CME

Treatment of deep vein thrombosis

What factors determine appropriate treatment?

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ABSTRACT

OBJECTIVE To identify patients with deep vein thrombosis (DVT) for whom in-hospital treatment should be considered.

QUALITY OF EVIDENCE The literature was searched for studies on outpatient treatment of DVT. Seventeen studies were assessed: seven were randomized controlled trials (level I evidence), and 10 were non-randomized trials (level II evidence).

MAIN MESSAGE Four criteria can be used to identify patients with DVT for whom outpatient treatment might not be appropriate: presence of massive DVT, presence of symptomatic pulmonary embolism, high risk of bleeding with anticoagulant therapy, and presence of comorbid conditions or other factors that warrant in-hospital care.

CONCLUSION Four criteria can be used to identify patients with DVT for whom in-hospital treatment should be considered.

RÉSUMÉ

OBJECTIF Identifier les cas de thrombose veineuse profonde (TVP) pour lesquels un traitement à l'hôpital devrait être envisagé.

QUALITÉ DES PREUVES On a fouillé la littérature à la recherche d'études sur le traitement extra-hospitalier de la TVP. Dix-sept études ont été évaluées, dont 7 essais randomisés (preuves de niveau I) et 10 essais non randomisés (preuves de niveau II).

PRINCIPAL MESSAGE On peut déterminer les cas de TVP pour lesquels un traitement extra-hospitalier risque d'être inapproprié en utilisant quatre critères : la présence d'une TVP massive, une embolie pulmonaire symptomatique, un haut risque d'hémorragie en cas de traitement anticoagulant et la présence d'un état de comorbidité ou d'autres facteurs requérant des soins hospitaliers.

CONCLUSION Quatre critères peuvent être utilisés pour déterminer les cas de TVP pour lesquels un traitement à l'hôpital devrait être envisagé.

This article has been peer reviewed.
Cet article a fait l'objet d'une évaluation externe.
Can Fam Physician 2005;51:217-223.

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Venous thromboembolism, which includes deep vein thrombosis (DVT) and pulmonary embolism, is the third most common vascular disease after coronary artery disease and stroke.[1,2] An estimated 45 000 patients each year in Canada have DVT. Since the late 1990s, the standard of care for initial treatment of DVT has been at least 5 days' treatment with a heparin preparation coadministered with an oral anticoagulant that, in North America, is usually warfarin. Heparin is given until warfarin attains a therapeutic effect, as defined by a target international normalized ratio (INR) of 2.0 to 3.0 for 2 consecutive days.[3]

The most common agent used for initiation of anticoagulant therapy is low-molecular-weight heparin (LMWH), which can be administered once or twice daily subcutaneously as a fixed dose, without laboratory monitoring.[4,5] Because LMWH can be administered subcutaneously either by a visiting nurse or by patients themselves, in-hospital treatment is not required.

Well designed randomized trials have demonstrated that outpatient treatment of DVT with LMWH is comparable in efficacy and safety to in-hospital treatment with intravenous heparin and more economical than in-hospital treatment.[6,7] Concerns remain, however, about the safety of treating *all* patients with DVT as outpatients. These concerns are, in part, due to the fact that outpatient DVT treatment was studied in closely monitored and structured clinical trials and that these studies excluded patients with more complicated disease, such as those with major comorbidity. With the increasing trend toward outpatient treatment of DVT, we still need to identify patients for whom outpatient treatment might be inadvisable.

The objective of this review is, therefore, to identify patients with DVT for whom in-hospital treatment should be considered. This article also describes the medications available for outpatient treatment of DVT.

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Quality of evidence

MEDLINE (1994 to March 2004), HEALTHSTAR (1994 to March 2004), and the Cochrane Controlled Trials Register (1994 to March 2004) databases were searched for clinical trials (randomized and non-randomized) of outpatient treatment of DVT using the key words "deep vein thrombosis," "venous thromboembolism," "treatment," "outpatient," and "randomized controlled trial." English and other-language articles were searched to avoid language-related selection bias, but only articles with English abstracts were reviewed.

The search strategy identified 17 trials in which patients with acute symptomatic DVT received treatment, either completely or in part, as outpatients.[8-25] These studies were reviewed to find criteria for identifying patients for whom outpatient management might not be appropriate and for whom in-hospital treatment would be warranted. Seven randomized controlled trials (RCTs) providing level I evidence, and 10 non-randomized clinical trials providing level II evidence, were assessed.

When is outpatient treatment of DVT appropriate?

For patients presenting with DVT, level I and II evidence from well designed clinical trials indicates that outpatient treatment is effective and safe.[8-25] Many hospitals and outpatient clinics currently have care paths to facilitate and standardize outpatient treatment (**Figure 1**). Outpatient treatment of DVT can be justified because, in general, the prognosis of such patients is good.

Among patients who receive appropriate anticoagulant therapy, 3% to 5% develop recurrent thromboembolism, and 3% to 5% develop major bleeding during the first 3 months of treatment.[26] The case-fatality rate of recurrent venous thromboembolism is 5%; one in 400 patients who develop recurrent disease dies.[27]

Four criteria can be used to identify patients for whom outpatient treatment might be inadvisable (**Table 1**). First, does the patient have massive DVT? Second, does the patient have objectively confirmed symptomatic pulmonary embolism? Third, is the patient at high risk of

anticoagulant-related bleeding complications? Fourth, does the patient have major comorbidity or other factors that might warrant in-hospital care? If the answer to any of these questions is yes, in-hospital treatment should be considered.

Does the patient have massive DVT? About 5% of patients presenting with symptomatic lower-limb DVT have massive DVT that is characterized by severe pain, swelling of the entire limb, acrocyanosis, and in the most severe cases, limb ischemia.

Figure 1. Care path for outpatient treatment of deep vein thrombosis

Patient ID:_____ DOB:_____ Weight:_____kg Allergies: _____	
BASELINE INVESTIGATIONS	
DVT confirmed by	_____
Location of DVT	_____
Hgb	_____ g/L
Platelet count	_____ x 106/L
INR	_____
aPTT	_____ seconds
Creatinine level	_____ mmol/L
LOW-MOLECULAR-WEIGHT HEPARIN	
Start on day 1	
Once-daily dosing:	
• dalteparin 200 IU/kg	
• enoxaparin 1.5 mg/kg	
• tinzaparin 175 IU/kg	
• nadroparin 171 IU/kg	
Twice-daily dosing:	
• dalteparin 100 IU/kg	
• enoxaparin 1.0 mg/kg	
Continue for at least 5 days *and* until INR is >2.0 for 2 consecutive days	
WARFARIN THERAPY	
Start on day 1: initial dose of 5-10 mg (5 mg for people >70 years)	
Give 5 mg daily on days 2, 3, and 4	
Subsequent dose is determined based on INR level	
LABORATORY MONITORING	
Week 1: measure INR and CBC on day 3-4 and day 6-7 after start of treatment	
Week 2 and 3: measure INR weekly	
Week 4-6: measure INR every 2 weeks	
After week 6: measure INR every 3-4 weeks	
CLINICAL FOLLOW UP	
Week 1: clinical examination at least once during initial 1-2 weeks of treatment to assess symptom improvement and need for graduated compression stockings to minimize symptoms related to venous insufficiency	
Week 4-5: optional clinical assessment	
Week 12: clinical assessment to determine whether anticoagulants can be stopped in patients with secondary DVT that occurred during exposure to transient risk factors (eg, surgery)	
Week 24: clinical assessment to determine whether long-term anticoagulant therapy is required (consider referral to hematology or thrombosis consultant)	

aPTT—activated partial thromboplastin time, CBC—complete blood cell count, DOB—date of birth, DVT—deep vein thrombosis, Hgb—hemoglobin, ID—identification number, INR—international normalized ratio.

Table 1. Criteria for assessing appropriateness of outpatient treatment of deep vein thrombosis: *Presence of one or more criteria suggests need for in-hospital care*

Does the patient have massive DVT?
Swelling of entire lower limb
Acrocyanosis
Venous limb ischemia
Extension of DVT into iliofemoral veins or inferior vena cava
Does the patient have symptomatic pulmonary embolism?
Requirement for supplemental oxygen or other supportive care
At risk for cardiorespiratory deterioration
Is the patient at high risk for anticoagulant-related bleeding?
Active bleeding (eg, active gastrointestinal bleeding source)
Recent (within 4 weeks) bleeding episode (eg, peptic ulcer disease)
Recent (within 1 week) surgery or trauma
Thrombocytopenia (platelet count <100 x 10^6/L)
Coagulopathy (INR >1.4 or aPTT >40 seconds)
Advanced cancer with intracerebral or intrahepatic metastases
Does the patient have major comorbidity or other factors that warrant in-hospital care?
Severe pain or discomfort related to DVT that warrants parenteral analgesia
Major comorbidity (eg, advanced cancer) that requires in-hospital care
Cognitive impairment or language barrier that precludes outpatient care
Impaired mobility that precludes outpatient visits or laboratory monitoring of anticoagulant activity

aPTT—activated partial thromboplastin time, DVT—deep vein thrombosis, INR—international normalized ratio.

Seen on venous ultrasound, massive DVT involves the iliofemoral vein segment and can extend into the inferior vena cava. Hospitalization is recommended for these patients to administer parenteral analgesia and to consider alternative modes of treatment with thrombolytic agents, or extended-duration LWMH, or unfractionated heparin therapy for 10 to 14 days. One study assessed the prognosis of patients with iliofemoral DVT who received conventional anticoagulant therapy[28] and showed that such patients were more than twice as likely to develop thrombosis than patients with less extensive DVT (11.2% vs 5.3%).

Does the patient have symptomatic pulmonary embolism? About 10% of patients presenting with symptomatic lower-limb DVT also have symptomatic pulmonary embolism.[26] For such patients, cardiorespiratory symptoms or the need for oxygen and other supportive therapy might preclude outpatient treatment. Some emerging evidence indicates that certain patients with symptomatic pulmonary embolism can be safely treated as outpatients, at least for part of their initial treatment.[10,29] Patients in these studies were hemodynamically stable, had an oxygen saturation >95% while breathing room air, and did not require parenteral analgesia. Until there are more studies investigating outpatient treatment of pulmonary embolism in diverse clinical settings, however, patients with DVT and symptomatic pulmonary embolism should receive in-hospital anticoagulant therapy, at least for the initial 2 to 3 days' treatment or until they have no ongoing requirement for supplemental oxygen or other supportive care.

Is the patient at high risk for anticoagulant-related bleeding? Between 5% and 10% of patients with newly diagnosed DVT have conditions that preclude anticoagulation therapy or make administration of anticoagulants problematic. Certain conditions confer a high risk of bleeding complications after initiation of anticoagulant therapy.[30-32] Patients with actively bleeding lesions, such as colonic neoplasms, will likely experience increased bleeding after anticoagulation commences. If the bleeding is severe or the lesion cannot be removed, placing an inferior vena cava filter (eg, Greenfield filter) could be warranted until anticoagulation can be safely administered.

Patients with recent (within 4 weeks) bleeding (eg, peptic ulcer disease) can receive anticoagulant therapy, but must be closely monitored to detect recurrent bleeding. Patients who have had recent surgery or trauma are also at increased risk of bleeding, particularly if they have extensive wound- or trauma-related injury that could begin to bleed again. Patients with thrombocytopenia (platelet count <100 x 10^6/L) or coagulopathy (INR >1.4; activated partial thromboplastin time [aPTT] >40 seconds) could be at increased risk of bleeding because of impaired hemostatic reserve. Finally, patients with advanced cancer who have intracerebral or intrahepatic metastases are at increased

risk of bleeding because metastases to these sites tend to be highly vascular. Hospitalization is recommended for patients with these conditions because, if bleeding does occur, it can be detected and treated promptly.

Does the patient have major comorbidity or other factors that could warrant in-hospital care? Most patients with DVT require simple supplementary measures that can be administered at home: rest, elevation of the symptomatic leg, and use of oral analgesics for relief of symptoms. Some ambulation should be encouraged because complete bed rest can promote thrombus progression. Symptoms typically take 7 to 14 days to resolve and usually do not start to improve until the third or fourth day of treatment. In-hospital care might be warranted, however, if patients have concomitant comorbidity (eg, advanced cancer) or if patients are unable to care for themselves.

Anticoagulation therapy for outpatient treatment of DVT

Low-molecular-weight heparin. Level I evidence from RCTs has established the efficacy and safety of outpatient treatment of DVT with LMWH.[8-10] Several LMWH preparations, administered once or twice daily by subcutaneous injection, are currently approved for the initial treatment of DVT (**Table 2**). Although there are no head-to-head RCTs comparing different LMWH preparations for treatment of DVT, the preparations likely have comparable antithrombotic efficacy and safety.[33]

Low-molecular-weight heparin preparations have several advantages over unfractionated heparin for treatment of DVT. First, LMWH preparations have stable pharmacokinetics and, therefore, when administered using a weight-based dosing regimen, have stable and predictable antithrombotic activity. This eliminates the need for laboratory monitoring of the anticoagulant effect. Second, LMWH preparations can be administered in a once-daily injection, which might be easier for patients to administer themselves and might be less costly, particularly if visiting health care providers are required to administer the injections. Third, compared with unfractionated heparin, LMWH preparations are associated with a lower risk of heparin-induced thrombocytopenia, an immune-mediated condition that, paradoxically, is associated with increased risk of venous and arterial thromboembolism.[3]

Unfractionated heparin. Outpatient treatment of DVT with twice-daily subcutaneous unfractionated heparin injections is efficacious and safe, based on level I evidence.[34] Laboratory monitoring is required, however, with aPTT testing 6 hours after each daily morning dose. As with intravenous heparin therapy, subcutaneous heparin doses are adjusted to achieve a target aPTT of 1.5 to 2.0 times the control aPTT. One advantage of unfractionated heparin is that it is less expensive than LMWH.

Anti–factor Xa inhibitors. Fondaparinux is a novel synthetically derived agent that exerts its antithrombotic activity by selective inhibition of factor Xa.[35] Fondaparinux is currently available for

Table 2. Low-molecular-weight heparin for outpatient treatment of deep vein thrombosis

LOW-MOLECULAR-WEIGHT HEPARIN PREPARATION (TRADE NAME)	MAXIMUM DOSE	RECOMMENDED DOSE	DAILY DOSE FREQUENCY	DAILY COST OF TREATMENT* ($)
Dalteparin (Fragmin)	20 000 IU/d	200 IU/kg	Once	31.35
		100 IU/kg	Twice	31.24
Enoxaparin (Lovenox)	200 mg/d	1.5 mg/kg	Once	26.40
		1.0 mg/kg	Twice	35.20
Nadroparin (Fraxiparine)	17 100 IU/d	171 IU/kg	Once	19.69
Tinzaparin (Innohep)	18 000 IU/d	175 IU/kg	Once	24.64

**Based on treatment with prefilled syringes for an 80-kg patient.*

prevention of DVT after orthopedic surgery and soon will be available for the initial treatment of DVT. Fondaparinux is administered in a once-daily, fixed-dose, subcutaneous injection of 7.5 mg (10 mg for patients >100 kg; 5 mg for patients <45 kg). A recently completed RCT showed that fondaparinux was as effective and as safe as enoxaparin for initial treatment of DVT.[23]

Oral anticoagulants. Whether LMWH or unfractionated heparin is used, oral anticoagulant therapy (usually warfarin in North America) is started on the first or second day of treatment.[3] Based on level I and II evidence, the usual dose of warfarin is 5 to 10 mg on the first day and 5 mg daily thereafter.[25,36] The INR should be tested at least twice during the first week of treatment, weekly during the next 2 to 3 weeks, every 2 weeks during the next 4 weeks, and every 3 to 4 weeks thereafter.[37]

Whatever warfarin dose regimen is used, treatment with LMWH or unfractionated heparin should be continued for at least 5 days and until the INR has been >2.0 for 2 consecutive days. Warfarin should be administered, with a target INR of 2.0 to 3.0, for 3 months to patients with DVT following exposure to a transient risk factor (eg, surgery, trauma, immobility) and for at least 6 months to patients with unprovoked (or idiopathic) DVT.[3] The optimal duration of anticoagulation for this last group is unknown, but long-term treatment should be considered for patients with recurrent venous thromboembolism and for patients with inherited thrombophilia (eg, factor V Leiden mutation) or acquired thrombophilia (eg, antiphospholipid antibody syndrome). For patients with DVT and cancer, recent evidence indicates that long-term treatment with LMWH is superior to oral anticoagulant therapy for preventing recurrent venous thromboembolism.[24]

Conclusion

For patients with newly diagnosed DVT, good-quality evidence demonstrates the efficacy and safety of outpatient anticoagulant therapy. Outpatient treatment, however, might not be appropriate for all patients. In-hospital treatment should be considered for patients with massive DVT, with symptomatic pulmonary embolism, at high risk of anticoagulant-related bleeding, and with major comorbidity or other factors that warrant in-hospital care.

EDITOR'S KEY POINTS

- For patients with newly diagnosed deep vein thrombosis (DVT), good evidence indicates that outpatient treatment is safe and effective using low-molecular-weight heparin and an oral anticoagulant until the international normalized ratio (INR) is in therapeutic range.
- Hospitalization is recommended for patients with massive DVT, with symptomatic pulmonary embolism, at high risk of anticoagulant bleeding, or with major comorbidity.

POINTS DE REPÈRE DU RÉDACTEUR

- Des preuves de bonne qualité indiquent que les patients présentant une thrombose veineuse profonde (TVP) nouvellement diagnostiquée peuvent être traités en externe de façon sûre et efficace avec une héparine de faible poids moléculaire et un anticoagulant oral jusqu'à ce que l'INR (International Normalized Ratio) soit dans la zone thérapeutique.
- On recommande l'hospitalisation lorsqu'il y a une TVP massive, une embolie pulmonaire symptomatique, un risque élevé d'hémorragie liée à l'anti-coagulation ou un état de comorbidité sérieux.

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