DVT and Pulmonary Embolism: Part II. Treatment and Prevention

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Treatment goals for deep venous thrombosis include stopping clot propagation and preventing the recurrence of thrombus, the occurrence of pulmonary embolism, and the development of pulmonary hypertension, which can be a complication of multiple recurrent pulmonary emboli. About 30 percent of patients with deep venous thrombosis or pulmonary embolism have a thrombophilia. An extensive evaluation is suggested in patients younger than 50 years with an idiopathic episode of deep venous thrombosis, patients with recurrent thrombosis, and patients with a family history of thromboembolism. Infusion of unfractionated heparin followed by oral administration of warfarin remains the mainstay of treatment for deep venous thrombosis. Subcutaneously administered low-molecular-weight (LMW) heparin is at least as effective as unfractionated heparin given in a continuous infusion. LMW heparin is the agent of choice for treating deep venous thrombosis in pregnant women and patients with cancer. Based on validated protocols, warfarin can be started at a dosage of 5 or 10 mg per day. The intensity and duration of warfarin therapy depends on the individual patient, but treatment of at least three months usually is required. Some patients with thrombophilias require lifetime anticoagulation. Treatment for pulmonary embolism is similar to that for deep venous thrombosis. Because of the risk of hypoxemia and hemodynamic instability, in-hospital management is advised. Unfractionated heparin commonly is used, although LMW heparin is safe and effective. Thrombolysis is used in patients with massive pulmonary embolism. Subcutaneous heparin, LMW heparin, and warfarin have been approved for use in surgical prophylaxis. Elastic compression stockings are useful in patients at lowest risk for thromboembolism. Intermittent pneumatic leg compression is a useful adjunct to anticoagulation and an alternative when anticoagulation is contraindicated. (Am Fam Physician 2004;69:2841-8. Copyright© 2004 American Academy of Family

This is part II of a two-part article on DVT and PE. Part I, "Diagnosis," appears in this on page 2829.

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See page 2745 for definitions of strength-of-recommendation labels.

Mortality from venous thromboembolic disease has decreased significantly in the past 10 to 20 years.[1] Increased survival may be due to better diagnostic strategies, improved recognition of risk factors, and better treatment guidelines. In the past decade, a great deal has been learned about the role of inherited and acquired thrombophilias as risk factors for venous thromboembolic disease. Although treatment of venous thromboembolism remains primarily supportive, there have been refinements in the intensity and duration of anticoagulation regimens for various therapeutic and preventive clinical situations.

Part I[2] of this two-part article addressed the diagnosis of deep venous thrombosis (DVT) and pulmonary embolism (PE). Part II discusses the evaluation for thrombophilias and other secondary causes of venous thromboembolic disease, presents an evidence-based approach to the treatment of DVT and PE, and reviews current recommendations for prevention of venous thromboembolism.

Evaluation for Thrombophilias and Other Secondary Causes

The evaluation for apparent venous thromboembolism begins with a careful history and physical examination. Attention should be given to important risk factors, including previous venous thromboembolism, recent trauma or immobilization, malignancy, use of estrogenic medications, and pregnancy. Multiple spontaneous miscarriages also may indicate underlying thrombogenic conditions.

The basic laboratory evaluation includes a complete blood count, platelet count, prothrombin time, activated partial thromboplastin time (APTT), and comprehensive metabolic panel to look for electrolyte, renal, or hepatic abnormalities. If an evaluation for thrombo-

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philias is being considered, blood should be set aside for screening tests before treatment with heparin and warfarin is initiated.

With the discovery that common thrombophilias are risk factors for venous thromboembolism, the question of when to launch an investigation has been raised. The combined prevalence of inherited thrombophilias and hyperhomocysteinemia is about 50 percent in all patients with DVT and PE.[3] Unfortunately, not all studies included a control group; therefore, it is difficult to establish a reliable estimate of the prevalence of thrombophilias in asymptomatic persons. Because of the lack of prospective studies, there is no clear evidence to guide the decision about when to evaluate patients for thrombophilias. The cost-effectiveness of the evaluation is a concern.

Based on a review of the literature, one investigator[3] proposed the following strategy: patients older than 50 years with an idiopathic first episode of venous thromboembolism and no family history should be considered "weakly thrombophilic" and should undergo a limited investigation *(Table 1)*.[3] Patients with an idiopathic episode of venous thromboembolism who are younger than 50 years, patients with recurrent thrombosis, and patients with a family history of venous thromboembolism should be considered "strongly thrombophilic" and should undergo a more extensive evaluation for thrombophilias. Patients with a first episode of thromboembolism, a clear risk factor for a first episode of venous thromboembolism, (e.g., trauma, immobilization), and no family history of thromboembolism require no work-up for thrombophilias.[3] Most patients with venous thromboembolic disease and a genetic or unchangeable thrombophilia should receive lifetime anticoagulation.[3]

There is no clear evidence that screening all or even selected patients for thrombophilias improves long-term outcomes. Until such evidence becomes available, the above guidelines, the physician's clinical judgment, and consultation with appropriate subspecialists should guide

TABLE 1
Risk-Specific Investigations for Thrombophilias

Clinical characteristics	*Risk of having a thrombophilia*	*Investigations*
First episode of venous thromboembolic disease with known risk factors for thromboembolism and no family history of thromboembolism*	Low	None
Age older than 50 years, idiopathic first episode of venous thromboembolic disease, and no family history of thromboembolism*	Moderate	Resistance to activated protein C with a clotting assay that dilutes patient plasma in factor V–deficient plasma, or genetic test for factor V Leiden mutation Genetic test for prothrombin G20210A mutation Clotting assay for lupus anticoagulant ELISA for antiphospholipid antibodies Plasma homocysteine level
Idiopathic venous thromboembolic disease before age 50 years *or* Recurrent thrombosis *or* Family history of thromboembolism*	High	All of the above and— Antithrombin assay (heparin cofactor assay) Protein C assay Protein S assay

ELISA = enzyme-linked immunosorbent assay.

**—Family history is defined as venous thromboembolic disease occurring in a first-degree relative before the age of 50 years.*

Adapted with permission from Bauer KA. The thrombophilias: well-defined risk factors with uncertain therapeutic implications. Ann Intern Med. 2001;135:367-73.

TABLE 2
Weight-Based Heparin Therapy with Adjustments Based on the APTT

Initial dosage	Bolus of 80 units per kg, then 18 units per kg per hour by infusion
APTT < 35 seconds (<1.2 times control)	Bolus of 80 units per kg, then 4 units per kg per hour by infusion
APTT = 35 to 45 seconds (1.2 to 1.5 times control)	Bolus of 40 units per kg, then 2 units per kg per hour by infusion
APTT = 46 to 70 seconds (1.5 to 2.3 times control)	No change
APTT = 71 to 90 seconds (2.3 to 3.0 times control)	Decrease infusion rate by 2 units per kg per hour.
APTT > 90 seconds (>3.0 times control)	Hold infusion for 1 hour, then decrease infusion rate by 3 units per kg per hour.

APTT = activated partial thromboplastin time.

Adapted with permission from Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. Ann Intern Med 1993;119:875.

management.

Physicians should be aware that antithrombin III, protein C, and S protein assays are inaccurate once a patient has begun anticoagulation therapy. Therefore, an investigation for thrombophilias should not be conducted until at least two weeks after warfarin therapy has been discontinued. Anticoagulation does not affect tests for other common thrombophilias, such as factor V Leiden mutation, hyperhomocysteinemia, and antiphospholipid antibody.

Treatment of DVT

The goals of treatment for DVT are to stop clot propagation and prevent clot recurrence, PE, and pulmonary hypertension (a potential complication of multiple recurrent PEs). These goals usually are achieved with anticoagulation using heparin followed by warfarin (Coumadin). Despite some controversy about the need to treat isolated calf-vein DVT, a recent evidence-based guideline on antithrombotic therapy recommends at least six to 12 weeks of anticoagulation.[4]

There are few evidence-based recommendations for the use of nonpharmacologic measures in patients with DVT. Usual advice for local care includes limb elevation and local application of heat. Activity should be minimal for several days (i.e., the patient's activity should be limited to walking to the bathroom and kitchen). Graded elastic compression stockings have been associated with a 50 percent reduction in the incidence of postphlebitic syndrome.[5]

UNFRACTIONATED HEPARIN

Treatment with unfractionated heparin is based on body weight, and the dosage is titrated based on the APTT. An APTT of 1.5 to 2.3 times control is desirable.[6] Weight-based heparin dosing and adjustments based on the APTT are provided in *Table 2*.[6] This approach to heparin therapy has been shown to achieve adequate anticoagulation quickly and safely.

Adverse reactions associated with heparin therapy include bleeding and thrombocytopenia. The risk of adverse reactions is highest in patients with any of the following: age greater than 65 years, recent surgery, or conditions such as peptic ulcer disease, liver disease, occult neoplasia, and bleeding diathesis. Transient thrombocytopenia may occur in 10 to 20 percent of patients, but major hemorrhagic complications occur in fewer than 2 percent of patients.[7]

Heparin can be stopped after four or five days of combined therapy with warfarin if the International Normalized Ratio (INR) of prothrombin clotting time exceeds 2.0.[8]

LOW-MOLECULAR-WEIGHT HEPARIN

Compared with unfractionated heparin, low-molecular-weight (LMW) heparin offers distinct advantages: it has a longer biologic half-life, it can be administered subcutaneously once or twice daily, dosing is fixed, and laboratory monitoring is not required. In addition, some adverse effects of unfractionated heparin, such as thrombocytopenia, appear to be less likely. In patients with DVT, subcutaneous administration of heparin is at least as effective as continuous infusion of unfractionated heparin in preventing complications and reducing the risk of recurrence.[9]

Outpatient management of DVT using LMW heparin for short-term anticoagulation until warfarin is at a therapeutic level is safe and cost-effective, despite the higher cost of the heparin.[10] Candidates for outpatient therapy must be hemodynamically stable, without renal failure, and not at high risk for bleeding. Furthermore, they must have a stable and supportive home environment, as well as access to daily monitoring until the INR is therapeutic. Like unfractionated heparin, LMW heparin is given in combination with warfarin for four to five days.[8] Simultaneous initiation of warfarin and unfrac-

TABLE 3
Initiation of Warfarin Therapy at 5 mg per Day

Day	*INR*	*Warfarin dosage (mg per day)*
1		5
2		5
3	< 1.5	10
	1.5 to 1.9	5
	2.0 to 2.9	2.5
	> 3.0	0
4	< 1.5	10
	1.5 to 1.9	7.5
	2.0 to 2.9	5
	> 3.0	0
5	< 2.0	10
	2.0 to 2.9	5
	> 3.0	0
6	< 1.5	10
	1.5 to 1.9	7.5
	2.0 to 2.9	5
	> 3.0	0

INR = International Normalized Ratio.

Adapted with permission from Crowther MA, Harrison L, Hirsh J. Reply. Warfarin: less may be better. Ann Intern Med 1997:127:333.

tionated heparin or LMW heparin has not been associated with any clinically important adverse outcomes.[4]

Enoxaparin (Lovenox) was the first LMW heparin approved by the U.S. Food and Drug Administration (FDA) for the treatment of DVT in a dosage of 1 mg per kg twice daily or 1.5 mg once daily. Dalteparin (Fragmin), another LMW heparin, is approved only for prophylaxis of DVT. In clinical trials of DVT treatment,[11,12] dalteparin has been given in a dosage of 200 IU per kg per day (single dose or two divided doses). The FDA has approved the use of tinzaparin (Innohep), in a dosage of 175 anti-Xa IU per kg per day, for the treatment of DVT.

WARFARIN

Once acute anticoagulation is achieved, warfarin is the drug of choice for long-term therapy to prevent clot recurrence. A standard warfarin protocol includes starting treatment at 5 mg per day and titrating the dosage every three to seven days to achieve an INR between 2.0 and 3.0 *(Table 3)*.[13] Attempts have been made to maintain patients at an even lower INR (between 1.5 and 2.0), but results have been contradictory.[14,15] Unless further data show otherwise, anticoagulation with a standard INR goal of 2.0 to 3.0 should be used.

Promising results have been shown for a protocol in which warfarin is initiated in a dosage of 10 mg per day *(Table 4)*.[16] In one study,[16] consecutive outpatients being treated with LMW heparin for DVT or PE were randomized to a 5-mg or 10-mg warfarin protocol. An INR higher than 1.9 was achieved an average of 1.4 days sooner in the patients who received warfarin according to the 10-mg protocol. Clot recurrence, bleeding events, and morbidity did not differ in the two treatment groups.

DURATION OF ANTICOAGULATION

The duration of anticoagulation depends on whether the patient has a first episode of DVT, ongoing risk factors for venous thromboembolic disease, and known thrombophilia. The most recent evidence-based recommendations from the American College of Chest Physicians are based on the risk of clot recurrence *(Table 5)*.[4,17]

SPECIAL SITUATIONS

Warfarin therapy is contraindicated during pregnancy. Therefore, long-term treatment with LMW heparin is used when DVT occurs in a pregnant woman.[4]

The incidence of recurrent venous thromboembolism is increased in patients with cancer. These patients also are more likely to have complications from long-term warfarin therapy. A large multicenter trial[18] in patients with cancer and venous thromboembolism found that the likelihood of recurrent clots was lower in the patients who received long-term prophylaxis with LMW heparin than in those who received warfarin. In this trial, 13 patients needed to be treated with LMW heparin instead of warfarin to avoid one episode of recurrent DVT. An interpretation of the study results must consider the fact that a significant proportion of patients in both groups died of cancer, and none died of PE.

Except in patients who are pregnant or have cancer, there is no advantage to using LMW heparin rather than warfarin for long-term anticoagulation.

OTHER THERAPIES

Most patients do well with unfractionated heparin or LMW heparin. Therefore, thrombolytic therapy is not recommended for the treatment of DVT, except in selected patients with massive ileofemoral thrombi or as part of a research protocol.[7] No evidence from adequately powered, randomized controlled trials indicates that thrombolytic

TABLE 4
Initiation of Warfarin Therapy at 10 mg per Day*

	Warfarin dosage (mg per day)			*Warfarin dosage (mg per day)*		
Day 3 INR	*Day 3*	*Day 4*	*Day 5 INR*	*Day 5*	*Day 6*	*Day 7*
<1.3	15	15	<2.0	15	15	15
1.3 to 1.4	10	10	2.0 to 3.0	7.5	5	7.5
			3.1 to 3.5	0	5	5
		> 3.5	0	0	2.5	
1.5 to 1.6	10	5	<2.0	7.5	7.5	7.5
1.7 to 1.9	5	5	2.0 to 3.0	5	5	5
		3.1 to 3.5	2.5	2.5	2.5	
		> 3.5	0	2.5	2.5	
2.0 to 2.2	2.5	2.5	<2.0	5	5	5
2.3 to 3.0	0	2.5	2.0 to 3.0	2.5	5	2.5
		3.1 to 3.5	0	2.5	0	
		> 3.5	0	0	2.5	
>3.0	0	0	<2.0	2.5	2.5	2.5
		2.0 to 3.0	2.5	0	2.5	
		3.1 to 4.0	0	2.5	0	
		> 4.0	0	0	2.5	

INR = International Normalized Ratio.

**—On days 1 and 2, all patients receive 10 mg per day.*

Adapted with permission from Kovacs MJ, Rodger M, Anderson DR, Morrow B, Kells G, Kovacs J, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. Ann Intern Med 2003;138:716.

TABLE 5
ACCP Recommendations for Long-Term Anticoagulation in Patients with DVT or PE (INR goal: 2.0 to 3.0)

Thromboembolism	*Duration of anticoagulation*	*Strength of recommendation**	*Reference*
First event with a reversible or time-limited risk factor for venous thromboembolic disease (e.g., trauma, surgery)	At least 3 months	A	4
First episode of idiopathic venous thromboembolic disease	At least 6 months	A	4
Recurrent idiopathic venous thromboembolic disease or continuing risk factor (e.g., thrombophilia)	At least 12 months	B	4
Symptomatic isolated calf-vein thrombosis	6 to 12 weeks†	A	17

ACCP = American College of Chest Physicians; DVT = deep venous thrombosis; PE = pulmonary embolism; INR = International Normalized Ratio.

**—ACCP ratings have been converted to American Family Physician's strength-of-recommendation taxonomy.*
†—Serial noninvasive studies of the lower extremities to assess for extension are an option.

Adapted with permission from Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, et al. Antithrombotic therapy for venous thromboembolic disease. Chest 2001;119(1 suppl):184S, with additional information from reference 17.

therapy reduces all-cause mortality (even in patients with massive ileofemoral thrombi). Furthermore, the risk of intracranial hemorrhage is greater with thrombolytic therapy than with unfractionated heparin therapy.

Treatment of PE

Anticoagulation is the mainstay of treatment for PE. Because of the risks of hypoxemia and hemodynamic instability associated with PE, close monitoring and supportive therapy are necessary. Therefore, outpatient treatment of PE is not advised.

Unfractionated heparin most commonly is used to treat patients with PE, although LMW heparin also is safe and effective.[9] Only enoxaparin and tinzaparin have received formal FDA approval for use in the treatment of PE.

Thrombolysis clearly is indicated in patients with massive PE and associated hemodynamic instability. However, the role of thrombolysis in patients with submassive PE remains controversial. In the largest study to date,[19] improved survival was observed in patients treated with alteplase plus heparin compared with heparin alone. Using death and major complications as the end point, the number needed to treat was 7.3. One fewer death was observed for every 82 patients treated with the combination therapy.[10]

In patients with PE, the usual dose of alteplase (Activase) is 100 mg given by intravenous infusion over a period of two hours. Streptokinase (Streptase) is given in a 250,000-IU loading dose, followed by 100,000 IU per hour for 24 hours. Delivery of thrombolytics directly into the thrombus by catheter has been described but has not been shown to be superior to peripheral infusion.

TABLE 6
Prevention of Venous Thromboembolism in Patients Undergoing Surgery

Risk level	*Options for prophylaxis*
Highest	
Major surgery in patients older than 40 years who have one of the following additional risk factors: previous venous thromboembolism, cancer, thrombophilia	LMW heparin Warfarin (Coumadin) Low-dose unfractionated heparin or LMW heparin, and graduated compression stockings or pneumatic compression stockings Intravenous unfractionated heparin
Hip or knee arthroplasty	
Hip fracture surgery	
Major trauma	
Acute spinal cord injury	
High	
Nonmajor surgery in patients older than 60 years or patients with additional risk factors	Low-dose unfractionated heparin administered every 8 hours LMW heparin Pneumatic compression stockings
Major surgery in patients older than 40 years or patients with additional risk factors	
Moderate	
Minor surgery in patients with additional risk factors	Low-dose unfractionated heparin administered every 12 hours LMW heparin Graduated compression stockings Pneumatic compression stockings
Nonmajor surgery in patients 40 to 60 years of age	
Major surgery in patients younger than 40 years who have no additional risk factors	
Low	
Minor surgery in patients younger than 40 years who have no additional risk factors	Aggressive mobilization

LMW = low-molecular-weight.

Adapted with permission from Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, et al. Prevention of venous thromboembolism. Chest 2001;119(1 suppl):134S.

Anticoagulation with warfarin should follow heparin therapy. The same regimens are used for DVT and PE *(Tables 3[13] and 4[16])*.

Use of an inferior vena cava filter occasionally is indicated when PE recurs despite anticoagulation or there are contraindications to such treatment. Evidence from a single clinical trial[20] showed added benefit from the use of a filter in patients who were receiving anticoagulation. The filter was associated with a lower 12-day rate of PE, but a higher rate of DVT recurrence and no difference in survival at two years of follow-up.[20] At this time, the inferior vena cava filter cannot be considered standard first-line therapy.

Finally, acute pulmonary embolectomy may be beneficial in the unstable patient who has not responded to conventional treatments.[21]

Prevention of Thromboembolic Disease

The need for preventive measures depends on a patient's risk factors for venous thromboembolism. Prolonged immobilization, such as may occur with hospitalization, trauma, or general debility, is one risk factor. Surgical patients, especially the elderly and patients undergoing orthopedic procedures, are at particularly high risk for thromboembolic disease. The risk of venous thromboembolism in critically ill patients generally is under-recognized; many of these patients have at least one significant risk factor.

Healthy younger patients undergoing minor surgery are at low risk for venous thromboembolism, and aggressive postoperative mobilization usually is sufficient. The highest risk category is reserved for patients with acute spinal cord injury or other major trauma, as well as patients undergoing lower-extremity orthopedic surgery and patients with risk factors for venous thromboembolism *(Table 6)*.[22]

The simplest approach to prophylaxis for venous thromboembolism is low-dose unfractionated heparin, 5,000 units administered subcutaneously every eight or 12 hours. However, LMW heparin has been shown to be as effective as unfractionated heparin for surgical prophylaxis of DVT over periods of seven to 10 days (with a possible dose-dependent advantage on bleeding complications) and appears to be at least as effective as warfarin in most postoperative settings.[22] In hip replacement surgery, LMW heparin or warfarin may be used for a minimum of seven to 10 days, and some studies have extended the period to over a month. Regimens for LMW heparin in different

TABLE 7

LMW Heparins: Regimens for Prevention of Venous Thromboembolism

General surgery in high-risk patient
Dalteparin (Fragmin): 5,000 units SC 8 to 12 hours before surgery and once daily after surgery
Enoxaparin (Lovenox)*: 40 mg SC 1 to 2 hours before surgery and once daily after surgery; or 30 mg SC every 12 hours starting 8 to 12 hours after surgery
General surgery in moderate-risk patient
Dalteparin: 2,500 units SC 1 to 2 hours before surgery and once daily after surgery
Enoxaparin: 20 mg SC 1 to 2 hours before surgery and once daily after surgery
Nadroparin†: 2,850 units SC 2 to 4 hours before surgery and once daily after surgery
Tinzaparin (Innohep): 3,500 units SC 2 hours before surgery and once daily after surgery
Orthopedic surgery
Dalteparin: 5,000 units SC 8 to 12 hours before surgery, then once daily starting 12 to 24 hours after surgery; or 2,500 units SC 6 to 8 hours after surgery, then 5,000 units SC once daily
Enoxaparin: 30 mg SC every 12 hours starting 12 to 24 hours after surgery; or 40 mg SC once daily starting 10 to 12 hours after surgery
Nadroparin†: 38 units per kg SC 12 hours before surgery, 12 hours after surgery, and once daily on postoperative days 1, 2, and 3, then increase to 57 units per kg SC once daily
Tinzaparin: 75 units per kg SC once daily starting 12 to 24 hours after surgery; or 4,500 units SC 12 hours before surgery and once daily after surgery
Major trauma
Enoxaparin: 30 mg SC every 12 hours starting 12 to 36 hours after injury if the patient is hemostatically stable
For acute spinal cord injury, enoxaparin: 30 mg SC every 12 hours
Medical conditions
Dalteparin: 2,500 units SC once daily
Enoxaparin: 40 mg SC once daily
Nadroparin†: 2,850 units SC once daily

LMW = low-molecular-weight; SC = subcutaneous.

**—Dosage for enoxaparin is expressed in anti-Xa units: 1 mg = 100 anti-Xa units.*

†*—Available in Canada.*

Adapted with permission from Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, et al. Prevention of venous thromboembolism. Chest 2001;119(1 suppl):136S.

prophylactic scenarios are provided in *Table 7*.[22]

Intermittent pneumatic leg compression devices are useful adjuncts to anticoagulation, as well as alternatives in patients with significant contraindications to the use of anticoagulants. Elastic compression stockings also are useful, but only in low-risk patients. Aspirin is not recommended for surgical prophylaxis.[23] Measures shown to be effective in the prevention of DVT in surgical patients, depending on level of risk, are listed in *Table 6*.[22]

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