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Management and Prevention of Venous Thromboembolism Including Surgery and the Pregnant State

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As the spectrum of venous thromboembolic disease states demanding both pharmacologic and non-pharmacologic prophylactic modalities continues to expand, the determination of the appropriate preventive regimen is of paramount importance. As a consensus develops regarding the clinical efficacy and safety of various antithrombotics for medical, surgical, and pregnant patients, clinicians must rely on existing evidence. For many populations, a definitive statement is difficult due to the heterogeneity of available study parameters. The development of a risk stratification may help to identify patients who will benefit from prophylaxis.

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Deep vein thrombosis (DVT) and pulmonary embolism (PE) are both part of the complex of diseases known as venous thromboembolism (VTE). VTE is common in sick, hospitalized patients but can occur in otherwise healthy, ambulatory individuals. DVT is estimated to occur in approximately two million Americans each year (1). Many of these cases involve small, asymptomatic thrombi confined to the calf that do not reach clinical significance. However, for those that do progress to a clinically significant level, PE can be the result. PE is responsible for approximately 500,000 hospitalizations and about 60,000 deaths per year (1,2).

VTE occurs along a spectrum and is often clinically silent; research has shown that 50%-60% of DVT cases are asymptomatic (3). Patients may be unaware of any problem, or may experience the 'post-phlebetic' or 'post-thrombotic' syndrome associated with chronic venous insufficiency. Death is the most disastrous consequence.

DVT is caused by the formation of clots that consist of red blood cells enmeshed in a fibrin network and are relatively poor in platelets (4). Thrombi typically begin in the deep veins of the calf and extend proximally except in special populations (e.g., those who have undergone hip or pelvis surgery or who are pregnant). Diagnosis is frequently difficult because symptoms can be vague or absent.

In the 19th century, the German pathologist Virchow recognized that three factors—stasis, injury or abnormality of the blood vessels, and hypercoagulability—contribute to venous thrombosis, especially in the venous sinuses (5). Venous stasis can result from numerous conditions including immobilization, venous outflow obstruction, congestive heart failure, varicose veins, pregnancy, and massive obesity. New hypercoagulable states continue to be uncovered and are reviewed elsewhere in this journal. One must emphasize that, with multiple defects, the risk of VTE is not additive but multiplicative. These conditions extend beyond malignancy, protein C or S or antithrombin III deficiency, lupus anticoagulant, and Factor V Leiden to include Factors XI and VIII greater than 90th percentile, prothrombin 20210 mutation, and dysfibrinogenemia.

Prevention is the most effective weapon against the morbidities of post-thrombotic syndrome and pulmonary

Table 1. Levels of thromboembolism risk in surgical patients without prophylaxis.

Level of Risk Examples	Calf DVT%	Proximal DVT%	Clinical PE%	Fatal PE%	Successful Prevention Strategies
Low risk Minor surgery in patients < 40 years of age with no additional risk factors	2	0.4	0.2	0.002	No specific measures
Moderate risk Minor surgery in patients with additional risk factors; nonmajor surgery in patients 40-60 years of age with no additional risk factors; major surgery in patients > 40 years of age with no additional risk factors	10-20	2-4	1-2	0.1-0.4	Aggressive mobilization LDUH q12h, LMWH, ES, or IPC
High risk Nonmajor surgery in patients > 60 years of age or with additional risk factors	20-40	4-8	2-4	0.4-1.0	LDUH q8h, LMWH, or IPC
Highest risk Major surgery in patients > 40 years of age plus prior VTE, cancer or molecular hypercoagulable state, hip or knee arthroplasty, hip fracture, hip fracture surgery; major trauma; spinal cord injury	40-80	10-20	4-10	0.2-5	LMWH, oral anticoagulants, IPC/ES + LDUH/LMWH, or ADH

DVT = deep vein thrombosis; PE = pulomonary embolism; LDUH = low dose unfractionated heparin; LMWH = low molecular weight heparin; ES = external stocking; IPC = intermittent pneumatic compression; VTE = venous thromboembolism

hypertension and the mortality associated with PE. Patients at high risk for developing VTE should be identified and prophylactic approaches implemented. Prophylaxis may be achieved by modulating blood coagulation or preventing stasis with pneumatic compression of the legs, graduated compression stockings, subcutaneous unfractionated heparin or low-molecular-weight heparin (LMWH), or oral anticoagulation.

Surgical Patients

In general, screening for VTE with duplex ultrasound or other modalities is not advocated for surgical populations with the exception of the high-risk trauma patient who has received suboptimal prophylaxis (6). The incidence of both DVT and PE is sharply reduced when anticoagulant prophylaxis is used regardless of the risk group (Table 1). Several concerns have slowed the wider application of appropriate prophylaxis including bleeding risk and cost. However, numerous reports have demonstrated cost-effectiveness (7,8) and small or no increases in major bleeding (9,10) with pharmacological prophylaxis (7,8). Prevention is obviously more effective than screening, clinical diagnosis, and treatment.

The type and intensity of prophylaxis is administered according to risk level from low to highest (Table 1). Accordingly, the intensity of the preventive measures escalates as risk factors increase. Patients at a low risk level are not given any specific measures, whereas patients at the highest risk level are given extensive preventive measures. Several antithrombotic regimens are summarized in Table 2, which includes worldwide experience and regimens. In the United States, only enoxaparin (Lovenox; Aventis; Strasbourg, France) and dalteparin (Fragmin; Pharmacia & Upjohn; Peapack, NJ) have been approved by the FDA for prophylaxis. In the general surgery population, the meta-analysis by Claggett and Reisch of 49 pooled studies revealed that unfracationated heparin q8h is superior to q12h of dosing (9).

In the gynecologic, urologic, orthopedic, and general surgery population, low-dose unfractionated heparin (LDUH) and LMWH have been extensively studied. LMWH has the advantage of being administered once daily and is less likely to cause heparin-induced

Table 2. Regimens to prevent venous thromboembolism.

Method	Description
Low dose unfractionated heparin	Heparin 5000 U SC, given q8-12h starting 1-2 h pre-op
Adjusted dose heparin	Heparin SC given q8h starting with approximately 3500 U SC and adjusted by +/- 500 U SC/dose to maintain a midinterval at high normal values
Low molecular weight heparin and heparinoids*	General surgery, moderate risk • Dalteparin 2500 U SC 1-2h pre-op and once daily post-op • Enoxaparin 20 mg SC 1-2h pre-op and once daily post-op • Nadroparin 2850 U SC 2-4h pre-op and once daily post-op • Tinzaparin 3500 U SC 2h pre-op and once daily post-op General surgery, high risk • Daltepain 5000 U SC 8-12h pre-op and once daily post-op • Danaparoid 750 U SC 1-4h pre-op and q12h post-op • Enoxaparin 40 mg SC 1-2h pre-op and once daily post-op • Enoxaparin 30 mg SC q12h starting 8-12h post-op Orthopedic surgery • Dalteparin 5000 U SC 8-12h pre-op and once daily starting 12-24h post-op • Dalteparin 2500 U SC 6-8h post-op the 5000 U SC once daily • Danaparoid 750 U SC 1-4h pre-op and q 12h post-op • Enoxaparin 30 mg SC q12h starting 12-24h post-op • Enoxaparin 40 mg SC once daily starting 10-12h pre-op • Nadroparin 38 U/kg SC 12h pre-op, 12h post-op, and once daily on post-op days 1-3 then increase to 57 U/kg SC once daily • Tinzaparin 75 U/kg SC once daily starting 12-24h post-op • Tinzaparin 4500 U SC 12h pre-op and once daily post-op Major trauma • Enoxaparin 30 mg SC q12h starting 12-36h post-injury if hemostatically stable Acute spinal cord injury • Enoxaparin 30 mg SC q12h Medical conditions • Dalteparin 2500 U SC once daily • Danaparoid 750 U SC q 12h • Enozaparin 40 mg SC once daily
Perioperative warfarin	Start daily dose with approximately 5-10 mg the day of or day after surgery; adjust the dose for a target INR of 2.5 (range 2-3)
IPC/ES	Start immediately before operation and continue until fully ambulatory

INR = international normalized ratio; IPC = intermittent pneumatic compression; ES = external stocking
*Dosage expressed in anti-Xa units (for enoxaparin 1mg = 100 anti-Xa units)

Table 3. Hemostatic changes in pregnancy.

Conditions promoting thrombosis	Conditions discouraging thrombosis
• Activation of factors V, VII, VIII, IX, X, XII, VIIIR:Ag, or fibrinogen • Depressed fibrinolytic activity • Acquired activated protein C resistance (without factor V Leiden mutation) • Hereditary thrombophilia • Antiphospholipid antilipid antibodies • Endothelial damage associated with parturition • Venous stasis of the lower extremities	• Expansion of plasma volume • Decreased factors XI and XIII • Thrombin neutralization by antithrombin

thrombocytopenia and thrombosis than standard heparin (11). Antithrombotic therapy or prophylaxis can also be used (with caution) in patients having spinal puncture or epidural catheters placed for regional anesthesia or analgesia (12).

For all patient groups, aspirin was not recommended because of more effective alternative agents. Aspirin has the appeal of being inexpensive and easy to administer with few side effects but has generally been found to be ineffective in preventing VTE, especially in general surgery and orthopedic patients. Pooling more than 30 antiplatelet trials of various scientific designs flawed the Antiplatelet Trialists' Collaboration meta-analysis, which showed a significant reduction of DVT and PE (by 37% and 71%, respectively); e.g., none of the studies utilized contrast venography for outcomes. The Pulmonary Embolism Prevention (PEP) trial assessed 4088 hip and knee arthroplasty patients and found no benefit with aspirin use for either arterial or venous events (13,14). The 6th American College of Chest Physicians (ACCP) consensus also reviewed the PEP collaborative group's findings as they pertained to hip fracture patients and did not recommend the routine use of aspirin as thromboprophylaxis in this population (12). So clearly, the use of aspirin plays no role in DVT prevention.

In two large trials of 4483 patients evaluating LMWH versus adjusted-dose warfarin in patients undergoing hip arthroplasty, the incidence of DVT was statistically significantly reduced in the LMWH group. There was an increase in excessive minor bleeding with the LMWH dalteparin (Fragmin®; Pharmacia & Upjohn, Bridgewater, NJ) administered preoperatively. This adverse event did not occur with enoxaparin (15,16).

Both LMWH and warfarin sodium carry American College of Chest Physicians (ACCP) grade 1A recommendations (the strongest possible) for elective hip and knee replacements. LMWH can be initiated 12 hours before surgery, 12-24 hours after surgery or 4-6 hours after surgery at half the usual high-risk dose and then continued with the usual high-risk dose the following day. Warfarin sodium is an effective and safe oral anticoagulant that requires an international normalized ratio (INR) of 2.0-3.0 for both treatment and prophylaxis and so should be initiated preoperatively in most instances (12).

The optimal duration of anticoagulant prophylaxis remains unknown. In the orthopedic trials, 7-14 days was the usual thromboprophylactic period, with subsequent trials demonstrating a 50% reduction of total and proximal DVT with extended prophylaxis (17). With the length of stays often less than 5 days, out-of-hospital prophylaxis for both clinical benefit and cost effectiveness needs to be assessed. The ACCP recommends at least 7-10 days of prophylaxis.

Medical Patients

Similar to major surgery, acute hospitalization for a medical indication poses a substantial risk of thromboembolic complications. Prophylaxis is felt to be underutilized in this population due to the lack of clear evidence gained from studies using experimental and flawed methodologies including the recruitment small numbers of nonrandomized, heterogeneous patients.

One of the primary reasons hospitalized patients are felt to be vulnerable to thromboembolic complications is the restricted mobility experienced during acute illness, as well as additional risk factors that may be accentuated by the diseases themselves. The common acute illnesses, which significantly increase the risk of DVT and PE, include congestive heart failure of New York Heart Association (NYHA) Functional Class III or IV, acute respiratory or complicated chronic respiratory insufficiency, acute infectious diseases excluding septic shock, acute arthritic episodes of the lower extremities, or spinal cord injury (18,19).

Currently, enoxaparin is the only agent approved by the FDA for the prophylaxis of VTE in acutely ill medical patients. For patients with ischemic stroke and impaired mobility, the routine use of unfractionated heparin (UFH), LMWH, or the heparinoid danaparoid carries ACCP grade 1A evidence (12,20-22). If anticoagulant prophylaxis is contraindicated, consider mechanical measures with external stocking or intermittent pneumatic compression.

Samama et al demonstrated that the risk of venous thromboembolism in hospitalized patients, including those with cancer, could be reduced by nearly one third with a once-daily regimen of a LMWH (23). The Phase III multicenter study enrolled more than 1100 patients and supported the threshold concept for anticoagulation. Thromboemboli were reduced by approximately 60% in the 40 mg once-daily enoxaparin group (23). Contrary to the surgical population at moderate risk, for whom 20 mg of enoxaparin is effective, there seems to be a threshold in acutely ill medical patients.

For pharmacological prophylaxis, both UFH and LMWH are available. The standard of care in the United Stated is the administration of 5000 U of UFH twice daily. Although low-dose UFH is used as prophylaxis against thrombosis, it cannot be considered a validated control treatment for medical patients. The few studies supporting its use include small numbers of patients (24-27), and the results of two studies that have evaluated mortality among medical patients given 5000 U of UFH subcutaneously twice daily are conflicting (20,27). In addition, the recommendations of consensus conferences are not definitive (20). In sharp contrast, the results for once daily LMWH are clearly and convincingly proven. LMWH has

Table 4. Recommendations for thromboprophylaxis in pregnancy.

Risk	Patients	Management
Low	Patients with a family history of deep vein thrombosis. Patients with protein C or S deficiency or heterozygous factor V Leiden with or without history ofvenous thrombosis.	These patients may receive only prophylaxis postpartum with low molecular weight heparin.
Moderate	Patients with homozygous factor V Leiden with or without previous venous thrombosis or family history. Patients with a single deep vein thrombosis and thrombophilia. Patients with a history of recurrent spontaneous abortion or severe pre-eclampsia/HELLP syndrome and thrombophilia.	Patients receive low molecular weight heparin during pregnancy and postpartum.
High	Patients with acute thromboembolic event in the current pregnancy. Patients with prosthetic heart valves. Patients with true antithrombin deficiency. Patients with history of repeated thromboembolic complications (previous thrombosis on anticoagulants). Patients with combined thrombophilic defects with or without a single episode of deep vein thromboisis.	Patients receive higher dose prophylaxis during pregnancy and postpartum. Oral anticoagulants, which are safe in breast feeding women, can be used after 1 or 2 days to 12 weeks following delivery.

HELLP = hemodialysis, elevated liver enzymes, low platelet count

Patients with deep vein thrombosis in a current pregnancy or those with antithrombin deficiency type I or II, women with prosthetic heart valves, and patients on long-term anticoagulant therapy (e.g. because of previous thrombosis) should be considered as high-risk patients. These women are given low molecular weight heparin.

significantly reduced the incidence of DVT in hospitalized medical patients.

Pregnancy

Pregnancy is in itself a hypercoagulable condition and venous thromboembolism remains an important cause of maternal mortality. Various risk factors and physiological changes favor the formation of venous thrombosis (Table 3). Inherited and acquired thrombophilia are also associated with recurrent pregnancy loss (28). Certainly, an anticoagulant may be required during pregnancy either for the prevention of thromboembolic disease in patients already on long-term antithrombotic treatment (i.e., valvular prostheses) or for the prevention of complications of risk factors such as hereditary or acquired thrombophilia.

Most pulmonary embolisms occur postpartum, most frequently in association with Cesarean section procedures. Given the limited data in the literature, no strong evidence exists about individual risk, selection of agents and dosing regimens, or

how long thromoprophylaxis should continue. All guidelines are empiric grade C recommendations (Table 4).

Because warfarin crosses the placenta and can cause embryopathy in any trimester, this agent should be avoided during pregnancy. The LMWHs appear to be at least as effective as UFH for thromboprophylaxis and have a lower risk of bleeding, heparin-induced thrombopenia, and possibly osteoporosis (29).

Like UFH, LMWH is cleared through the kidney and could be subject to changes in pharmacokinetics in pregnancy. However, several studies have shown that LMWH does not cross the placenta in any trimester (30-32), and, despite the absence of licensing, LMWH is widely used during pregnancy. In most cases, a monitoring of anti-Xa activity is unnecessary.

Summary

Appropriate prophylaxis utilizing both pharmacological and nonpharmacological modalities with an evidence or knowledge-based approach should be applied to many hospitalized patient groups. A risk stratification scheme for the likelihood of VTE development will identify those patients who will benefit from prophylaxis in this setting and should also protect provider and hospitals from legal liability once implemented throughout the institution. Guidelines to prevent VTE have been widely distributed and generally have been assumed to be effective.

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