

# Medical management of deep vein thrombosis

Manoranjan Mahapatra<sup>\*</sup>, Pravas Mishra, Tulika Seth, Renu Saxena

*Department of Hematology, All India Institute of Medical Sciences, New Delhi, India*

**Abstract.** Making a diagnosis of deep vein thrombosis requires both clinical assessment and objective testing. Once a patient is diagnosed with an acute deep vein thrombosis, low-molecular-weight heparin is the agent of choice for initial therapy and oral anticoagulant therapy is the standard for long-term secondary prophylaxis. Therapy should continue for at least 3 months; the decision to continue treatment beyond 3 months is made by weighing the risks of recurrent thrombosis and anticoagulant related bleeding, and is influenced by patient preference.

Key words: Thrombosis, vein, management

## 1. Introduction

Deep vein thrombosis (DVT) is a common but elusive illness that can result in suffering and death if not recognized and treated effectively. It affects approximately 0.1% of persons per year. The incidence is much lower in the young and higher in the elderly. Although many patients develop DVT in the presence of risk factors, such as malignancy and immobility, DVT can also occur without obvious provocation (idiopathic DVT). Although the management of DVT is often straightforward, problems leading to morbidity and mortality can result from misdiagnosis, treatment failure, and anticoagulant-related bleeding. Proper anticoagulation is the first critical step in the effective treatment of DVT. The secondary stage of treatment involves the maintenance of adequate anticoagulation to prevent the development of recurrent thromboembolism (1).

Two main advances in the treatment of DVT have been made in the last decade. The first is the introduction of low-molecular-weight heparin (LMWH) as a replacement for unfractionated heparin (UFH) and the second is an improved ability to identify patients who are likely to benefit from a longer duration of anticoagulant

therapy. Several new anticoagulants with more convenient and potentially safer profiles are now undergoing clinical evaluation in randomized controlled trials.

## 2. Approach to treatment

The objectives of treating venous thrombosis are to prevent local extension of the thrombus, prevent the thrombus from embolizing, and, in certain clinical circumstances, accelerate fibrinolysis. Anticoagulants are effective in most patients for preventing clinically important local extension of thrombosis, but they must be continued for weeks to months after the acute event. Of the two anticoagulants in current use, heparin acts immediately by catalyzing the inhibition of activated coagulation factors (principally thrombin and factor Xa) by antithrombin III (AT-III), while coumarins act much more slowly by inhibiting synthesis of fully gamma-carboxylated vitamin K-dependent coagulation proteins. The fibrinolytic enzymes streptokinase, urokinase, and TPA accelerate the rate of dissolution of thrombi and emboli. Thrombolysis is more expensive than anticoagulant therapy and is associated with a higher risk of bleeding, so its use should be restricted to patients who are likely to benefit from it. There is also good evidence that patients with symptomatic proximal or calf vein thrombosis have a high recurrence rate without treatment. Anticoagulation reduces mortality and recurrence in patients with acute pulmonary embolism and

<sup>\*</sup>Correspondence: Dr. Manoranjan Mahapatra MD, FICP, FIACM, Associate Professor, Department of Hematology, All India Institute of Medical Sciences, New Delhi, India. Email: mrmahapatra@hotmail.com

Table 1. Low molecular weight heparins (LMWH)

Agent	Dosing schedule
Enoxaparin	1 mg/kg SC q 12 hr; 1.5 mg/kg SC q 24 hrs Creatinine clearance $\leq 0.5$ mL/sec, 1 mg/kg SC q 24 hr
Dalteparin	200 IU/kg SC q 24 hr
Tinzaparin	175 IU/kg SC q 24 hr
Fondaparinux	< 50 kg: 5 mg SC q 24 hr 50kg-100 kg: 7.5 mg SC q 24 hr >100 kg: 10 mg SC q 24 hr

Table 2. Risk stratification of recurrent VTE and duration of anticoagulants

Risk Group	Patient characteristics	Risk of recurrence	Duration of anticoagulants
Low	Reversible major risk factors (major surgery, pelvic or leg trauma, major medical illness)	<5%/year	3 months
Moderate	Weak risk factors (estrogen use, long distance travel, minor trauma) and no inherited or acquired thrombophilia identified	<10%/year	6 months
High	Unprovoked thrombotic event with no inherited or acquired thrombophilia identified Unprovoked thrombotic event with heterozygous factor V Leiden or prothrombin G20210A mutation	Around 10%/year	6months*
Very high	Recurrent unprovoked events with or without thrombophilic state identified Unprovoked thrombotic event with antithrombin, protein C, or protein S deficiency; homozygous factor V Leiden; double heterozygosity; antiphospholipid antibody; advanced malignancy syndrome; advanced malignancy	>12%/year	extended or indefinite

\*May consider longer duration of therapy based on patient preference and should be reviewed annually

reduces recurrence in patients with DVT.

### 3. Initial treatment

Anticoagulation is a critical component of effective treatment. In 1996, Koopman and colleagues (2) and Levine and associates (3) demonstrated that LMWH can be used to safely and effectively treat patients with proximal DVT at home. The past decade offers a substantial evidence base, including numerous randomized controlled trials (4). Despite these findings, anticoagulation with LMWH has not been universally embraced, because many physicians continue to use intravenous UFH. Although the higher acquisition cost of LMWH could be partially responsible, cost analyses have suggested that even in the inpatient setting,

LMWH is less costly than UFH (5). Treatment with LMWH demonstrates improved outcomes, cost-effectiveness, and a significantly reduced incidence of heparin-induced thrombocytopenia. Heparin-induced osteoporosis appears to be reduced as well.

Currently, dalteparin, enoxaparin, tinzaparin, and fondaparinux (Table 1) are approved in the United States for the treatment of VTE (6,7). Each of these LMWHs has a different molecular weight, anti-Xa to anti-IIa activity, plasma half-life, and recommended dosage regimens (8).

Although laboratory monitoring is not usually required for patients receiving LMWHs, it is recommended to check the anti-Xa level in patients who have advanced renal disease, are morbidly obese, or are pregnant, because there are theoretical reasons why they might respond

differently to weight-adjusted doses of LMWHs (9,10).

If necessary, the LMWH dose should be adjusted to a target anti-Xa level of 0.6 to 1.0 IU/mL at 4 hours after an injection of a twice-daily regimen, and 1.0 to 2.0 IU/mL for once-daily administration (11). The usual intravenous regimen for UFH is a loading dose of 5000 U followed by a continuous infusion of at least 30 000 U every 24 hours. The dose of UFH is adjusted according to the aPTT by following a validated standard nomogram to maintain a therapeutic heparin level (9). Oral anticoagulant therapy can be started on the first day of treatment and LMWH/UFH should not be stopped until the INR has been at least 2.0 for 2 consecutive days. A platelet count can be done on days 5 to 7 to check for heparin-induced thrombocytopenia if the patient is receiving UFH (1).

#### 4. Long-term anticoagulant therapy

After an initial course of LMWH or UFH, continuing anticoagulant therapy with coumarin derivatives is required to prevent recurrence. Warfarin is the most common agent used as an oral anti-coagulant. Usually, warfarin is started with an average maintenance dose of 5 mg on the first and second days with the expectation that the INR will be in the range of 2.0 to 3.0 in 4 or 5 days. A smaller dose (2-4 mg) is used in the elderly, in patients who have a low body weight, or in those with compromised nutrition (12). The use of a loading dose is discouraged because it may be associated with a transient period of excessive anticoagulation without a corresponding antithrombotic effect. The INR is measured after the first 2 or 3 doses of warfarin, and subsequent doses are adjusted to maintain the INR within the target range. Because the therapeutic window for oral anticoagulant therapy is narrow, frequent monitoring of the INR is essential to reduce the risks of recurrent thrombosis and anticoagulant-related bleeding. Appropriate adjustments in the dose of warfarin usually require twice-weekly monitoring for the first 1 to 2 weeks, followed by weekly monitoring for the next 4 weeks, then once every 2 weeks for a month, and finally every 4 weeks if the INRs have remained in the therapeutic range on a stable warfarin dose and the patient has not experienced any adverse effects. It is unwise to leave the INR unchecked for longer than a 4-week interval even in patients who have maintained a stable warfarin dose because of the

potential interactions of warfarin with food or drugs (13).

#### 5. Duration of anticoagulant therapy

The duration of anticoagulant therapy is influenced by the estimated competing risks of bleeding and recurrent thrombosis and is influenced by patient's preference. The risk of bleeding during the initial period of anticoagulation with UFH or LMWHs is 2% to 5%, whereas the estimated risk of major bleeding with oral anticoagulant therapy is about 3% annually (14). In general, patients should be treated with anticoagulant therapy for a minimum of 3 months. Patients with a reversible risk factor have a low risk of recurrence after 3 months of anticoagulant therapy. In contrast, patients with idiopathic or unprovoked DVT who are treated for only 3 months have a 10% to 27% risk of recurrence in the year after anticoagulants are discontinued (15). Recent evidence suggests that extending therapy beyond 6 months in patients with idiopathic thrombosis does not reduce the risk of recurrent thrombosis to less than 10% in the year after discontinuing anticoagulant therapy. Continuing warfarin after this period protects the patient against future recurrence but also exposes the patient to the risk of anticoagulant-related bleeding (16,17). Based on results of prospective studies and extrapolation from studies on the risk of recurrence after a first episode of venous thrombosis, patients can be stratified into low-, moderate-, high-, and very high-risk groups for recurrence when anticoagulants are discontinued (1) (Table 2).

#### 6. Treatment of DVT in pregnancy

Warfarin is generally avoided because of the risk of warfarin embryopathy and other potential teratogenic effects. UFH has a number of limitations, including heparin-induced osteoporosis, the need for twice-daily subcutaneous injections and the necessity for aPTT monitoring. These disadvantages are virtually eliminated with LMWH. Although there have been no randomized controlled trials comparing UFH with LMWH in pregnancy, there is no reason to expect that the advantages of LMWH in the nonpregnant population would not apply to pregnant women. The controlled delivery date allows discontinuation of LMWH 24 hours prior to induction, thereby reducing the risk of bleeding during delivery.

## 7. Conclusion

Effective therapy for VTE consists of 2 stages: the initial achievement of adequate anticoagulation following diagnosis, and the prevention of recurrent thromboembolic events. Treatment with LMWH remains the current standard of care for effective anticoagulation. Therapy for the prevention of recurrent thromboembolic events in patients with idiopathic VTE as the initial event involves warfarin administered for 6 to 12 months, although research suggests that treatment for up to 2 years may demonstrate significant clinical benefit.

## References

1. Hirsh J, Lee AY. How we diagnose and treat deep vein thrombosis. *Blood* 2002; 99: 3102-3110.
2. Koopman MM, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 1996; 334: 682-687.
3. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep vein thrombosis. *N Engl J Med* 1996; 334: 677-681.
4. Tapson VF. What will it take to initiate a move toward a more aggressive therapeutic approach to venous thromboembolism. *Am J Med* 2008; 121: S20-S27.
5. Gould MK, Dembitzer AD, Sanders GD, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a cost-effectiveness analysis. *Ann Intern Med* 1999; 130: 789-799.
6. Hirsh J, Levine M. Low molecular weight heparin. *Blood* 1992; 79: 1-17.
7. Weitz J. Low molecular weight heparins. *N Engl J Med* 1997; 337: 688-698.
8. Merli GJ. Treatment of venous thromboembolism. *Am J Med* 2008; 121: S2-S9.
9. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001; 119: 64S-94S.
10. Gould MK, Dembitzer AD, Sanders GD, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. *Ann Intern Med* 1999; 130: 789-799.
11. Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997; 337: 688-698.
12. Harrison L, Johnston M, Massicotte MP, et al. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997; 126: 133-136.
13. Ansell J, Hirsh J, Dalen J, et al. Managing oral anticoagulant therapy. *Chest* 2001; 119: 22S-38S.
14. Levine MN, Raskob G, Landefeld S, et al. Hemorrhagic complications of anticoagulant treatment. *Chest* 2001; 119: 108S-121S.
15. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999; 340: 901-907.
16. Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. *N Engl J Med* 1995; 332: 1661-1665.
17. Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. *N Engl J Med* 2001; 345: 165-169.