

Primary Prophylaxis of Venous Thromboembolism in Surgical Patients

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Venous thromboembolism is a major risk for surgical patients during the perioperative period. Prevention of perioperative venous thromboembolism remains a critical component of surgical patient care. The risk for venous thromboembolism in surgical patients can be stratified by their risk factors and by the type of operation. Pharmacological prophylaxis for venous thromboembolism includes unfractionated heparin, low-molecular weight heparin, fondaparinux, warfarin, antiplatelet therapy, and direct thrombin inhibitors. Mechanical devices such as graduated compression stockings, intermittent pneumatic compressions, and venous foot pumps are also effective modalities for venous thromboembolism prophylaxis. The optimal preventive measure of venous

thromboembolism should be based on the degree of risk for venous thromboembolism with the intensity of prophylaxis while balancing potential treatment benefits and risks in each individual patient. The epidemiology of venous thromboembolism, the methods for achieving venous thromboembolism prophylaxis, and the approach to institute venous thromboembolism prophylaxis in surgical patients undergoing various operative interventions are reviewed in this article.

Keywords: venous thromboembolism; deep-venous thrombosis; pulmonary embolism; complication; heparin; inferior vena cava filter; LMWH; warfarin; mechanical prophylaxis; pharmacological prophylaxis

More than 23 million patients undergo operations each year in the United States.¹ Prevention of perioperative complications remains one of the most important aspects of clinical care in patients undergoing surgical treatment. Venous thromboembolism (VTE) is a major risk for surgical patients during the perioperative period. The VTE, which occurs with a relatively high frequency among surgical patients, refers to thrombotic occlusion within the venous system and includes deep-vein thrombosis (DVT) and pulmonary embolism (PE). Because DVT typically occurs in the lower extremity, this condition is further defined as distal DVT (occlusion confined to

the deep calf veins) or proximal DVT (thrombosis at or above the popliteal vein). Without appropriate prophylaxis against VTE, a distal or proximal DVT may result in PE, which can be fatal.

It is estimated that without prophylaxis, DVT occurs after approximately 20% of all major surgical procedures, and PE occurs after 1% to 2%.² There are more than 31 million patients admitted each year for medical conditions, and up to 16% of patients will develop DVT in the absence of prophylaxis.^{3,4} The prevalence of VTE is even higher in orthopedic patients: over 50% of major orthopedic procedures are complicated by DVT and up to 30% by PE.^{3,4} In the absence of prophylaxis, the frequency of fatal postoperative PE ranges from 0.1% to 0.4% in patients undergoing elective general surgery and from 1% to 5% in patients undergoing elective hip or knee surgery, emergency hip surgery, major trauma, or spinal cord injury.⁵⁻⁷

The emphasis on prevention of VTE, as opposed to treating only symptomatic episodes, has a multifactorial rationale. Although most cases of postoperative VTE remain asymptomatic,^{4,8} VTE is associated with

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significant morbidity, mortality, and costs of care.^{9,10} The 1-year mortality rate of DVT is estimated to be 16% to 30%, with most deaths occurring within the first month.^{4,11} The VTE prophylaxis does not afford complete protection; however, it has been shown to be both cost-effective and clinically efficacious, with reduction of DVT by 70% or more.¹¹⁻¹⁴ In addition, prophylactic anticoagulation therapy is effective in preventing DVT and PE-related mortality.^{2,15,16} However, studies continue to show common underutilization of VTE prophylaxis. Observational studies have documented that nearly half of the hospitalized patients who developed DVT did not receive adequate VTE prophylaxis.^{3,4} Additionally, autopsy studies have shown that for the majority of cases of confirmed PE, this diagnosis was not considered prior to death.¹² Barriers to appropriate VTE prophylaxis include the perception that VTE has a very low incidence, has a lack of acceptance of the importance of VTE prophylaxis, and concerns about hemorrhagic complications in surgical patients.

This article reviews the epidemiology of VTE, the methods for achieving VTE prophylaxis, and the approach to instituting VTE prophylaxis in surgical patients.

Risk Factors, Pathogenesis, and Clinical Course

Patients undergoing surgical procedures are at an increased risk for developing VTE due, in part, to the physiologic stress and potential postoperative immobility.¹⁷ The VTE often results from a combination of risk factors, including inherited, acquired, environmental, and idiopathic conditions.¹⁸ Relevant risk factors leading to the development of VTE vary widely and include factors such as age, underlying medical comorbidities, type of surgery, duration of postoperative immobilization, underlying hypercoagulable disorders, and the presence of an underlying malignancy (Table 1).^{3,4,19} The 2004 American College of Chest Physicians (ACCP) recommendations for VTE prophylaxis divide surgical patient into 4 risk categories (Table 2).¹⁹

The pathogenesis of venous thrombosis involves Virchow's triad: damage to the vessel wall, venous stasis, and hypercoagulability. The VTE typically originates in the venous sinuses of the calf muscles but can occur in the proximal veins due to trauma or surgery.⁷ In all, 25% of postoperative DVT cases involve proximal deep veins, which are much more likely to cause symptoms and result in PE.²⁰ Of distal DVT cases, 10% to 20%

Table 1. Common Risk Factors for Venous Thromboembolism

Surgery
Trauma (major or lower extremity)
Immobility, paresis
Malignancy
Cancer therapy (hormonal, chemotherapy, or radiotherapy)
Previous venous thromboembolism
Female sex factor
Pregnancy and the postpartum period
Estrogen-containing oral contraception or hormone replacement
Selective estrogen-receptor modulators
Acute medical illness
Heart or respiratory failure
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Obesity
Smoking
Varicose veins
Inherited or acquired thrombophilia
Central venous catheterization
Increasing age

are thought to propagate to proximal DVT.^{3,4,11} It has been estimated that half or more of DVTs begin intraoperatively.^{2,21} Several of these clots resolve spontaneously, and the addition of postoperative prophylactic agents facilitates this resolution. For patients at greatest risk, longer duration of prophylaxis correlates with further reductions in the incidence of DVT, which adds evidence to the concept that many cases of DVT occur later in the course.

Associated signs and symptoms of DVT result from venous outflow obstruction and from inflammation of the vessel wall and perivascular tissue.¹⁸ The potential complications of DVT include worsening acute venous symptoms with development of phlegmasia and potential limb loss, development of PE and subsequent death, recurrent thromboembolic events, and the development of chronic venous insufficiency due to postthrombotic syndrome. Rarely, a venous thrombosis may become massive, resulting in phlegmasia cerulea dolens or phlegmasia alba dolens. In phlegmasia cerulea dolens, the thrombosis extends to collateral veins, which can lead to massive fluid sequestration. Clinical symptoms include significant leg swelling, bluish discoloration, and pain. In phlegmasia alba dolens, the thrombosis involves major deep-venous channels of the extremity therefore sparing collateral

Table 2. Levels of Thromboembolism Risk in Surgical Patients Without VTE Prophylaxis

Level of Risk	DVT (%)		PE (%)		Successful Prevention Strategies
	Calf	Proximal	Clinical	Fatal	
Low risk					
Minor surgery in patients <40 y with no additional risk factor	2	0.4	0.2	<0.01	No specific prophylaxis; early and aggressive mobilization
Moderate Risk					
Minor surgery in patients with additional risk factors; or surgery in patients aged 40-60 y, with no additional risk factors	10-20	2-4	2-4	0.1-0.4	LDUH (every 12 h), LMWH (<3400 U daily), GCS or IPC
High risk					
Surgery in patients >60 y, or age 40-60 y with additional risk factors (prior VTE, cancer, molecular hypercoagulability)	20-40	4-8	2-4	0.4-1.0	LDUH (every 8 h), LMWH (>3400 U daily), or IPC
Highest risk					
Surgery in patients with multiple risk factors (age >40 y, cancer, prior VTE), hip or knee arthroplasty, or major trauma	40-80	10-20	4-10	0.2-5	LMWH (>3400 U daily), fondaparinux, oral VKA (INR, 2-3), or IPC/GCS + LDUH/LMWH

Abbreviations: VTE, venous thromboembolism; DVT, deep-vein thrombosis; PE, pulmonary embolism; GCS, graduated compression stockings; INR, international normalized ratio; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

veins. The venous drainage is decreased but still present, and it is frequently associated with lymphangitis. Clinical symptoms include a large, swollen, and painful limb made pale by severe edema. Limb loss can be a devastating sequelae if phlegmasia was left untreated. Calf vein thrombi often undergo spontaneous thrombolysis and rarely result in symptomatic PE²²; however, approximately 25% of untreated calf thrombi extend into the proximal veins, usually within a week after presentation.²³ The risk of PE (either symptomatic or asymptomatic) with proximal DVT is approximately 50%, and most fatal emboli usually originate from proximal thrombi.^{24,25} The development of postthrombotic syndrome is a function of the extent of thrombosis, its subsequent effect on venous valvular competence, and long-term residual obstruction. The consequences of postthrombotic syndrome and chronic venous insufficiency are quite severe, with persistent edema, pain, and recurring skin problems (eg, ulcerations). These problems lead to decreased quality of life and considerable economic burden.

Pharmacological Prophylaxis

Pharmacological prophylaxis is the most effective modality for prevention of VTE in surgical patients. A brief review of the mechanisms of action is provided to better understand the different drugs and their unique properties.

Anticoagulants

Heparin. Heparin is a highly sulfated glycosaminoglycan that binds to antithrombin, which markedly accelerates inactivation of thrombin, activated factor X (factor Xa), and activated factor IX (factor IXa).²⁶ Additional antithrombotic effects include release of a tissue factor pathway inhibitor and some platelet-binding proteins.^{26,27} At therapeutic concentrations, heparin has a half-life of about 60 minutes. Its clearance is dose dependent. Heparin has decreased bioavailability when administered subcutaneously in low doses but has approximately 90% bioavailability when administered in high therapeutic doses.²⁸

Low-dose unfractionated heparin (UFH) has been in clinical use for many years. In general surgery patients, UFH has been shown to reduce VTE by 70%.²⁹ A downside to UFH is the unpredictable treatment response to full anticoagulation. Heparin binds to a number of plasma proteins, a phenomenon that reduces its anticoagulant effect by limiting the accessibility of heparin to antithrombin. The concentration of heparin-binding proteins also increases during illness, which contributes to the variability in anticoagulant response.³⁰ Because of this variability, response to heparin should be monitored with the activated partial thromboplastin time (aPTT). The dose should be adjusted as necessary to achieve a therapeutic range, which for many aPTT reagents corresponds to an aPTT ratio of 1.5 to

2.5.²⁸ It is also this binding to plasma proteins, specifically platelet factor 4, that can lead to heparin-induced thrombocytopenia (HIT).^{31,32}

Standard prophylactic dosing for patients undergoing general surgical procedures is typically 5000 U of low-dose UFH subcutaneously 1 to 2 hours preoperatively, which is continued twice or thrice daily postoperatively until the patient is ambulatory or is discharged home.¹⁹ For orthopedic patients, low-dose UFH is typically given at a dose of 5000 U subcutaneously 2 hours before surgery and 5000 U every 8 or 12 hours after surgery.¹⁹ The more frequent dosing seems to be somewhat more effective without any increased complications observed. Bleeding risk from UFH in prophylactic doses has been shown to be 2% higher than placebo, but most of these instances are wound hematoma because major bleeding has not been found to be higher than placebo.³⁰ Higher risks of osteopenia and osteoporosis have also been reported in patients treated with long-term UFH.³³

Low-Molecular Weight Heparin. Low-molecular weight heparin (LMWH) is derived from standard commercial-grade heparin by chemical depolymerization to yield fragments approximately one third the size of heparin.²⁶ Depolymerization of heparin results in a change in its anticoagulant profile, bioavailability, and pharmacokinetics, resulting in a lower incidence of HIT and osteopenia.^{27,28} The LMWH works by binding to and markedly enhancing the activity of antithrombin. In contrast to UFH, there is much more specificity against activated factor X with very little effect against thrombin. Decreased binding to plasma proteins translates into increased bioavailability and longer half-life, enabling weight-based daily dosing without laboratory monitoring. Another benefit of LMWH is that long-term dosing is associated with lower rates of osteoporosis than that occurring with UFH.³⁴

In contrast to UFH, LMWH is cleared almost entirely by the kidneys. Renal clearance of LMWH is therefore less predictable in patients with severe renal insufficiency, defined in most studies as a creatinine clearance of less than 30 mL/min. In these patients, laboratory monitoring of anti-Xa levels is prudent. The LMWH dosing is also less predictable in morbidly obese patients (body mass index > 50) due to metabolic variables and may require monitoring during full anticoagulation. Decreased binding to plasma proteins, specifically platelet factor 4,

results in a decreased incidence of HIT. Even so, patients with HIT should not receive LMWH because cross-reactivity with UFH does occur.^{31,32}

The LMWHs used in VTE prophylaxis are enoxaparin, dalteparin, danaparoid, and nadroparin. Common prophylactic dosing regimens for LMWH are provided in Table 3.

Fondaparinux

Fondaparinux is a new parenteral synthetic anticoagulant composed of the 5 saccharide units that comprise the active site of heparin that binds antithrombin.^{35,36} The fondaparinux-antithrombin complex inhibits factor Xa but has no direct activity against thrombin. Fondaparinux is rapidly absorbed and is 100% bioavailable when administered subcutaneously. It is not metabolized, is renally excreted, and has a dose-independent elimination half-life of 15 hours, which makes it suitable for once-daily administration. Fondaparinux has been approved for thrombosis prophylaxis in hip and knee joint replacement surgery and is being evaluated for VTE prophylaxis in the high-risk abdominal patient and for treatment of DVT and PE. One potential advantage of fondaparinux over LMWH or UFH is that the risk for heparin-induced thrombocytopenia is substantially lower.³⁷ Dosing regimen of fondaparinux is provided in Table 3.

Warfarin

Warfarin is an oral anticoagulant that competitively inhibits production of vitamin K-dependent clotting factors in the liver by producing hemostatically defective, vitamin K-dependent coagulant proteins (prothrombin, factors VII, IX, X, and the anticoagulant proteins C and S).³⁸ Warfarin is completely absorbed after oral administration, with peak concentration generally achieved within the first 4 hours. Its anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of this anticoagulant ranges from 2 to 5 days. The elimination of warfarin is completely by metabolism, with its metabolites principally excreted into the urine.³⁴

The dose of warfarin must be monitored closely because the anticoagulant response varies widely among individuals. Laboratory monitoring is performed by measuring the prothrombin time (PT), a

Table 3. Commonly Used Antithrombotic Dosing Regimens for VTE Prophylaxis

Medication	Adult Dosing Regimens
UFH Enoxaparin (Lovenox)	Initial dose: 80 U/kg IV bolus maintenance: 18 U/kg/h continuous IV infusion Treatment of established DVT with or without PE: 1 mg/kg SC q12h can be administered in the hospital or in an outpatient setting under supervision Alternatively, 1.5 mg/kg SC once qd, administered at same time qd is approved for in-hospital treatment of DVT without symptomatic PE Prevention of DVT: 30 mg SC q12h or 40 mg/d Average duration of treatment is 7-14 d
Dalteparin (Fragmin)	2500-5000 U SC qd for prevention of DVT Current recommended dose in patients undergoing abdominal surgery is 2500 U SC/d Average duration of treatment is 7-14 d
Fondaparinux sodium (Arixtra)	Symptomatic DVT and acute symptomatic PE: <50 kg BW: 5 mg SC/d for 5 d 50-100 kg BW: 7.5 mg SC/d for 5 d >100 kg BW: 10 mg SC/d for 5 d Treatment should be continued until therapeutic oral anticoagulant effect is established (INR 2-3) with at least 2 determinations For prophylaxis of VTE: 2.5 mg SC/d; initial dose recommended to be given 6-8 h following surgery, after hemostasis established; administration < 6 h after surgery associated with increased risk of major bleeding Approved for use in hip fracture surgery, knee-replacement surgery, and hip-replacement surgery. Only FDA-approved anticoagulant drug for hip fracture surgery. Also, used and approved for extended prophylactic dosing for 21 d following hip fracture surgery.
Warfarin (Coumadin)	5-10 mg PO qd; adjust dose according to desired INR Therapy is initiated without a loading dose at a dose range of 5-10 mg qd for 70-kg adult. Monitor PT/INR daily during initiation of therapy to measure anticoagulation effect. After initial 5-10 d and stabilization of warfarin dose, measure PT/INR 2-3 times q w for 2-4 w, then monthly thereafter.

Abbreviations: VTE, venous thromboembolism; UFH, unfractionated heparin; IV, intravenous; DVT, deep-vein thrombosis; PE, pulmonary embolism; SC, subcutaneous; BW, body weight; INR, international normalized ratio; FDA, Food and Drug Administration; PT, prothrombin time.

test responsive to depression of 3 of the 4 vitamin K-dependent clotting factors (prothrombin and factors VII and X). Commercial PT reagents vary markedly in their responsiveness to warfarin-induced reduction in clotting factors, a problem that has been overcome by the introduction of the international normalized ratio (INR).³⁹

The starting dose of warfarin is typically 10 mg, with an average maintenance dose of approximately 5 mg. As noted above, the dose required varies widely among individuals. Elderly patients, for example, require lower doses. Evidence indicates that it might be safer to use a starting dose of 5 mg of warfarin because, compared with 10 mg, the 5 mg starting dose does not result in a delay in achieving a therapeutic INR and is associated with a lower incidence of supratherapeutic INR values during the first 5 days of treatment.³⁹ In some patients, unexpected fluctuations in dose response occur, which may reflect changes in diet, inaccuracy in PT testing, undisclosed drug use, poor compliance, or surreptitious self-medication. Patients receiving warfarin are

also sensitive to fluctuating levels of dietary vitamin K, which is obtained predominantly from leafy green vegetables. The effect of warfarin can be potentiated in sick patients with poor vitamin K intake, if they are treated with antibiotics and intravenous feeding without vitamin K supplementation, and in states of fat malabsorption.

Moderate-dose warfarin (INR, 2.0-3.0) is effective for preventing postoperative VTE in patients in all risk categories.³⁹ Warfarin therapy can be started preoperatively, at the time of surgery, or in the early postoperative period. Although the anticoagulant effect is not achieved until the third or fourth postoperative day, warfarin treatment started at the time of surgery or in the early postoperative period is effective in highest-risk patients, including patients with hip fractures and those who undergo joint replacement. However, warfarin is not generally used for perioperative VTE prophylaxis in surgical patients because it typically requires several days to reach its therapeutic level. In addition, prophylaxis with warfarin is less convenient than prophylaxis

with low-dose UFH or LMWHs because warfarin requires careful laboratory monitoring.

Antiplatelet Therapy

Aspirin is a nonsteroidal anti-inflammatory drug commonly used in treating fever, pain, and bodily inflammation. Aspirin exerts its pharmacological effect by suppressing the production of prostaglandins and thromboxanes via irreversible inhibition of the cyclooxygenase enzyme. Prostaglandins are hormones produced in the body and have diverse effects in the body, including, but not limited to, transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation. Thromboxanes are responsible for the aggregation of platelets that form intraluminal thrombus.⁴⁰ Because aspirin can inhibit platelet aggregation, it has been considered for VTE prophylaxis. However, aspirin therapy is considered ineffective for VTE prophylaxis in surgical patients. Original support for its usage came from collections of very small studies with small numbers of patients, which are quite old. More recent studies involving aspirin have shown that it is far inferior to LMWHs and UFH.^{19,41,42} Additionally, aspirin has been linked to increased risk of bleeding, which further discourages its use.⁴⁰ Given the available literature, antiplatelet therapy is not the standard of care for the prevention of VTE in surgical patients.

Direct Thrombin Inhibitors

Ximelagatran is a direct thrombin inhibitor that is currently being evaluated for primary prevention and for acute and long-term treatment of VTE.⁴³ Ximelagatran has no known food or drug interactions and is administered orally. Once absorbed from the gastrointestinal tract, ximelagatran is converted to melagatran, a partial mimetic of fibrinopeptide A, which blocks the active site of thrombin.⁴⁴ Ximelagatran is primarily eliminated by the kidneys and has a half-life of about 3 hours, mandating twice-daily administration. It has been studied for VTE prophylaxis in orthopedic patients and appears to be equally efficacious as LMWH.⁴³ However, it has not yet received US Food and Drug Administration approval.

Complications of Antithrombotic Therapy

Bleeding remains the most common complication of antithrombotic therapy.^{45,46} The risk of bleeding

caused by antithrombotic agents is influenced by the dose and by patient-related factors, the most important being recent operation or trauma. Other patient characteristics that increase the risk of bleeding are older age, recent stroke, generalized hemostatic defect, a history of gastrointestinal hemorrhage, and serious comorbid conditions.^{45,46} Bleeding complications are similar among UFH and LMWH.⁴⁷ With UFH, the incidence of bleeding is influenced by dosage and administration, bleeding events being more common with intermittent intravenous therapy than with continuous intravenous therapy.⁴⁸ Fondaparinux is associated with a higher incidence of bleeding complication than LMWHs.^{35,36} Bleeding associated with warfarin is influenced by the intensity of anticoagulant therapy.⁴⁹ The risk for bleeding is reduced to about one third if the targeted INR range is lowered from between 3.0 and 4.5 to between 2.0 and 3.0. Both heparin-induced bleeding and warfarin-induced bleeding are increased by concomitant use of aspirin, which impairs platelet function and produces gastric erosions. When the INR is less than 3.0, warfarin-associated bleeding frequently has an obvious underlying cause or is from an occult gastrointestinal or renal lesion.

Nonhemorrhagic side effects of heparin include the following: (1) urticaria at sites of subcutaneous injection; (2) thrombocytopenia, which occurs in 2% to 4% of patients treated with high-dose heparin and is complicated by arterial or venous thrombosis in about 0.2% of treated patients; (3) osteoporosis and osteopenia, which occur with prolonged high-dose heparin use; and, rarely, (4) alopecia, adrenal insufficiency, and skin necrosis.⁴⁷ The incidence of thrombocytopenia is lower with LMWHs than with heparin. Similarly, there is evidence that the risk of osteopenia is lower with LMWH than with heparin.⁴⁷

Common complications associated with aspirin include gastrointestinal symptoms, including dyspepsia, bleeding, or mucosal ulceration. To avoid these gastrointestinal complaints, it is recommended that aspirin be taken at or after meals. Long-term complication associated with aspirin usage is chronic nephritis, which may lead to chronic renal failure, particularly if aspirin is used in combination with other painkillers with renal excretion.⁵⁰

The most important nonhemorrhagic side effect of warfarin is skin necrosis, an uncommon complication usually observed on the third to eighth day of therapy.⁵¹ Skin necrosis is caused by extensive thrombosis of the venules and capillaries within the subcutaneous fat. An association has been reported

between warfarin-induced skin necrosis and protein C deficiency and, less commonly, protein S deficiency (this complication can also occur in patients without these deficiencies). Because warfarin inhibits vitamin K–dependent coagulation factors, including proteins C and S, patients with either deficiency who require antithrombotic therapy should receive heparin or UFH first and then should be transitioned to warfarin oral anticoagulation. This approach reduces the likelihood of depleting protein C or S levels in these patients.

Nonpharmacological Prophylaxis

Mechanical prophylaxis

Mechanical prophylaxis is an attractive option for VTE prophylaxis because there is no associated increased risk of bleeding. Therefore, it is most useful in patients who are deemed to be at high risk for bleeding complications from pharmacological prophylaxis. Mechanical means of VTE prophylaxis include graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices, and venous foot pumps (Table 3). The mechanism of action is reduction in stasis and perhaps a local increase in fibrinolytic activity. Both GCS and IPC devices increase venous blood flow and decrease venous stasis. The IPC devices also stimulate endogenous fibrinolytic activity by causing gentle trauma to the vascular endothelial cells of the lower leg and by altering rheological characteristics and perfusion pressure.^{52,53} The IPC is the method of choice for preventing VTE in patients undergoing neurosurgery, is effective in patients undergoing major knee surgery, and is as effective as low-dose UFH heparin in patients undergoing abdominal surgery.⁵⁴

In direct comparison studies, mechanical prophylaxis has been found to be better than no prophylaxis but less effective than pharmacological means.⁵⁵ However, the combined use of GCS and low-dose UFH in surgical patients is significantly more effective than use of low-dose heparin alone. The GCS are relatively inexpensive and should be considered in all high-risk surgical patients, even if other forms of prophylaxis are used.⁵⁶ The GCS should be used with caution in patients with significant arterial insufficiency because there have been reports of worsening limb ischemia and tissue loss.⁵⁷

Perhaps the biggest problem with mechanical prophylaxis using either IPC or GCS modality, however, is compliance. Firstly, stockings must be adequately sized and properly fitted. Compression devices such as

IPC only work while in place and commonly are found at the foot of the bed or on the floor in the patient's room in clinical practice. Patient compliance with mechanical prophylaxis is generally well maintained when the treatment is conducted within a clinical study protocol. However, it appears that outside clinical trials where compliance is carefully maintained, day-to-day use proves less reliable and is less efficacious. Perhaps most encouraging for mechanical prophylaxis is the finding that when combined with pharmacological prophylaxis, there is enhanced protection over pharmacological treatment alone. This additive effect is predictable based on the approach of both relieving venous stasis and correcting or preventing hypercoagulability.^{21,58-60}

Inferior Vena Cava Filters

Placement of prophylactic inferior vena cava (IVC) filters is effective for prevention of PE. Naturally, there is no effect on incidence of DVT because it is not a prophylactic measure against DVT. Accepted indications for IVC filters are patients with PE despite anticoagulation, patients with symptomatic VTE and a contraindication to anticoagulation or a complication of anticoagulation, and patients requiring pulmonary embolectomy for PE.⁶¹ Relative indications have included patients with a large DVT (free-floating iliofemoral DVT), problems with compliance with anticoagulation therapy, and patients with VTE and limited cardiopulmonary reserve.

Although the incidence of complications is small, IVC filters do pose some risk of caval thrombosis, and in some reports, they have been shown to increase the chance of a future DVT. Additionally, many patients who are at greatest risk for developing PE are only at risk for a relatively short period. These factors led to the recent development of retrievable IVC filters. The IVC filters can be safely removed as long as 1 year after implantation, which has encouraged the placement of these filters in a large number of patients. Prophylactic retrievable IVC filters have been most commonly placed in patients felt to be at high risk for VTE in whom anticoagulation is not advisable or is contraindicated (eg, trauma patients with spine or brain injuries, patients undergoing bariatric surgery). However, review of the literature shows no strong evidence to support those practices because PE is still an uncommon occurrence even in highest-risk groups.⁶¹ Therefore, the indications for placement of retrievable filters remain in evolution and currently must be based on

individual or regional practice patterns until large trials are available to provide evidence to support specific recommendations.

Approach to Primary Prophylaxis of VTE

The most effective approach to reducing VTE-related morbidity and mortality is to institute primary prophylaxis in patients at risk for VTE. On the basis of well-defined clinical criteria, the 2004 ACCP recommendations¹⁹ for VTE prophylaxis classifies surgical patients as low, moderate, high, or highest risk for VTE (Table 2).¹⁴ The choice of prophylaxis should be tailored to the patient's risk. Clearly, early mobilization is the least costly and a highly effective method of VTE prophylaxis for many low-risk patients. For patients who are medically and physically able to get out of bed and who are at low risk for VTE, this is sufficient. Immobilized or higher-risk patients require a more active means of VTE prophylaxis, which is accomplished either by modulating activation of blood coagulation or by preventing venous stasis using the following proven approaches: low-dose subcutaneous UFH, IPC of the legs, warfarin, adjusted doses of subcutaneous UFH, GCS, LMWHs, or fondaparinux.^{6,34,62,63}

Indications for Prophylaxis

General Surgery

Clearly, the type and length of surgery are directly related to the incidence of VTE. As always, the approach to prophylaxis should be tailored to the patient's risk for developing VTE (Table 2). In the low-risk group of patients (patients undergoing relatively minor procedures [eg, laparoscopic cholecystectomy]), no specific prophylaxis other than early mobilization is needed based on the extremely low incidence of VTE in this patient population. Higher-risk patients require active prophylaxis. In general, UFH and LMWH are more efficacious than mechanical prophylaxis alone, and patients treated with LMWH are less likely to develop symptomatic DVT. However, the overall incidence of symptomatic DVT, PE, risk of death, and complications are similar between the 2 agents.¹⁹ Prophylaxis recommendations for moderate-risk patients are UFH twice daily or LMWH and for high-risk patients are UFH thrice daily or LMWH. Highest-risk patients should

receive UFH thrice daily or LMWH combined with GCS and/or IPC. In select general surgery patients at highest risk (eg, those undergoing cancer surgery), consideration should be given for prolonged prophylaxis of DVT (up to 1 month) after hospital discharge. If anticoagulants are contraindicated because of an unusually high risk of bleeding, GCS, IPC of the legs, or both should be used.¹⁹

Trauma Surgery

Trauma patients, in particular those with spinal cord injury, severe brain injury, pelvic fracture, or burns and those with lengthy periods of immobilization, are at very high risk for VTE, with a reported rate of 60% or greater.⁶⁴ Pharmacological VTE prophylaxis in this group has been studied, and LMWH has been found to be superior to UFH, with 60% less proximal DVT.^{65,66} Therefore, it is recommended that these patients receive LMWH. If the patients cannot be treated with LMWH because of bleeding concerns, mechanical prophylaxis should be initiated and then LMWH started once the risk of bleeding is reduced. For patients with prolonged immobility, including any period of inpatient rehabilitation, the ACCP recommends prophylaxis until discharge.¹⁹ Burn patients as well are at risk for VTE, and it is recommended that those with 1 additional risk factor for VTE begin prophylaxis with UFH or LMWH as soon as possible.¹⁹

Orthopedic Surgery

In general, LMWH, fondaparinux, and warfarin provide effective VTE prophylaxis in patients undergoing hip surgery, whereas LMWH, warfarin, fondaparinux, and IPC provide effective VTE prophylaxis in patients undergoing major knee surgery.^{16,19} The ACCP guidelines recommend that prophylaxis for all patients undergoing orthopedic operations should be at least 10 days.^{16,19} Extended prophylaxis with LMWH or warfarin for 28 to 35 days after hospital discharge should be considered after major orthopedic surgery. Extended prophylaxis is also strongly recommended for high-risk patients (eg, patients with previous VTE or active cancer).^{16,19}

Low-dose UFH is less effective than warfarin, adjusted-dose heparin, or LMWHs in patients undergoing major orthopedic surgical procedures.⁷ For patients undergoing hip or major knee surgery, LMWH is more effective than warfarin but is also

associated with more frequent bleeding, both of which may be caused by a more rapid onset of anticoagulation with postoperatively initiated LMWH than with warfarin.^{67,68} It is uncertain whether the superior efficacy of LMWH over warfarin for preventing venographically detectable venous thrombosis is mirrored by fewer symptomatic episodes of VTE with LMWH.^{67,68} Results in joint surgery patients suggest that fondaparinux is somewhat more effective than LMWH but is also associated with a higher incidence of bleeding complications.^{35,36} Aspirin has also been shown to reduce the frequency of symptomatic VTE and fatal PE after hip fracture.¹² The relative efficacy and safety of aspirin versus LMWH, fondaparinux, or warfarin in patients who have a hip fracture or who have undergone hip or knee arthroplasty is uncertain. However, studies have shown that aspirin is much less effective than LMWH or warfarin in preventing venographically detectable venous thrombosis. Therefore, aspirin is not recommended as the sole agent for postoperative prophylaxis.^{16,19,55} Ultimately, selection of a prophylactic agent must be based on the patient's specific risk profile for complications.

The following lists the ACCP's recommendations for the various VTE prophylactic strategies for orthopedic procedures.¹⁹

Elective hip or knee arthroplasty. Patients undergoing elective total hip replacement should receive one of the following VTE prophylaxis strategies: (1) LMWH (at a usual high-risk dose, started 12 hours before surgery or 12-24 hours after surgery; or 4-6 hours after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day); (2) fondaparinux (2.5 mg started 6-8 hours after surgery); or (3) adjusted-dose warfarin started preoperatively or the evening after surgery (INR target = 2.5, INR range = 2.0-3.0). Patients undergoing elective knee arthroplasty should receive VTE prophylaxis with LMWH (using a high-risk dose), fondaparinux (2.5 mg/d), or warfarin (target INR = 2.5, INR range = 2.0-3.0).¹⁹

Knee arthroplasty. Low-risk patients do not require any specific prophylaxis intervention other than early mobilization. In patients at higher risk due to preexisting VTE risk factors or following a prolonged or complicated procedure, LMWH is indicated.¹⁹

Hip fracture surgery. Patients undergoing hip fracture operation should receive routine fondaparinux, LMWH at the usual high-risk dose, low-dose UFH,

or adjusted-dose warfarin (target INR = 2.5, INR range = 2.0-3.0). Patients whose surgery may be delayed should receive prophylaxis with either low-dose unfractionated heparin or LMWH during the time between hospital admission and surgery. In the event that anticoagulant prophylaxis is contraindicated due to high risk of bleeding during hip operation, these patients should receive mechanical prophylaxis including both GCS and IPC.¹⁹

Vascular Surgery

Interestingly, vascular surgery patients appear to be at low risk for VTE. Randomized trials have shown no benefit of prophylaxis over placebo, although the studies were small.^{69,70} The ACCP recommends no specific VTE prophylaxis unless additional risk factors are present, in which case, UFH or LMWH is recommended. Preoperative dosing is rarely needed as most of these patients receive UFH intraoperatively, but postoperative treatment should be considered for those who remain at bed rest for a prolonged period.

Gynecologic and Urologic Surgery

On the basis of the ACCP recommendations, no specific VTE prophylaxis is needed other than early mobilization for patients undergoing brief (<30 min) gynecologic surgery, transurethral, or low-risk urologic procedures.¹⁹ Patients undergoing laparoscopic gynecologic surgical procedures should undergo at least one of the VTE prophylactic strategies, such as low-dose UFH, LMWH, IPC, or GCS. In contrast, patients undergoing major gynecologic operations should be treated with VTE prophylaxis until discharged from the hospital. Elderly women (≥ 60 years) undergoing gynecologic cancer surgery or who have had a previous episode of VTE should receive VTE prophylaxis for 2 to 4 weeks following hospital discharge. Patients undergoing major or open urologic procedures should receive VTE prophylaxis, such as low-dose UFH twice or thrice daily. Alternative VTE strategies may include LMWH, IPC, and/or GCS prophylaxis. Urological patients with multiple VTE risk factors (Table 1) should be treated with combinations of GCS and/or IPC with low-dose UFH or LMWH.¹⁹

Neurosurgery

Neurosurgery patients should routinely receive VTE prophylaxis. The GCS reduce venous stasis and

prevent postoperative VTE in surgical patients with neurologic disorders, including paralysis of the lower limbs.⁷¹ The IPC with or without GCS is effective prophylaxis for VTE in patients undergoing intracranial surgery and does not increase the risk of bleeding.^{16,34} Alternatively, these patients can be treated with low-dose UFH or postoperative LMWH. High-risk neurosurgical patients with multiple VTE risk factors should receive a combination of mechanical prophylaxis (GCS and/or IPC) and pharmacological prophylaxis including low-dose UFH or LMWH.¹⁹

Conclusion

Probably the most important factor in preventing VTE is recognizing the need to institute primary VTE prophylaxis. Choice of prophylactic modality is best based on risk group assessment, with individual adjustment based on certain high-risk groups, such as patients with previous VTE. Pharmacologic prophylaxis continues to be the most effective method. Future developments will likely include the approval of oral agents with greatly improved ease of administration. The role of removable filters will hopefully become better defined with further study.

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