

## 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 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 ultrasound (US) 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 adequate and 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.

#### Treatment Regimens:

A number of treatment regimens are now available for acute DVT. Depending on the clinical presentation, one of following regimens should be used for the initial 3 months:

1. Full-dose low molecular weight heparin (LMWH) overlapping with warfarin for at least 5 days and until the INR is at least 2.0 for at least 2 days.
2. Full-dose IV heparin overlapping with warfarin for at least 5 days and until the INR is at least 2.0 for at least 2 days.
3. Apixaban 10 mg PO BID for 1 week before reducing dose to 5 mg PO BID.
4. Rivaroxaban 15 mg PO BID for 3 weeks before reducing dose to 20 mg PO once daily.
5. Full-dose SC LMWH or IV heparin for at least 5-10 days before switching to dabigatran 150 mg PO BID.

6. Full-dose LMWH for the 1<sup>st</sup> month or so before switching to a DOAC or warfarin.

## **Anticoagulants:**

### **LMWH**

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 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), and no requirement for routine laboratory monitoring or hospitalization.

### **LMWH doses**

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

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

Tinzaparin (Innohep<sup>®</sup>): 175 U/kg SC once daily.

- The dose of LMWH is generally rounded up to the nearest pre-filled syringe dose.
- For obese patients, the dose of LMWH is based on their actual body weight (and not capped at 18,000 U/day).
- For patients with severe renal insufficiency (creatinine clearance <30 mL/min), clinical data on the use of LMWH for the treatment of VTE are limited and LMWHs should be used with caution (or avoided). If used, the dose of LMWH should be reduced. If LMWH is to be used long-term in the setting of severe renal insufficiency, monitoring with anti-factor Xa levels may be required.

### **Unfractionated Heparin (UFH)**

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 increased risk for bleeding, in whom rapid reversal of the anticoagulant effect may be needed; and (3) patients who receive thrombolytic therapy.

- Heparin bolus: 5,000 U (or 70 U/kg)
- Initial heparin infusion: 20 U/kg/hr
- Target activated partial thromboplastin time (aPTT): 2.0-3.0 times the control aPTT
- Heparin, 333 units/kg SC initial dose, 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. 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. 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 be associated with INR testing. Patients should not reduce intake of foods high in vitamin K, but should be encouraged to maintain a consistent diet.

## **Rivaroxaban (Xarelto®)**

Rivaroxaban is an oral anticoagulant that works through direct inhibition of clotting Factor Xa. In Canada, rivaroxaban is approved for the treatment of DVT and/or PE and for the prevention of recurrent DVT and PE as a simple, 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, rivaroxaban may enable treatment of confirmed VTE 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 willing to accept or unable to manage self-injection.

- Dosing: 15 mg PO 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, patients with a CrCl <30mL/min, or patients with severe liver disease. There is uncertainty about the effectiveness of rivaroxaban in patients with active cancer; therefore, LMWH is recommended in these patients at this time.

## **Dabigatran (Pradaxa®)**

Dabigatran is an oral anticoagulant that works through direct inhibition of clotting Factor IIa (thrombin). In Canada, dabigatran is approved for the treatment of acute DVT and/or PE after a 5-10 day initial treatment period with a parenteral anticoagulant (usually a LMWH) and for the prevention of recurrent DVT and PE.

- Dosing: 150 mg PO twice daily for the duration of treatment. Dose reduction has not been studied in this setting.
- Dabigatran should not be used in women who are pregnant or breast-feeding or in patients with a CrCl <30mL/min. There is uncertainty about the effectiveness of dabigatran in patients with active cancer; therefore, LMWH is recommended in these patients at this time.
- Idarucizumab, a specific antidote for dabigatran, is now approved by Health Canada for rapidly reversing the anticoagulant activity of dabigatran.

## Apixaban (Eliquis®)

Apixaban is an oral anticoagulant that works through direct inhibition of clotting Factor Xa. In Canada, apixaban is approved for the treatment of DVT and/or PE and for the prevention of recurrent DVT and PE. Like rivaroxaban, apixaban does not require an initial treatment period with a parenteral anticoagulant.

- Dosing: 10 mg PO twice daily for the first 7 days, followed by 5 mg twice daily. Studies excluded patients with CrCl < 25mL/min.
- After at least 6 months of treatment, consideration can be given to reducing the dose to 2.5 mg PO twice daily for long-term prevention of recurrent VTE.
- Apixaban should not be used in women who are pregnant or breast-feeding, patients with a CrCl <15mL/min or on dialysis, or patients with severe liver disease. There is uncertainty about the effectiveness of rivaroxaban in patients with active cancer; therefore, LMWH is recommended in these patients at this time.

## 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 6-18 months of anticoagulation. Combined data from these trials confirmed a statistically significant 32% reduction in recurrent VTE compared to placebo, with no increase risk in 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 adverse to long-term anticoagulation, low dose ASA may be considered.

### 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. General recommendations are given in **Table 1** below. For more details, see The Clinical Guide: Venous Thromboembolism: Duration of Treatment.

**TABLE 1: DURATION OF ANTICOAGULANT TREATMENT FOR VTE**

CATEGORIES OF VTE	DURATION OF ANTICOAGULANT TREATMENT
Provoked by a transient risk factor*	3 months
First unprovoked <sup>†</sup> VTE	Minimum of 3 months and then reassess
Proximal unprovoked DVT or PE with no or only minor risk factors for bleeding	Long-term therapy with annual review
Isolated symptomatic distal DVT or isolated distal DVT with risk factors for extension	3 months <sup>‡</sup>

Second unprovoked VTE	Minimum of 3 months and then reassess for indefinite therapy. For patients with no or only minor risk factors for bleeding, long-term therapy with annual review <sup>¶</sup>
Cancer-associated VTE	Minimum of 3 months and then reassess. Continue if overt evidence of cancer or continuing to receive anti-cancer therapy. Refer to Cancer and Thrombosis guide for further details.

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

† Absence of a transient risk factor or active cancer.

‡ This decision is sensitive to patient preference.

<sup>¶</sup> 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 such patients, treatment with pharmaco-mechanical, catheter-directed thrombus reduction therapy should be considered since it rapidly relieves venous obstruction with few adverse effects. Two small randomized trials have shown that catheter-directed thrombolysis reduces the risk for the post-thrombotic syndrome. Intravenous UFH should be used around the 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.

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

See Central Venous Catheter Related Venous Thrombosis 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 5,000-10,000 U SC daily, enoxaparin 40-80 mg SC daily, tinzaparin 4,500-10,000 U SC daily) or fondaparinux 2.5 mg SC daily, for up to 45 days may be used. For extensive SVT, moderate-to-full doses of LMWH should be considered.

### **Isolated distal DVT:**

In patients with an isolated distal DVT anticoagulation is generally suggested especially if the patient is symptomatic, has risk factors for extension at initial assessment (severe symptoms, greater than 5

cm in length, in multiple deep veins, close to the popliteal vein, no reversible risk factor, previous VTE, in-patient, or positive D-dimer), or has progression of the DVT on repeat imaging.

**Pregnancy:**

See Pregnancy: Venous Thromboembolism Treatment guide.

**Cancer :**

See Cancer and Thrombosis guide.

**PEDIATRICS:**

Once DVT is confirmed, treatment may be initiated with either age-appropriate UFH or LMWH followed by 3 months (reversible cause) or 6-12 months (idiopathic) or long-term (recurrent) treatment with either LMWH or vitamin K antagonists. Massive DVT should be treated with pharmaco-mechanical, catheter-directed thrombus reduction therapy as in adults.

**OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**

- Apixaban (Eliquis®)
- Cancer and Thrombosis
- Central Venous Catheter Related Venous Thrombosis
- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis: Diagnosis
- Post Thrombotic Syndrome (PTS)
- Pulmonary Embolism: Treatment
- Rivaroxaban (Xarelto®)
- Pregnancy: Venous Thromboembolism Treatment
- Unfractionated Heparin and Low-molecular-weight Heparin
- Vena Cava Filter
- Venous Thromboembolism: Duration of Treatment
- Warfarin

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