DEEP VEIN THROMBOSIS (DVT): TREATMENT

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 or initial LMWH following by a DOAC, unfractionated heparin (UFH) or low molecular weight heparin (LMWH) bridging to warfarin or LMWH monotherapy. 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 significant 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. Studies 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 daily.

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. 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 with this drug.

Edoxaban (Lixiana®): Edoxaban is an oral anticoagulant that works through direct inhibition of clotting factor Xa. Studies excluded patients with CrCl < 30 mL/min. Like dabigatran, 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 60 kg) 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; this is the preferred long-term treatment for active cancer patients 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 patient’s actual weight and are not capped at 18,000 units. 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.

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

In patients with **severe renal insufficiency** (creatinine clearance [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. Optimal dosing of UFH has not been studied in this setting.

**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 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. Whether or not catheter-directed thrombolysis is used for patients with massive DVT, it is critical that adequate anticoagulation be used especially in the first 1-3 months of treatment. [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]

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:
[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

REFERENCES:


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Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.