring with anti-factor Xa levels may be required.

Unfractionated Heparin

UFH use in the treatment of DVT is limited by a narrow therapeutic range, inter-individual variation in anticoagulant effect 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 be avoided; (2) patients at increased risk for bleeding, in whom rapid reversal of the anticoagulant effect may be needed; and (3) patients who receive thrombolytic therapy. In addition, UFH is an alternative to LMWH if LMWH is not feasible because of cost considerations or intolerance.

UFH can be used intravenously, administered to achieve an activated partial thromboplastin time (aPTT) of 1.5 to 2.0 times the control aPTT. UFH can also be given subcutaneously with a 333 U/kg initial dose, followed by 250 U/kg twice daily, and without 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. Initial dosing is typically 5 mg once daily, but the therapeutic dose is highly variable. The elderly, infirm and those with low body-weight typically require a lower dose. Initial dosing with 2-3 mg should be considered in such patients. Frequent monitoring is required until a stable, in-range INR is reached, after which reduced frequency of testing is appropriate. Warfarin is associated with many drug and food interactions that affect INR. Alterations in concomitant medications and new concurrent illness should be associated with INR testing. Patients should not be encouraged to reduce intake of foods high in vitamin K, but maintain a consistent, balanced diet.

Rivaroxaban (Xarelto®)

Rivaroxaban is an oral anticoagulant that works through inhibition of factor Xa. In 2012, Health Canada approved rivaroxaban for the treatment of DVT without symptomatic pulmonary embolism, offering a simplified, non-parenteral treatment option. For many primary care physicians not comfortable with the use of LMWH, or not having the necessary time and resources to teach patients self-injection, this should enable treatment without the need to refer to emergency rooms, resulting in more rapid treatment initiation, greater convenience for the patient and physician, as well as potentially reducing health care costs. It is also valuable for patients not likely to accept or manage self-injection.

Recommended dosing is 15 mg twice daily for the first 21 days, followed by 20 mg once daily for the duration of treatment. Rivaroxaban should not be used in women who are pregnant or breast-feeding.

Dabigatran (Pradaxa®), Apixaban (Eliquis®)

Large phase 3 studies that have been completed, or are ongoing, demonstrate benefit of these agents for the treatment of DVT. However, dabigatran is not approved by Health Canada for this clinical indication.

ASA (Aspirin®)

Two extended treatment studies of patients with a first unprovoked DVT demonstrated that low-dose acetyl salicylic acid (ASA) provides benefit over placebo for patients having completed 6-18 months of anticoagulation. ASA should not be used for initial treatment of DVT and likely provides less benefit than continued anticoagulation for extended treatment.

DURATION OF THERAPY:

For further detail, see Duration of Anticoagulant Therapy guide. See **Table** below.

Table: Duration of Anticoagulant Treatment

Categories of VTE	Duration of Treatment
Provoked by a transient risk factor*	3 months
First unprovoked† VTE	Minimum of 3 months and then reassess
Proximal DVT or PE with no or only minor risk factors for bleeding	Long-term therapy with annual review
Isolated distal DVT	3 months‡
Second unprovoked VTE	Minimum of 3 months and then reassess. For patients with no or only minor risk factors for bleeding, long-term therapy with annual review¶
Cancer-associated VTE	Minimum of 3 months and then reassess. Continue if active cancer (overt evidence of cancer) or continuing to receive anti-cancer therapy

* Transient risk factors include: surgery, hospitalization or plaster cast immobilization, all within 3 months; estrogen therapy, pregnancy, prolonged travel (e.g. > 8 hours), lesser leg injuries or immobilizations more recently (e.g. within 6 weeks). The greater the provoking reversible risk factor (e.g. recent major surgery), the lower is the expected risk of recurrence after stopping anticoagulant therapy.

† Absence of a transient risk factor or active cancer.

‡ This decision is sensitive to patient preference.

¶ Indefinite therapy is suggested if there is moderate risk of bleeding, and 3 months is suggested if there is a high risk of bleeding; both of these decisions are sensitive to patient preference.

SPECIAL CONSIDERATIONS:

Massive lower extremity DVT

Massive DVT is defined as iliofemoral thrombosis with severe symptoms. In patients with massive DVT, treatment with pharmaco-mechanical, catheter-directed thrombolysis should be considered since it rapidly relieves venous obstruction with few adverse effects. Two small randomized trials have shown that thrombolytic therapy reduces the risk for the post-thrombotic syndrome. Intravenous UFH should be used after thrombolytic therapy. Patients still require anticoagulation for at least 3 months after receiving thrombolytic therapy.

Upper extremity DVT (UEDVT)

See Central Venous Catheter-Related DVT guide.

If UEDVT occurs in association with a central venous catheter, the catheter should be left in place, if still needed. Treatment should generally follow the principles of lower extremity DVT.

Superficial vein thrombosis (SVT)

Topical or oral non-steroidal anti-inflammatory drugs may provide symptomatic relief. In patients with lower limb SVT > 5 cm, low-to-intermediate dose LMWH (e.g. dalteparin SC 5,000-10,000 U daily, enoxaparin SC 40-80 mg daily, tinzaparin SC 4,500-10,000 U daily) or fondaparinux 2.5 mg SC daily, for up to 45 days may be used.

Patients contraindicated for anticoagulation

See Vena Cava Filter guide.

Pregnancy

See Thromboprophylaxis: Pregnancy guide.

Cancer

See Cancer and Thrombosis guide.

PEDIATRICS:

Once DVT is confirmed (see DVT: Diagnosis guide), treatment may be initiated with either age-appropriate UFH or LMWH followed by 3 months (etiology-determined) or 6-12 months (idiopathic) or long-term (recurrent) treatment with either LMWH or vitamin K antagonists. Life-, organ- or limb-threatening DVT should be treated with thrombolysis, either pharmacologic (tissue plasminogen activator) or mechanical, or thrombectomy. Following removal of the thrombus, anticoagulation should be administered as above. See Pediatrics guide.

REFERENCES:

Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123:1788-1830.

Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141 (2 Suppl):e419S-e494S.