Venous thromboembolic disease: decisions in treatment and prophylaxis

In a number of circumstances, there is strong evidence for adopting a more aggressive approach to prevention than is customarily used.

Brydon J.B. Grant, MD, and Ali A. El-Solh, MD

Last month, the authors reviewed strategies for optimizing the recognition of acute thromboembolic disease, covering clues that can be derived from the clinical presentation and stepwise approaches to the investigation of suspected deep-vein thrombosis (DVT) and pulmonary embolism (PE).

TREATMENT OF DVT

Anticoagulation is the mainstay of treatment for DVT. Once the patient has been adequately anticoagulated with heparin, you can initiate warfarin therapy. (See the following section on the treatment of pulmonary embolism for a discussion of the administration of anticoagulants.)

The optimal duration of oral anticoagulant therapy is uncertain. In the absence of well-defined criteria, treatment of DVT is continued for 3 to 6 months. Trials of shorter periods of therapy have revealed that 4 weeks of anticoagulation may be adequate for patients with postoperative venous thromboembolism, but a longer course is necessary for those without such reversible risk factors as recent surgery.[1] Other investigators have suggested that it is reasonable to treat patients with reversible risk factors for 6 weeks and extend anticoagulation up to 6 months in those with a first episode of DVT.[2] Consider lifelong therapy for patients with recurrent episodes of DVT or an inherited hypercoagulable state.

The rationale for using thrombolytic therapy in DVT stems primarily from concern about the high incidence of postphlebitic syndrome.[3] There is, however, an increased risk of bleeding with these agents. The question of whether the benefits of thrombolysis outweigh the risks of bleeding remains unsettled.[4]

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KEY PRACTICE POINTS

In the absence of well-defined criteria, treat DVT for at least 3 months.

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Consider thrombolytic therapy in hemodynamically unstable patients with acute massive PE.

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Low-dose heparin has been shown to reduce the incidence of DVT after MI, general surgery, and stroke.

Dr Grant is Professor of Medicine, and Dr El-Solh is Pulmonary and Critical Care Fellow, Section of Pulmonary and [illegible], Department of Veterans Affairs Medical Center and Department of Medicine, State University of New York at Buffalo.

Table 1

Heparin therapy for venous thromboembolism

Initial		80-U/kg bolus, then 18 U/kg/h
Maintenance		
PTT (sec)	*(times control)*	
<35	<1.2	80-U/kg bolus, then increase by 4 U/kg/h
35–45	1.2–1.5	40-U/kg bolus, then increase by 2 U/kg/h
46–70	1.5–2.3	No change
71–90	2.3–3.0	Decrease by 2 U/kg/h
>90	>3.0	Hold infusion for 1 h, then decrease by 3 U/kg/h
Testing		Check PTT every 4–6 h until 46–70 sec, then check daily Check platelet count daily, stop heparin if count falls below 100,000/mm³
Duration		At least 4–5 days' overlap with warfarin

TREATMENT OF PE

Pulmonary embolism is treatable when recognized early. Hospital mortality is about 26% for untreated PE[5] and 2.5% for treated PE.[6]

There are three main modes of therapy for PE: anticoagulation, thrombolysis, and inferior vena cava (IVC) interruption. Unless there is a clear contraindication such as active hemorrhage, early initiation of anticoagulation is the treatment of choice in patients with a high probability of PE. The role of thrombolytic agents in PE remains unsettled, and this therapy continues to be highly individualized. IVC interruption reduces the risk of PE but does not treat DVT.

Anticoagulation. Heparin, a glycoaminoglycan, is the cornerstone of therapy for PE. It combines with the plasma cofactor antithrombin III and binds irreversibly to thrombin, inactivating it. In addition, heparin potentiates the inhibition of activated factors IX, X, and XI and prevents the formation of stable fibrin clots by inhibiting the activation of the fibrin stabilization factor.

Keep the activated partial thromboplastin time (PTT) within the therapeutic range in patients treated with heparin, since inadequate anticoagulation creates a predisposition to recurrent emboli. Published guidelines[7,8] for administering and adjusting heparin therapy are summarized in Table 1.

Carefully monitor patients receiving heparin for signs of bleeding using daily hematocrits and platelet counts. Management includes avoidance of antiplatelet compounds. In patients with massive bleeding, infuse protamine sulfate immediately at a dose of 1 mg for each estimated 100 U of heparin in circulation.

A serious side effect of both low-dose (5,000 U SC q12h) and full-dose (Table 1) heparin therapy, thrombocytopenia is reported to occur in up to 30% of patients. This complication appears to be mediated by heparin-dependent IgG platelet-aggregating antibodies. It usually develops within 1 to 20 days of initiating therapy; therefore, have the platelet count checked regularly. Rarely, a life-threatening condition known as the white-clot syndrome involving disseminated thromboses has been associated with heparin-induced thrombocytopenia.

In general (with the exception of the first trimester of pregnancy), start the oral anticoagulant warfarin as soon as the diagnosis of venous thromboembolism has been confirmed (Table 2). Warfarin interferes with the activation of posttranslational vitamin K–dependent gamma-carboxylation of coagulation factors II, VII, IX, and X. In addition, warfarin inhibits the vitamin K–dependent factors C and S by the same mechanism. Therefore, it acts as an anticoagulant at the same time that it induces a potential thrombogenic effect. For this reason, a 4- or 5-day overlap of heparin and warfarin is recommended.

It is currently agreed that an INR (International Normalized Ratio) of 2.0 or 3.0 times baseline is sufficient to halt the thrombotic process. Once the decision to continue anticoagulation is made, start warfarin early in the course of therapy and maintain it for at least 3 months. Then, base the

decision to end treatment on whether the factors originally predisposing to PE have been resolved.

Thrombolysis. Thrombolytic therapy promotes rapid resolution of PE, reverses right-ventricular failure, and provides return of flow to the pulmonary circulation. Thrombolysis may ultimately prove to bring greater improvement in quality of life than does anticoagulation, but this has yet to be substantiated.

There is no evidence that mortality from PE is altered significantly with the early institution of thrombolytic therapy. Nevertheless, 1980 National Institutes of Health guidelines for the treatment of PE, which are still in use, recommend the use of thrombolytic therapy.[9] Consider thrombolytic therapy in hemodynamically unstable patients who have suffered an acute massive PE.

Intracranial bleeding is the most feared complication of thrombolytic therapy. Avoid invasive procedures, including arterial and venous blood draws, in patients receiving thrombolytics. If the thrombolytic agent is infused directly into the pulmonary artery, take care to minimize bleeding from the puncture site.

Absolute contraindications to thrombolytic therapy[10] and appropriate dosages[7] of the three thrombolytics approved for the treatment of PE are given in Table 3.

Inferior vena cava interruption. Inferior vena cava filters are mechanical devices placed percutaneously, most commonly below the renal veins, to prevent migration of thrombi from the lower extremities to the lung. Placement of an IVC filter is indicated in patients with PE when

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Table 2

Warfarin therapy for venous thromboembolism

Initial	10 mg daily for 2 days, starting when PE is confirmed
Maintenance	Adjust dosage to achieve INR of 2.0–3.0
Testing	Test INR daily until dosage is stabilized
Duration	3 months for first episode 12 months for second episode Lifelong if over two episodes or there is continuing risk

Table 3

Thrombolytic therapy for PE

Contraindications

Major internal hemorrhage in previous 6 months

History of intracranial disease, such as cerebrovascular accident, aneurysm, abscess, head trauma, malignancy

Surgical procedure within past 10 days, ophthalmologic surgery within past 6 weeks

Hypertension (diastolic >110 mm Hg or systolic >200 mm Hg) or retinopathy with retinal hemorrhages or exudates

Infective endocarditis, pericarditis, or cardiopulmonary resuscitation within the past 2 weeks

Bleeding disorder

Severe trauma within previous 2 months

Hematocrit <30%, occult blood on stool examination

Pregnancy or first 10 days postpartum, lactation, severe hepatic or renal disease

Management

Stop heparin, start thrombolysis when PTT or TT <1.5 times control

Use alteplase 100 mg over 2 h or urokinase 4,400 IU/kg load, then 4,400 IU/kg/h for 12 h, or

Streptokinase 250,000 IU load, then 100,000 IU/h for 24 h

Restart heparin infusion, bolus if PTT or TT <1.5 times control

Table 4

Prophylaxis for venous thromboembolism

Condition	Recommendation
Moderate-risk general surgery and age >40 years	Low-dose heparin (5,000 U SC) 2 h before and q12h after surgery, elastic stockings or intermittent pneumatic compression in peri/postoperative period
High-risk general surgery and age >40 years	Low-dose heparin q8h or low-molecular-weight heparin (eg, enoxaprin 30 mg SC q12h)
High-risk general surgery and age >40 years prone to wound complications, intracranial neurosurgery	Intermittent pneumatic compression
Very high risk general surgery	Warfarin to achieve INR of 2.0–3.0
Hip replacement, hip fracture surgery	Low-molecular-weight heparin, warfarin to achieve INR of 2.0–3.0
Knee replacement	Low-molecular-weight heparin or intermittent pneumatic compression
General medical patients with risk factors, ischemic stroke, lower-extremity paralysis	Low-dose heparin q12h or low-molecular-weight heparin
Long-term central line in cancer patients	Warfarin 1 mg daily
Acute myocardial infarction	Low-dose heparin q8h or warfarin to achieve INR of 2.0–3.0

there are contraindications to anticoagulation or a recurrence of PE despite therapeutic anticoagulation. This device has an excellent long-term patency record, even when used without concomitant anticoagulation.[11]

In patients with extensive trauma, particularly involving the head and lower extremities, the placement of an IVC filter offers protection against possible future PE. Perforation of the IVC, filter migration, and infections are among the few complications that are associated with the use of this technique.

Other approaches. Surgical embolectomy may be considered when anticoagulants and thrombolytics are contraindicated. The procedure carries a high mortality and is available only in specialized centers.

PROPHYLAXIS

The Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy has provided new recommendations for the prevention of venous thromboembolism.[12] Table 4 summarizes the circumstances in which there is compelling evidence for the effectiveness of prophylaxis based on randomized clinical trials having high statistical power. The reader is referred to the report of the conference[12] for further details and for a discussion of other circumstances in which prophylaxis is recommended although the evidence is less strong; for example, low-risk surgery, very high risk surgery with multiple risk factors, acute spinal injury, and multiple trauma.

Low risk is defined as uncomplicated minor surgery in patients under 40 who have no clinical risk factors. (Risk factors include prolonged immobilization or paralysis; prior venous thromboembolism; cancer; obesity; major surgery; varicose veins; congestive cardiac failure; stroke; fractures of the pelvis, hip, and leg; and, possibly, high-dose estrogen use.) Moderate risk consists of major surgery in those over 40 with no other risk factors, whereas high risk is major surgery in those over 40 who have additional risk factors or myocardial infarction. Very high risk is major surgery in those over 40 with prior venous thromboembolism, malignant disease, orthopedic surgery, stroke, hip fracture, or spinal cord injury. □

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