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Deep Venous Thrombosis: Guide to Tailoring the Prophylactic Regimen

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ABSTRACT: Initiate prophylactic therapy when you suspect that a patient is at significantly increased risk for deep venous thrombosis (DVT). This includes those undergoing surgery (especially orthopedic surgery), persons with illnesses associated with increased risk of DVT (such as CHF or cancer), and those with a congenital deficiency of proteins C and S and antithrombin III. Risk factors for DVT also include obesity, prolonged bed rest, age older than 40, and a history of DVT or pulmonary thromboembolism. Low-dose unfractionated heparin (5,000 U every 8 or 12 hours), low-intensity warfarin (with an INR of 2 to 3), and intermittent pneumatic compression are the mainstays of therapy; tailor their use to fit the patient's risk profile, and continue therapy for as long as the risk exists. Low molecular weight heparin is an effective alternative to unfractionated preparations and may be preferable in some settings.

Pulmonary thromboembolism is probably the most common preventable cause of in-hospital mortality. Fatal pulmonary thromboembolism occurs as often as 100,000 times each year in the United States.

Prophylactic therapy has proved to be efficacious and cost-effective not only in preventing deep venous thrombosis (DVT) in the legs but also in decreasing the incidence of pulmonary thromboembolism.[1] However, prophylactic measures are often not used to their full benefit.

Here we will review the appropriate use of heparin and warfarin—the two major prophylactic agents—and the role of external intermittent pneumatic compression of the calf muscles. We also will discuss the use of the international normalized ratio (INR) in monitoring the effect of warfarin and the emerging role of low molecular weight heparin (LMWH).

Our recommendations are primarily based on the Fourth American College of Chest Physicians (ACCP) Conference on Antithrombotic Therapy.[2] The published papers from that conference are well referenced and summarize much of the data collected in the past few years. They contain recommendations for alternative prophylactic approaches in various risk groups in much more detail than is possible here.

NATURAL HISTORY OF DVT

Most thrombi first form in the deep venous system of the calf. The majority (80%) of these remain localized and eventually resolve on their own, but approximately 20% propagate above the knee. Roughly half of these will become emboli, accounting for 95% of all clinically significant pulmonary thromboemboli.[3] DVT prophylaxis can thus prevent the morbidity and mortality caused by pulmonary emboli.

Patients at risk. A number of studies have defined the risk of DVT formation and of fatal pulmonary thromboembolism within various pa-

tient populations (Table 1). The epidemiologic data base continues to grow, and an excellent recent review article is available.[4]

While the risk tends to be highest in the surgical population, several common illnesses, such as CHF, MI, and stroke, are strongly associated with DVT. Other less common illnesses associated with DVT include malignancy (particularly adenocarcinomas), homocystinuria, and clotting disorders. Congenital deficiency of proteins C and S and antithrombin III has been found in patients with "idiopathic" DVT, and antithrombin III resistance has recently been reported in 5% of the "normal" population.

Factors that increase the risk of DVT formation in both medical and surgical patients include obesity, prolonged bed rest, age (older than 40), and a history of DVT or pulmonary thromboembolism. Pregnancy and possibly high-dose estrogen use have been implicated as well.

When compared with the general population, all surgical patients are at increased risk for DVT during the immediate postoperative period. This risk is highest during the first 3 postoperative days, but it does not return to normal until after the patient is fully ambulatory.[5]

Clagett and associates[4] have estimated the level of risk in various groups of surgical and medical patients. Thoracic surgery seems to carry less risk of thrombosis than abdominal operations, which, in turn, are less risky than pelvic surgery.

Orthopedic patients are at highest risk, particularly after pelvic fracture repair or total hip replacement. In this setting, thrombi are not necessarily propagated from the calf veins. Rather, they may form in the iliofemoral veins on the side on which the operation is performed, probably in relation to local endothelial damage at the time of surgery or injury.

Table 1—Patients at risk for DVT

Patients	Incidence of DVT (%)	Effective prophylaxis
Surgical		
General surgery (overall)	25	LDUH *or* LMWH
Low risk (under age 40 or no risk factors)		Early ambulation and ES may be adequate
High risk		Add ES and IPC to LDUH *or* to LMWH *or* to low-intensity warfarin
Increased risk of wound hematoma		ES and IPC
Neurosurgery	10-20	ES and IPC
Orthopedic surgery		
Hip fracture or replacement	40-70	LMWH *or* low-intensity warfarin
Knee replacement	60	LMWH *or* IPC
Medical		
Patients with MI	10-20	LDUH
ICU patients (eg, those with CHF, chest infections, respiratory failure)	10-20	LDUH *or* LMWH
Patients with ischemic stroke	40	LDUH *or* LMWH

DVT, deep venous thrombosis; LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparin; ES, graded elastic compression stockings; IPC, intermittent pneumatic compression.

Data from Clagett GP et al.[4]

COAGULATION

The mechanisms that promote thrombosis formation can still be best understood in terms of the triad of factors identified by Virchow in 1858: abnormalities of the blood, of the vessel wall, and of blood flow.

Role of venous stasis. Venous return from the legs is enhanced by the pumping action of the leg muscles, which compresses the vessels and facilitates emptying. All of the patient groups listed in Table 1 share a decreased mobility and thereby a de-

creased venous flow in the legs. Venous stasis may predispose the patient to thrombosis by allowing accumulation of relatively high concentrations of thrombin, which initiates local fibrin deposition. This is followed by platelet aggregation and thrombus formation. Normal venous flow dilutes thrombin and enables its inactivation by natural anticoagulant pathways.

The blood and the vascular endothelium maintain a tightly regulated dynamic balance of coagulant and anticoagulant activity. Under normal conditions, the remarkable coagulant potential of the blood is held in check by the anticoagulant and fibrinolytic activity of the vascular endothelium.

The coagulation cascade. Coagulation is produced by the sequential activation of a cascade of circulating serine proteases (Figure 1) leading to the conversion of prothrombin (factor II) to thrombin (factor IIa). Thrombin cleaves the soluble protein fibrinogen into insoluble fibrin, which—along with platelets—forms either a hemostatic plug at breaks in the vessel wall or an intravascular thrombus.

The coagulation cascade is divided into the intrinsic and extrinsic pathways. The activated partial thromboplastin time (aPTT) clinically determines intrinsic cascade activity; the prothrombin time (PT) determines extrinsic activity.

The intrinsic cascade is activated by the contact of blood with a foreign surface (eg, collagen in vivo or glass in vitro). The extrinsic cascade is spontaneously activated when factor VII binds to tissue factor, its protein cofactor. Unregulated activation of the extrinsic cascade is ordinarily prevented in vivo because, under normal conditions, tissue factor is not expressed by the vascular endothelium.

Coagulation factors VIII and V are not serine proteases; they are cofactors that markedly enhance (300,000-fold) the rate of activation of the cascade.[1] Factor VIII increases the rate by which factor IX activates X, and factor V accelerates the rate by which Xa activates prothrombin (II) (Figure 2).

The vascular endothelium plays a key role in the overall regulation of fibrinolysis. Endothelial cells are the major producers of tissue plasminogen activator (tPA), which is the most important in vivo activator of plasminogen. The plasmin produced removes fibrin clots by lysing fibrin (Figure 3).

Regulating coagulation. Coagulation can be regulated by either of two strategies: inhibition of the action of the serine proteases (Figure 1) or inhibition of coagulation cofactor activity (Figure 2). Both types of activity are regulated by the body, and the endothelium is the major site of this regulation of coagulation.

Antithrombin III. The best-known natural anticoagulant system is that of antithrombin III, a protein that binds one to one with the active site of serine proteases and thereby prevents their action. Antithrombin III has been demonstrated to inhibit at least factors IX and X and thrombin. Its effectiveness is enhanced by the glycoprotein

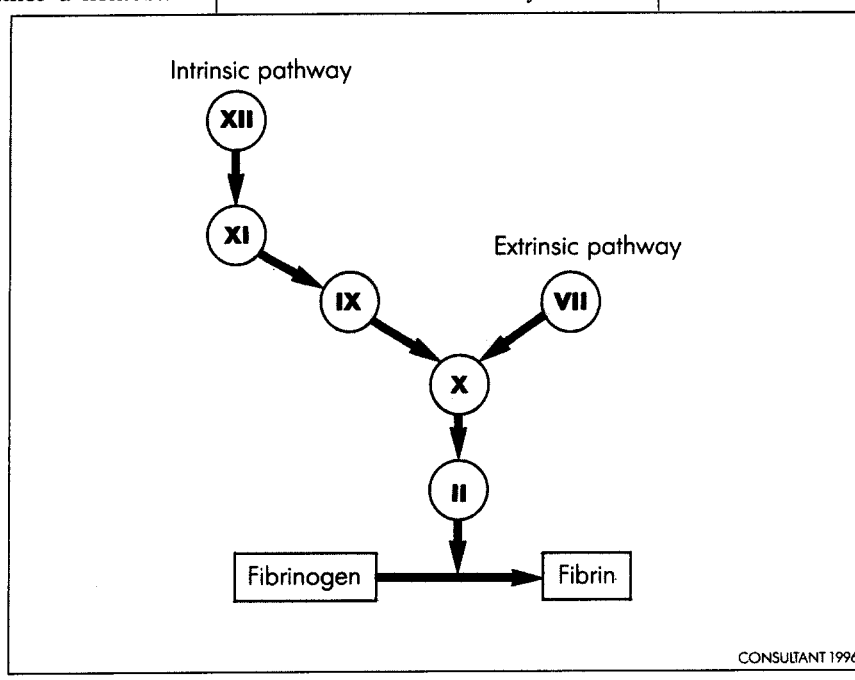

Figure 1—Sequential activation of serine proteases. This leads to conversion of prothrombin (factor II) to thrombin (factor IIa) and subsequent conversion of fibrinogen to fibrin. (Coagulation factors VIII and V are not serine proteases and therefore are not listed.)

heparin. Exogenous heparin mimics the action of heparan sulfate, a naturally occurring protein found on the endothelial cell surface.

Protein C. The protein C anticoagulant system is not as well appreciated as that of antithrombin III, but it may be even more important in the natural regulation of thrombosis. Protein C is vitamin K–dependent and is synthesized by the liver. When it is activated at an endothelial receptor, protein C inactivates coagulation cofactors VIIIa and Va. Small decrements in cofactor activity can result in marked decreases in thrombin generation. The interaction of heparin-antithrombin III and protein C with the coagulation cascade is seen in Figure 4.

Although the interactions of the coagulation and fibrinolytic systems are complex, the general concepts (particularly those relating to thrombosis) can be stated simply. Predisposing conditions to thrombosis both promote stasis and favor the development of a procoagulant state.

Inflammation and tissue injury evoke an acute-phase response, during which the concentrations of the coagulant proteins increase.[6] Changes occur that diminish the concentrations of activated protein C and of tPA and, thereby, the antithrombogenic activity of the endothelium. Conditions such as surgery, MI, and CHF all shift the balance between coagulation and anticoagulation in favor of thrombosis.

WHEN TO INITIATE PROPHYLAXIS

In general, initiate DVT prophylaxis whenever you recognize that a patient is at significantly increased risk for DVT formation. Continue the prophylaxis for as long as that risk exists. Although guidelines have been developed for the use of prophylactic methods in certain clinical situations (Table 2), these are *only* guidelines; they should be tailored to the individual patient and situation.

Prophylactic regimens may be modified for a particular situation, but they must not be used to defer evaluation of the clinical suspicion of thrombosis or of pulmonary thromboembolism. DVT prophylaxis is inadequate to forestall the propagation of a thrombus or to prevent pulmonary thromboembolism once thrombosis has occurred.

HEPARIN

Low-dose unfractionated heparin (LDUH), 5,000 U every 8 or 12 hours, continues to be a mainstay of DVT prophylaxis, although LMWH preparations are an effective alternative and are perhaps preferable in some situations. Two LMWH preparations are currently available in the United States; high cost impedes their present use. They should theoretically have greater effectiveness and fewer hemorrhagic side effects than LDUH;

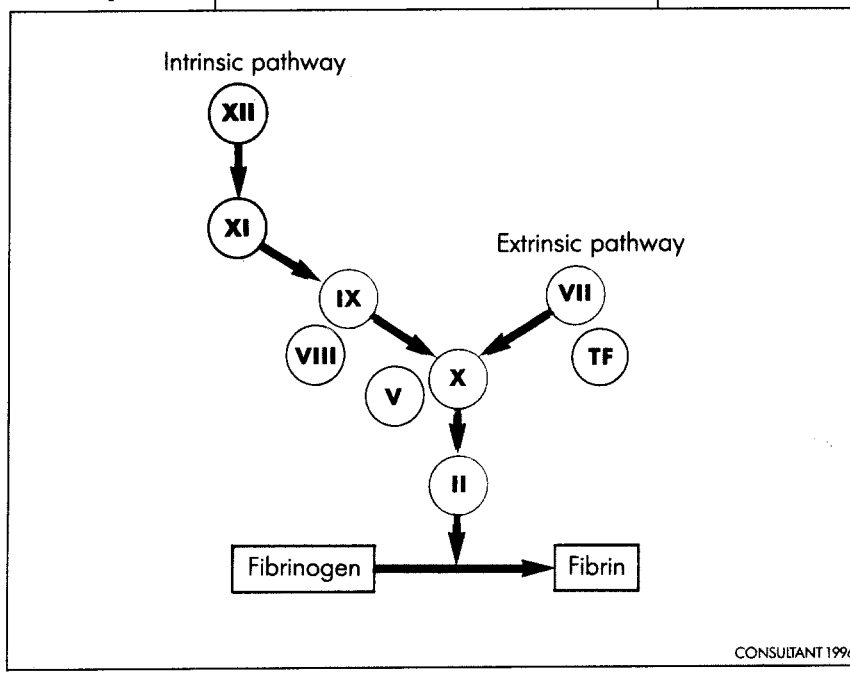

Figure 2—Action of cofactors (blue). Factors VIII and V are cofactors, which assist in binding the vitamin K–dependent proteases (red) to phospholipid membranes. The prothrombin activation rate is markedly enhanced by factors VIII and V. Tissue factor (TF) is another cofactor required for activation of VII. All vitamin K–dependent coagulation factors require cofactors for full expression of activity; they also require calcium, which helps link proteases and cofactors to platelet and endothelial membranes. Factors XII and XI are not vitamin K–dependent.

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however, clinical data are still being collected. Do not assume that various LMWH preparations require equivalent dosages or are equally effective.

For patients about to undergo surgery, initiate heparin therapy 2 hours before the operation and continue until the patient is ambulatory. A number of well-designed, controlled studies have demonstrated that prophylaxis decreases the incidence of DVT and pulmonary thromboembolism by about 50%. The prophylactic effect is achieved even though the aPTT is not prolonged. Patients who are receiving prophylactic heparin doses have shown no increase in clinically significant bleeding when compared with controls; however, wound hematomas may be more frequent in some groups of surgical patients.

In surgical patients at either relatively low or high risk for DVT, alternative approaches to prophylaxis may be appropriate. In patients younger than 40 who are undergoing low-risk general surgery, early ambulation may be adequate prophylaxis; in those at higher risk, graded compression elastic stockings and intermittent pneumatic compression might be added to drug therapy. Low-intensity oral anticoagulation (INR, 2 to 3) and adjusted-dose heparin therapy are alternatives for some high-risk patients. In patients at increased risk for wound hematomas or intracranial bleeding, intermittent pneumatic compression may be an effective and safe alternative to the use of anticoagulants.

As noted, orthopedic surgery patients have an especially high risk of DVT and pulmonary embolism. For those who are undergoing hip or knee replacement or hip fracture surgery, LMWH, oral anticoagulation, and/or intermittent pneumatic pressure are recommended.

Although heparin is the mainstay of prophylactic therapy, it is far from ideal. It must be given by injection two or three times a day, it can cause thrombocytopenia, and long-term use is associated with a 10% incidence of osteopenia.[7]

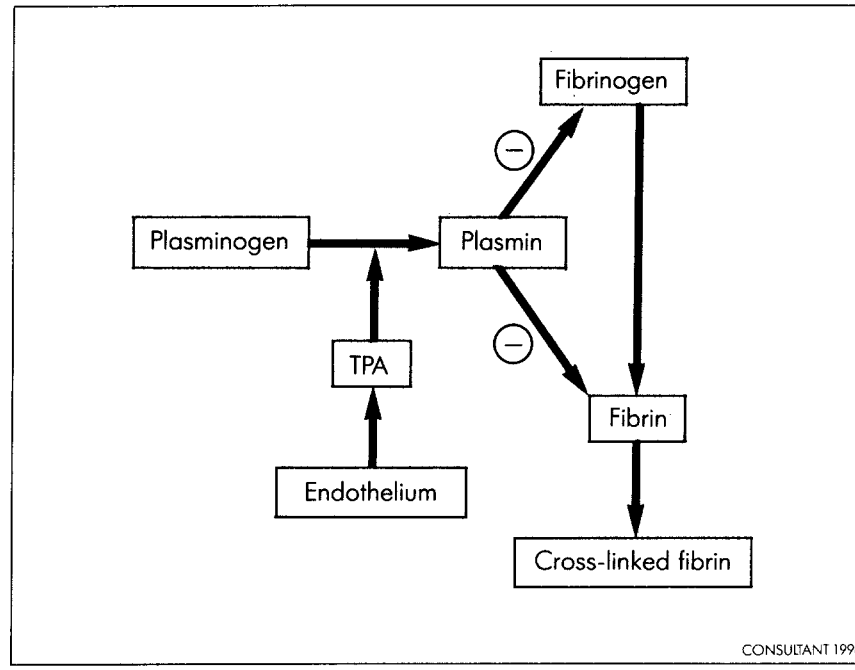

Figure 3—Fibrinolysis occurs when tissue plasminogen activator (tPA) produced by endothelial cells converts plasminogen to the proteolytic enzyme plasmin. Plasmin lyses fibrin that has not been cross-linked and can also degrade fibrinogen. Fibrin and fibrinogen degradation products are produced.

WARFARIN

A vitamin K antagonist, warfarin provides a relatively inexpensive alternative to heparin for DVT prophylaxis. This oral agent decreases the functional concentrations of the vitamin K–dependent coagulant proteins, factors VII, X, II, and IX.

Still under investigation are the optimal dosages of warfarin prophylaxis in various surgical and medical patients. In 1983, Francis and colleagues[8] gave low-dose warfarin to patients undergoing either hip or knee replacement. Treatment was started 10 to 14 days before surgery and was adjusted to prolong the PT by 1.5 to 3 seconds. The average preoperative dosage was 3 mg daily. Postoperatively, the dosage was increased to an average of 6 mg daily to prolong the PT to 1.5 times control.

The incidence of DVT in patients using this regimen was 21% compared with 51% in a control group treated with IV dextran. This degree of prophylaxis is comparable to results that can be achieved with adjusted-dose heparin. The patients experienced no excessive bleeding.

Since this study was performed, there has been growing agreement that PT measurements should be corrected for variation in laboratory reagents and expressed as an INR. An INR of 2 to 3 is recommended for most DVT prophylaxis.

Poller and coworkers[9] gave warfarin, 1 mg/d, to patients undergoing major gynecologic surgery, starting at least 6 days before the operation. DVT formation was reduced from 30% to 9% when compared with controls, with no increase in bleeding. The incidence of DVT formation was not statistically different from that of patients receiving full-dose warfarin anticoagulation. Another group has demonstrated the

Table 2—Modalities of deep venous thrombosis prophylaxis

Modality	Dosage or method
Low-dose unfractionated heparin	5,000 U SC q8h or q12h
Low molecular weight heparin	SC dose, according to weight, q12h
Adjusted-dose heparin	Initially, 3,500 U SC q8h; adjust dose to maintain aPTT at upper limit of normal range
Low-intensity warfarin	To achieve INR of 2 to 3
External pneumatic compression	Intermittent compression of calf; initiate before surgery if possible

aPTT, activated partial thromboplastin time; INR, international normalized ratio.

efficacy of low-dose warfarin in the prevention of central line–associated thrombosis.[10]

Although prophylactic anticoagulant therapy is effective when initiated preoperatively, concern over the possibility of increasing intraoperative bleeding has limited its acceptance. A study from McMaster University examined the effectiveness of therapy initiated in the immediate postoperative period, when patients were given 10 mg of warfarin.[11] Subsequent daily doses were adjusted to achieve a PT of 16 seconds by the fifth postoperative day. Findings demonstrated that anticoagulation initiated postoperatively in patients undergoing hip surgery could be effective (20% incidence of DVT in treated patients, 46% in controls) with no increase in bleeding.

Consider long-term warfarin prophylaxis to achieve an INR of 2 to 3 in certain medical patients who are at increased risk for DVT. This includes those with severe chronic obstructive pulmonary disease, CHF, paraplegia, and nonhemorrhagic stroke.

Patients with uncomplicated MIs also benefit from DVT prophylaxis. Continue warfarin prophylaxis for 3 months in patients with anterior MIs, which carry a high incidence (20% to 40%) of mural thrombus. The incidence of major bleeding with the use of long-term, low-dose anticoagulation is less than 4%; major bleeding tends to occur in patients who have a structural defect, such as a peptic ulcer or a CNS lesion.[12]

Warfarin has several drawbacks. Administration of the oral form to ob-

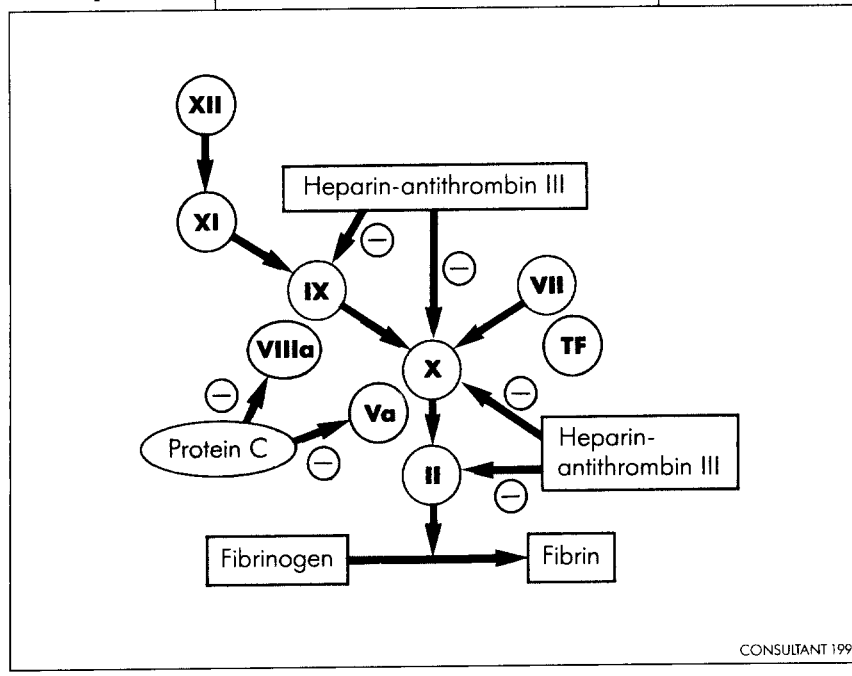

Figure 4—Two natural anticoagulant systems. Heparin-antithrombin III inactivates the serine proteases (such as factors IX, X, and II), and protein C inactivates cofactors VIIIa and Va. Heparin and heparan sulfate molecules are found on the surface of normal endothelium. Protein C is activated when bound to an endothelial receptor. The net effect of these two anticoagulant systems is to make normal endothelium highly antithrombogenic. TF, tissue factor.

tunded patients may be difficult. Many commonly used drugs affect its metabolism and plasma concentration; thus, dose titration may be complicated. Warfarin is contraindicated in pregnancy because of its teratogenicity and its prolonged anticoagulant effect. Warfarin-induced skin necrosis is an uncommon side effect that is probably a consequence of reduction of the anticoagulant protein C.

EXTERNAL INTERMITTENT PNEUMATIC COMPRESSION

Recognition of the devastating effects of wound hemorrhage in patients undergoing CNS surgery and of the prominent role played by stasis in the formation of DVT led to the development and use of external intermittent pneumatic compression of the calf muscles in the early 1970s. The simple machinery consists of an air compressor and two inflatable sleeves that are placed around the calves. These are intermittently inflated to 50 mm Hg for about 2 minutes and then deflated for the same length of time.

Although this modality has not been studied as extensively as heparin or warfarin, the record accumulated demonstrates that it does provide safe and effective prophylaxis if initiated immediately before surgery and continued as long as the risk of DVT exists. External intermittent pneumatic compression reduces the incidence of DVT formation by about 50% or more.[13,14]

At first, it was thought that pneumatic compression decreased DVT formation solely by preventing stasis, but newer evidence suggests that it also prevents a postoperative decrease in fibrinolytic activity.[15] One study demonstrated that intermittent compression applied to the arms also decreases the incidence of DVT in the legs.[16]

Despite this systemic response, no increase in bleeding has been noted with intermittent compression. One of its major drawbacks is its expense, which is greater than that of heparin or warfarin. Some patients find this treatment uncomfortable, and it adds another piece of equipment to the already crowded hospital room.

ADDITIONAL REGIMENS

Other agents have been tried for DVT prophylaxis. Aspirin alone fails to provide adequate prophylaxis in acutely ill patients. When given with heparin or warfarin, it appears to increase the incidence of bleeding but adds little prophylactic benefit. Aspirin is therefore not recommended. However, aspirin and antiplatelet agents may have a role in the management of other thrombotic diseases.[2]

Limited data are available on the effectiveness of graded compression elastic stockings. Until more is known, they should be viewed as an inexpensive and safe adjunct to other forms of prophylaxis.

The effectiveness of dextran seems comparable to that of heparin, but it is expensive, must be given intravenously, and cannot be used when intravascular volume expansion is contraindicated. On rare occasions, dextran has been associated with complement activation and anaphylaxis; however, the agent might be useful in selected patients. Wound hematomas may be less common with dextran than with other anticoagulants. ■

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