

Venous Thromboembolism Prophylaxis in the General Surgical Patient

J.A. CAPRINI and J.I. ARCELUS

ABSTRACT

General surgery is associated with a significant risk of venous thromboembolism (VTE). The high prevalence and frequently silent onset of this condition underscore the importance of risk assessment and appropriate prophylactic measures. Individual risk assessment is critical for the selection of appropriate prophylactic methods for general surgical patients. Intermittent pneumatic compression and graduated compression stockings have been shown to reduce the risk for postoperative development of VTE in moderate-risk surgical patients. In very high-risk surgical patients, such as those with malignant disease, pharmacologic prophylaxis given for up to four weeks is necessary. Unfractionated heparin and low-molecular-weight heparins are safe and effective for VTE prophylaxis in this patient population. However, recent data from prospective registries show that most patients who develop postoperative symptomatic VTE had received some form of prophylaxis, which was obviously ineffective.¹ Therefore, more effective methods are necessary for very high-risk patients. A novel selective factor Xa inhibitor, fondaparinux, also has been shown to be safe and effective for VTE prophylaxis in patients who have undergone abdominal surgery, especially in patients with cancer. These results suggest that fondaparinux may further improve VTE prevention in the general surgical population. No method of VTE prophylaxis is appropriate for every patient; therefore, the benefits and risks of each method of VTE prophylaxis should be weighed for the individual patient so that the optimal prophylactic regimen can be initiated.

INTRODUCTION

Patients undergoing major surgery are at an up to 20-fold increased risk for development of venous thromboembolism (VTE), an often asymptomatic condition that encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE).² Kakkar and colleagues demonstrated in 1975 that the observed rate of DVT in general surgical patients who did not receive VTE prophylaxis was nearly 30%.³ A meta-analysis of randomized trials in general, orthopedic, and urologic surgery, conducted prior to 1988, reported similar results (27% incidence of DVT and 3.4% incidence of fatal PE).⁴ Pooled data from more than 50 trials published between 1970 and 1985 show that the overall postoperative incidence of DVT as assessed by fibrinogen uptake test (FUT), a nuclear study in which radiolabeled fibrin is incorporated into newly formed thrombi, and/or venogram ranges from 19 to 29% in untreated patients who undergo general surgery. The rate of PE in these studies was approximately 1.6%, and the rate of fatal PE was 0.9%. The majority of patients included in this pooled analysis underwent elective gastrointestinal surgery; some study populations also included patients who had undergone gynecologic, thoracic, urologic, or vascular surgery.

In the United States, DVT is reported to affect up to 145 individuals per 100,000 individuals per year in the general population, and it is accompanied by PE in up to 69 individuals per 100,000.⁵ Approximately 14 to 16% of all symptomatic VTE diagnosed in the western world is diagnosed in postoperative patients and almost half of them are general surgical patients.¹ Because of the strong data demonstrating

the high risk of VTE in general surgical patients, clinical studies without prophylaxis are no longer performed in this patient population, and thus, the current risk of VTE in unprotected patients is unknown. The incidence of VTE in this patient population without prophylaxis was approximately 30% in studies done in the mid- to late 1970s using very sensitive objective diagnostic methods.^{4,6} With pharmacologic prophylaxis, the incidence ranges from 4.6 to 8%. Despite the seriousness of the condition and its prevalence, it has been demonstrated that 25 to 62% of general surgical patients do not receive any form of prophylaxis.^{7,8} On the other hand, recent data reveal that more than 50% of patients developing postoperative VTE had receive pharmacological prophylaxis.^{1,9} Clearly, there is a need to improve VTE prevention in general surgical patients.

VTE is difficult to diagnose because it is often asymptomatic and, when present, symptoms are nonspecific. Symptoms of DVT include leg pain, heaviness, and swelling. Symptoms of PE include chest pain, shortness of breath, tachypnea, fever, transient orthostatic hypotension, fainting spells, sudden death, and postoperative stroke. Although many surgeons may think that postoperative VTE is uncommon, many most likely see the signs of VTE often, but overlook their possible connection to VTE. In 70 to 80% of patients who die from PE in the hospital, this diagnosis was not even considered prior to the patient's death.^{10,11}

The prevention of VTE is important because both symptomatic and asymptomatic VTE are associated with long-term consequences, even when the condition is diagnosed and treated. A common serious complication associated with DVT is post-thrombotic syndrome (PTS), which is characterized by permanent vein damage that results in chronic leg swelling that worsens during the day and may be accompanied by the presence of varicose veins, edema, skin discoloration, and skin ulcerations.^{12,13} In a prospective study of 528 patients with venography-confirmed DVT, 19% of whom were postoperative, the cumulative incidence of PTS at two, five, and eight years following initial diagnosis and treatment was 24.5%, 29.6%, and 29.8%, respectively.¹³ PTS also represents a significant economic impact of DVT. It has been estimated that 15 million Americans are afflicted with PTS and that two million work days are missed annually due to the condition.¹⁴

Recurrent DVT or PE is also a common clinical consequence of VTE. The cumulative incidence of recurrent VTE after two, five, and eight years of follow-up was 17.2%, 24.3%, and 29.7%, respectively.¹³ A rare, but serious consequence that is associated with both symptomatic and asymptomatic DVT is fatal PE. It has been estimated that less than 50% of patients are alive one year following an acute PE.¹⁵ In addition, almost 1% of patients who survive an acute PE will develop chronic pulmonary hypertension.¹⁶ PE also is associated with embolic stroke in patients with patent foramen ovale (PFO), a condition estimated to be present in

10% to nearly 30% of the general population.¹⁷⁻²⁰ PE can lead to elevated pressures in the right side of the heart, which can lead to expansion of PFO. A clot or part of a clot can move from the right chamber to the left chamber of the heart through the expanded PFO, causing cerebral and peripheral ischemic events characteristic of paradoxical embolism (passage of a clot from a vein to an artery).²¹ These serious, disabling, and sometimes fatal consequences of VTE underscore the importance of prevention in patients at risk, including patients undergoing general surgery.

Although a high incidence of VTE has been demonstrated in general surgical patients, risk for VTE varies among general surgery patients, and different methods of prophylaxis are appropriate for different levels of risk. An optimal approach to risk assessment and VTE prophylaxis should combine evidence-based, consensus, and clinical practice guidelines with clinical experience where a lack of science exists. Several risk factor assessment models have been proposed to predict risk.²²⁻²⁹

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

Although the risk for VTE is increased in all patients undergoing general surgery, the relative risk for postoperative development of this complication varies among individual patients based on several factors, including the length of immobilization following surgery, the type of surgery performed, and the presence of comorbid conditions (see Table 42.1).^{2,15,30-33} Important patient-specific risk factors for VTE include age (older than 40 years), ethnicity, and body mass index greater than 25.^{5,30,32,34-36} A recent retrospective study in general surgical patients found that, although a steady rise in the incidence of VTE is seen between 40 and 75 years of age, this increase does not continue above the age of 75 years.³⁰

Immobilization for an extended period of time is a well-established risk factor for VTE, and early mobilization following surgery has been shown to lower the risk for postoperative VTE.^{32,33} There is also strong evidence that the type of surgical procedure that a patient undergoes is predictive of the risk for postoperative VTE.³⁰ Major general surgery (usually defined as abdominal or thoracic operations that require general anesthesia lasting ≥ 45 minutes) is associated with a high risk of VTE. Orthopedic surgery also is associated with an even higher risk for VTE. In a retrospective study of more than one million surgical patients, the incidence of symptomatic VTE was highest among patients who underwent orthopedic surgery of the hip or knee as well as those who had invasive neurosurgery involving brain incision, excision, or biopsy.³⁰ Other procedures associated with a substantially increased risk for VTE included major vascular surgery, small- or large-bowel resection, gastric

TABLE 42.1 Risk Factors for VTE^{15,33}

Patient factors	
• Age >40 years	• Pregnancy
• Prolonged immobility	• Puerperium
• Obesity	• High dose estrogen therapy
• History of DVT or PE	• Varicose veins
Medical/surgical risk factors	
• Major surgery (especially involving the abdomen, pelvis, lower extremities)	• Acute respiratory failure
• Malignancy (especially pelvic, abdominal, metastatic)	• Congestive heart failure
• Myocardial infarction	• Inflammatory bowel disease
• Stroke	• Nephrotic syndrome
• Fractures of the pelvis, hip, or leg	• Pacemaker wires
• Polycythemia	• Paraproteinemia
• Paroxysmal nocturnal hemoglobinuria	• Behcet's syndrome
Hypercoagulable states	
• Lupus anticoagulant and antiphospholipid antibodies	• Disorders of plasminogen and plasminogen activation
• Homocysteinemia	• HIT
• Dysfibrinogenemia	• Protein C deficiency
• Myeloproliferative disorders	• Protein S deficiency
• Antithrombin deficiency	• Hyperviscosity syndromes
• Factor V Leiden	• Prothrombin gene mutation 20210A
• Disseminated intravascular coagulation	

bypass, radical cystectomy, kidney transplantation, and below-the-knee amputation.³⁰ A lower risk of VTE was reported with radical neck dissection, inguinal hernia repair, appendectomy, laparoscopic cholecystectomy, transurethral prostatectomy, repair of a cystocele or rectocele, cruciate ligament repair, and thyroid or parathyroid surgery.³⁰

Certain medical conditions, including congestive heart failure, chronic obstructive pulmonary disease, recent myocardial infarction, stroke, nephrotic syndrome, inflammatory bowel disorder, and systemic lupus erythematosus are known to increase the risk for VTE.^{15,33} There is a particularly strong association between cancer and VTE.^{35,37} Cancer patients undergoing surgery have a two- to five-fold increased risk for postoperative VTE, compared with noncancer patients undergoing the same procedures.^{37,38} In addition, among patients with DVT, those with cancer have a more than two-fold increased risk for VTE recurrence than those without cancer.³⁷ In a retrospective study of 986 patients who underwent venous ultrasonography because of suspected DVT, 12% of patients with confirmed DVT were subsequently found to have cancer.³⁹ Conversely, it has been shown that clinically apparent VTE is present in as many as 15% of all cancer patients, with much higher incidences reported in postmortem studies.^{40,41} The likelihood for the development

TABLE 42.2 Categories of Risk for VTE in Patients Undergoing General Surgery and Recommended Prophylactic Regimens⁹⁹

Low risk (1 factor)	Moderate risk (2 factors)	High risk (3–4 factors)	Highest risk (≥5 factors)
Early ambulation	GCS or IPC	LDUH (5,000 U BID) or LMWH (≤3400 U QD) or fondaparinux (2.5 mg QD)	GCS or IPC and LDUH (5,000 U TID), LMWH (>3,400 U QD), or fondaparinux (2.5 mg QD)

of VTE in cancer patients is increased among those with more advanced clinical disease and varies by tumor type.^{42,43} Malignancies stemming from the uterus, brain, ovary, pancreas, stomach, kidneys, and colon are among those that have been associated with the highest relative risk for VTE.⁴²

Acquired or inherited thrombophilia disorders can also increase risk of VTE. A mutation in the factor V gene resulting in resistance to the action of protein C, known as factor V Leiden, is the most common cause of familial thrombophilia.⁴⁴ This mutation can increase the risk of VTE to 50- to 80-fold that of the general population in individuals who are homozygous for the mutation and to three-fold in heterozygous individuals.^{44,45} The second most common cause of familial thrombophilia is the prothrombin 20210A mutation. This mutation is associated with a three-fold increase in the risk for VTE. Another thrombophilia disorder is antiphospholipid antibody syndrome. Thromboembolic events are reported in approximately one-third of antiphospholipid-positive patients. The risk of recurrent thrombosis in these patients ranges from 22 to 69%.⁴⁶ Other thrombophilia disorders include hyperhomocysteinemia; protein C, protein S, and antithrombin deficiencies; and elevated levels of coagulation factors, including factors II, VIII, IX, and XI. Detection of these disorders is critical for identification of a patient's true risk for VTE and should be a factor in a patient's decision of whether or not to undergo elective surgery.

VENOUS THROMBOEMBOLISM PROPHYLAXIS

Aside from aggressive mobilization, the American College of Chest Physicians does not recommend specific measures for patients at low risk for VTE (risk factor score of 0 to 1; see Table 42.2). Pharmacologic therapies (unfractionated heparin [UFH, 5000 U bid] or low-molecular-weight

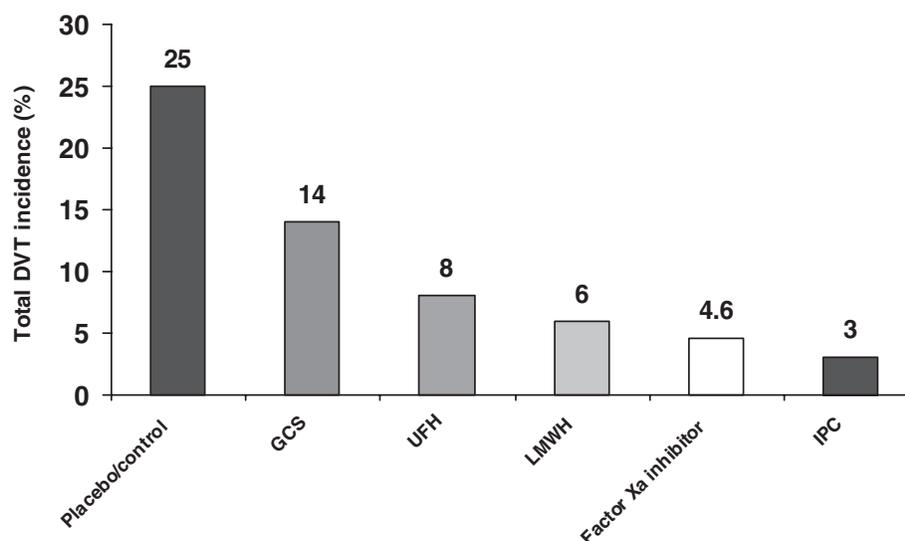


FIGURE 42.1 Incidence of VTE with currently available prophylactic methods following general surgery.*

*All incidences are for DVT after general surgery based on meta-analyses from Geerts 2001 except the incidence for Factor Xa inhibitor, which includes venographically proven DVT, symptomatic DVT, and PE and is based on the results from PEGASUS.⁹⁴

heparin [LMWH, <3400UQD]) and nonpharmacologic interventions are recommended for the prevention of VTE in patients at moderate risk (risk factor score of 2). For patients at high risk (risk factor score of 3–4), pharmacologic therapies (UFH [5000 U TID] or LMWH [>3400 UQD]) and intermittent pneumatic compression (IPC) are recommended for protection against VTE. For patients at highest risk for VTE (risk factor score ≥ 5), pharmacologic therapy using high-risk doses always is recommended in the absence of contraindications, and the adjunctive use of mechanical prophylaxis also is recommended.

Nonpharmacologic Interventions for the Prevention of Venous Thromboembolism

Nonpharmacologic VTE prevention strategies often are appealing because they do not increase the risk for bleeding; however, they have not been as extensively studied as pharmacologic prophylaxis.⁴⁷ It is recommended that early and “aggressive” ambulation be a routine part of postoperative care in all patients unless there is an absolute contraindication. Although early mobilization following surgery has been shown to significantly lower the risk for postoperative VTE,³² it is recommended as the sole method of prophylaxis only for low-risk patients, those younger than 40 years of age without any additional risk factors for VTE who are undergoing minor surgery (outpatient surgery lasting less than 45 minutes). For surgical patients at moderate risk for VTE (major surgery with 2 additional risk factors), mechanical methods of prophylaxis, including graduated compression stockings (GCS) and IPC, have been very safe and

effective modalities and have been very well accepted in the United States, particularly in patients at high risk for bleeding complications.

The results of several meta-analyses suggest that IPC can reduce the risk of DVT in general surgical patients; however, these meta-analyses included a small number of small clinical trials.^{47–49} The incidence of DVT in general surgical patients who received IPC was 3% (95% CI, 1% to 8%) in one recent meta-analysis of two studies (see Figure 42.1), a result similar to that observed in previous meta-analyses.^{47–49} Several head-to-head clinical trials have shown that IPC has similar efficacy to low-dose UFH and LMWH for the prevention of DVT in general surgery patients.^{50–53} Although there is strong evidence supporting the use of IPC alone in moderate-risk patients, it has not been studied as thoroughly as pharmacologic agents and is recommended only as an adjunctive therapy in surgical patients at high and highest risk for VTE (see Table 42.2).

Elastic stockings also have been shown in meta-analyses to substantially reduce the incidence of lower extremity DVT in patients who have undergone general surgery.⁵⁴ A recent systematic review conducted by the Cochrane Collaboration analyzed seven randomized controlled trials in surgical patients (4 general surgery [abdominal/pelvic/thoracic], 1 gynecologic surgery, 1 neurosurgery, 1 orthopaedic surgery). The incidence of lower-limb DVT in patients who used elastic stockings was significantly reduced, compared with those who did not use this intervention (15% vs 29%, $P < .00001$).⁵⁵ The incidence of DVT following general surgery was 14% (95% CI, 10% to 20%) with GCS in a meta-analysis of three studies. In another meta-analysis of

11 studies that investigated the prophylactic efficacy of GCS in patients who had undergone moderate-risk surgery (9 abdominal surgery, 1 gynecologic surgery, and 1 neurosurgery), elastic stockings reduced the risk for lower-limb DVT by 68%.⁵⁴ The current evidence suggests that GCS is effective in moderate-risk general surgical patients, but there is little data exploring the efficacy of this intervention in high-risk general surgical patients or surgical patients with cancer. Limitations of GCS include a lack of standardization of stockings, difficulty fitting patients of unusual size or shape, and poor compliance.

Clinical trials have shown that combining GCS or IPC with pharmacologic prophylaxis, such as heparin, results in better protection against VTE than either of these approaches used alone.^{55,56} The incidence of DVT was only 1.5% in a group of 328 surgical patients who received a pharmacologic and antistasis agent, compared with 26.8% in a control group who did not receive prophylaxis.⁵⁷ In a study in cardiac patients (N = 2551) randomized to receive subcutaneous heparin alone or in combination with IPC, the incidence of PE was 62% lower (1.5% vs 4%) in those who received combination therapy ($P < .001$).⁵⁸ In 249 patients who had suffered a stroke, combined modality therapy resulted in a reduction of DVT (0.23% vs 9.2%) and PE (0% vs 2.4%).⁵⁹ These findings suggest that although mechanical prophylaxis may not be appropriate as a sole intervention in patients at high risk for VTE, it may offer additional protection in patients receiving pharmacologic therapy.

Further support for the benefit of combined mechanical and pharmacologic prophylaxis for the prevention of VTE came from the APOLLO study. In this double-blind, placebo-controlled trial, patients undergoing major abdominal surgery (N = 1309) received IPC with or without the Factor Xa inhibitor fondaparinux.⁶⁰ Combined IPC and fondaparinux therapy produced a significant reduction in the incidence of all VTE from 5.3% (IPC alone) to 1.7% ($P = .004$). The rates of proximal DVT were also significantly reduced in the combined therapy group from 1.7% (IPC alone) to 0.2% ($P = .037$). Patients who received fondaparinux treatment had significantly more major bleeding episodes than those who received IPC alone (1.6% vs 0.2%, $P = .006$); however, none of these bleeds were fatal or involved critical organs. In addition, a major bleeding rate of 1.6% is comparable to the major bleeding rates observed with abdominal surgery (colorectal surgery) with enoxaparin and UFH.⁶¹ Although patients might be at a higher risk for bleeding with the addition of pharmacologic anticoagulation treatments, combined therapy has been shown to be significantly more effective for the prevention of VTE following major surgery than mechanical prophylaxis alone.

Inferior vena caval (IVC) filters are not routinely used for the prevention of DVT, but rather for the prevention of PE in patients who either fail or have contraindications to other prophylactic therapies, particularly anticoagulants.⁶² Pro-

phylactic use of IVC filters is indicated for patients with established VTE with an absolute contraindication to anticoagulation, serious complication while on anticoagulation (i.e., hemorrhage, thrombocytopenia, or drug reaction), or documented failure on anticoagulation.⁶² In addition, IVC filters can be effective in patients with pelvic fractures or closed head injuries who are at high risk for thrombosis or have had a previous thrombosis.

IVC filters are generally safe and have been shown to reduce the incidence of PE and fatal PE to 2.6 to 3.8% and 0.3 to 1.9%, respectively, in patients at risk for VTE.⁶³ An increase in recurrent DVT has been observed with IVC filters. Decousus and colleagues demonstrated a reduction in symptomatic and asymptomatic PE at 12 days, from 4.8 to 1.1% in patients with DVT who received filters, but at two years the incidence of recurrent DVT was significantly increased in these patients (20.8% vs 11.6%, $P = .02$).⁶⁴ However, eight-year follow-up on these patients was recently reported, and although the significant reduction in the incidence of PE was maintained ($P = .01$), at eight years there were no significant differences in recurrent DVT ($P = .08$), PTS, or overall mortality with and without filters.⁶⁵ Several types of IVC filters are available, but the Greenfield filter is the only filter with good long-term follow-up.^{66,67} Although relatively rare, other complications associated with IVC filter placement and long-term use include migration of the filter, postfilter caval thrombosis, and PTS.^{63,68}

In summary, nonpharmacologic prophylaxis can be very effective in reducing the incidence of DVT in general surgical patients at moderate risk for VTE (see Table 42.2). However, they have not been as extensively studied as pharmacologic agents and are not recommended as the sole method of prophylaxis in patients at higher risk for VTE. However, in conjunction with pharmacologic agents, mechanical prophylaxis can be very effective in reducing the incidence of VTE in these patients. On the other hand, mechanical prophylaxis with stockings or IPC is recommended in patients with a high risk for bleeding.

Pharmacologic Methods for the Prevention of Venous Thromboembolism

Commonly used pharmacologic therapies for prevention of VTE in patients undergoing general surgery include subcutaneous UFH and LMWH (enoxaparin, dalteparin, nadroparin, or tinzaparin). Low-dose subcutaneous UFH was the first pharmacologic agent to be widely investigated for prevention of VTE in patients undergoing general surgery. In the early 1970s, Kakkar and colleagues demonstrated that this therapy significantly reduced the risk for both DVT and PE in this patient population.⁶⁹ Low-dose UFH is highly effective therapy for the prevention of VTE in patients undergoing general surgery, including those with underlying malignancy.^{64,69} In a landmark prospective randomized

study of 4121 patients undergoing major surgery (primarily abdominal, gynecologic, or urologic surgery), UFH prophylaxis reduced the incidence of DVT from 25% to 8% ($P < .005$).⁶ Patients treated with UFH also had a significantly reduced incidence of PE ($P < .005$) and death from PE ($P < .005$) compared with control patients.⁶

A meta-analysis of 46 trials by Collins and colleagues that included 16,000 patients who had undergone general, orthopedic, or urologic surgery confirmed Kakkar's results, with a DVT incidence of 27% without prophylaxis compared with 10.6% with UFH and a fatal PE incidence of 3.4% and 1.7%, respectively.⁴ The incidence of DVT was 8% (95% CI, 7% to 8%) with UFH following general surgery in a recent meta-analysis of 47 clinical studies. It has been suggested that the administration of 5000U of UFH TID is more effective than 5000UBID, without increased bleeding,^{4,47} but no direct comparison studies have been conducted. In general, UFH can be given twice daily in moderate- to high-risk patients but should be given three times daily in higher-risk patients.

Although UFH is effective for the prevention of DVT and PE in general surgical patients, bleeding complications associated with this therapy present a serious safety concern.^{4,6,47} Cancer patients may be at higher risk for hemorrhagic complications with UFH than noncancer patients.⁷⁰ Another limitation of UFH is its association with heparin-induced thrombocytopenia (HIT). UFH has been associated with up to a 5% incidence of HIT, an antibody-mediated process characterized by a dramatic drop in platelets.⁷¹ In 20% of cases, HIT develops into thrombosis. UFH can also cause osteopenia by binding to osteoblasts, which stimulates osteoclast activation and results in bone breakdown when used long term. The short half-life of UFH (0.5 to 2 hours) relative to other anticoagulants is another limitation of UFH because it necessitates more frequent dosing; however, the short half-life can also be an advantage in the case of bleeding complications or renal failure. Another advantage of UFH is that an antidote, protamine sulfate, is available for situations when immediate reversal is required, although reversal is not without risks.

LMWHs appear to be at least as effective as UFH for the prevention of DVT in clinical trials of patients undergoing general surgery (see Figure 42.1). Overall, the residual incidence of VTE in abdominal surgery patients receiving LMWH ranges from about 5 to 15%, with the highest rates in patients with cancer.^{76,77} The incidence of DVT with LMWHs following general surgery was 6% (95% CI, 6% to 7%) in a recent meta-analysis of 21 clinical studies. Available LMWHs appear to be similarly effective for the prevention of VTE. Both enoxaparin and dalteparin have been shown to reduce the incidence of DVT in patients undergoing general surgery to rates of approximately 6 to 8%; however, direct comparison studies have not been conducted.^{75,78}

LMWHs appear to be effective in VTE prophylaxis, even in patients with cancer.^{76,77,79,80} The incidence of VTE in patients with cancer who were given enoxaparin was slightly lower than that observed in patients given UFH (14.7% vs 18.2%) in a study of patients undergoing abdominal surgery for malignant disease ($N = 1115$).⁷⁶ In addition, when patients undergoing planned curative surgery for abdominal or pelvic cancer were given LMWH for six to 10 days and then randomized to receive extended prophylaxis with LMWH or placebo for 21 days, the incidence of venographically demonstrated VTE at three months was significantly reduced (5.5% vs 13.8%, $P = .01$) with extended prophylaxis.⁷⁷ There was no significant increase in bleeding with extended prophylaxis. These results suggest that LMWH is at least as effective as UFH in general surgical patients with cancer and that extended prophylaxis with LMWH is safe and can significantly reduce the incidence of VTE in general surgical patients with cancer.

It has been suggested that survival may be increased in patients with cancer who receive LMWH compared with UFH, although the reason for this is not clear. In women with previously untreated breast and pelvic cancer who had undergone primary surgery, those who received LMWH ($n = 160$) had significantly better long-term survival at 650 days than those who received UFH ($n = 164$, $P = .0066$).⁸¹ A significant survival benefit (12.6% vs 27%, $P = .041$) also was observed with LMWH in a subset of patients with cancer who were treated for DVT with a LMWH or UFH.^{82,83} In a randomized controlled study where patients with advanced cancer ($N = 385$) were randomized to receive a LMWH once-daily for one year or placebo, there was no significant difference in survival at one, two, or three years; however, in a subset of patients with a better prognosis, survival was significantly ($P = .03$) improved at two and three years (78% vs 55% and 60% vs 36%, respectively).⁸⁴ These results suggest that there may be some survival benefit of LMWH in patients with cancer, particularly those at early stages of malignancy.

Although there is some evidence that LMWH therapy may lead to fewer bleeding complications than observed with UFH, results from clinical studies have been inconsistent, and bleeding remains an important safety concern associated with LMWH, particularly when it is used at higher doses.^{73-76,85-87} Advantages of LMWHs over UFH include a higher anti-Xa activity compared with antithrombin activity, better bioavailability at low doses, no monitoring required, and a longer half-life (4 hours vs 0.5 to 2 hours), allowing for once-daily dosing in some patients. However, a long half-life can sometimes be a disadvantage in the case of bleeding complications. In addition, LMWHs are incompletely reversed by protamine sulfate.⁸⁸ Other disadvantages of LMWHs include renal excretion, precluding use in patients with severe renal failure, and increased cost relative to UFH. Furthermore, LMWHs also carry a risk for HIT and

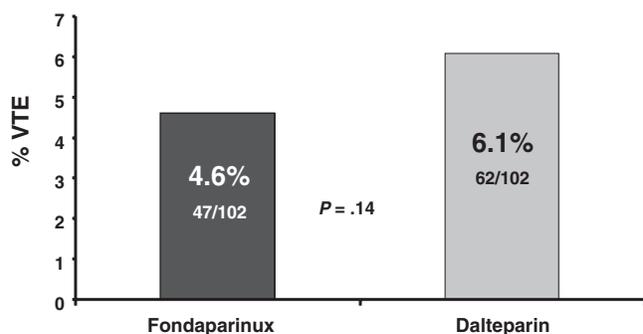


FIGURE 42.2 VTE reduction with fondaparinux versus dalteparin in high-risk abdominal surgical patients.⁹⁴

should not be used in patients at risk for or with established HIT, although they appear to be associated with a lower incidence than UFH.

Fondaparinux is the first in a new class of antithrombotics known as factor Xa inhibitors, which are characterized by targeted inhibition of coagulation. Fondaparinux is a novel synthetic pentasaccharide that selectively binds to anti-thrombin III with enhanced neutralization of factor Xa.⁹⁰ It has demonstrated greater efficacy than LMWH in VTE prophylaxis following total joint replacement^{91,92} and hip fracture surgery⁹³ and has been evaluated for VTE prophylaxis in patients undergoing general surgery. In the Pentasaccharide in General Surgery Study (PEGASUS), the efficacy and safety of postoperative fondaparinux (2.5 mg once daily) was compared with that of the LMWH dalteparin started preoperatively in high-risk abdominal surgical patients.⁹⁴ This multicenter, randomized, double-blind study included 2900 high-risk abdominal surgical patients, in which high risk was defined as patients older than 60 years of age or older than 40 years of age with one or more risk factors including cancer, obesity (BMI >30 for men and >28.6 for women), history of VTE, heart failure (NYHA grade III or IV), chronic obstructive pulmonary disease, or inflammatory bowel disease.⁹⁴

PEGASUS showed that the rates of VTE (venographically-proven DVT, symptomatic DVT, or fatal or nonfatal PE) up to day 10 among patients treated with fondaparinux and dalteparin were 4.6% and 6.1% ($P = .14$), respectively, representing a 24.5% reduction in the incidence of VTE in favor of fondaparinux (see Figure 42.2).⁹⁴ At postoperative day 32, symptomatic DVT was seen in 0.8% of patients treated with fondaparinux and in 1.0% of patients who received dalteparin.⁹⁴ The difference in the incidence of major bleeding between the two treatment groups was not significant (3.4% fondaparinux vs 2.4% dalteparin, $P = .12$).⁹⁴ These results demonstrate that fondaparinux is at least as effective, if not more, than UFH and LMWH in preventing VTE in general surgical patients (see Figure 42.1). Based on this data, fondaparinux was recently approved in the United States for VTE prevention in abdominal surgical patients undergoing

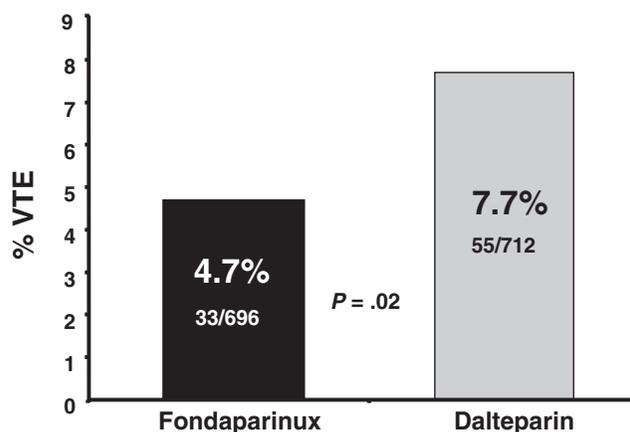


FIGURE 42.3 VTE reduction with fondaparinux versus dalteparin in high-risk abdominal surgical patients with cancer.⁹⁴

general anesthesia for longer than 45 minutes who are older than 40 years of age and have one of the following risk factors: neoplastic disease, obesity, chronic obstructive pulmonary disease, inflammatory bowel disease, history of DVT or PE, or congestive heart failure. In addition, it is indicated for abdominal surgical patients undergoing general anesthesia lasting longer than 45 minutes who are older than 60 years of age with or without one or more of the risk factors just listed.

A post-hoc analysis was performed to compare the effects of the two therapies in the 68% of the evaluable study population who underwent surgery for cancer.⁹⁴ In the cancer subpopulation, fondaparinux significantly reduced the incidence of VTE compared with dalteparin from 7.7 to 4.7% ($P = .02$), representing a 39% reduction in the incidence of VTE (see Figure 42.3). The incidence of major bleeding was similar between groups (3.4% fondaparinux vs 2.5% dalteparin). These preliminary findings suggest that postoperative fondaparinux is at least as effective and safe as preoperative dalteparin for the prevention of VTE after abdominal surgery and is significantly more effective than dalteparin in cancer patients undergoing the same procedures.

Another advantage of fondaparinux is that, unlike UFH and LMWH, it has not been associated with HIT. Because the fondaparinux molecule does not bind to platelet factor 4, it cannot form the complex that reacts with the platelet-activating antibody, and it does not cross-react with HIT antibodies from patients with confirmed type II HIT.^{95,96} Fondaparinux has also been shown to be safe for extended prophylaxis (4 weeks),⁹⁷ although this was shown in patients who had undergone hip fracture surgery, not in general surgical patients. In addition, because fondaparinux does not interfere with thrombin binding, it has no negative effect on wound healing. Further, fondaparinux has a 17-hour half-life, which allows for once-daily dosing, and there is no dose alteration required in patients weighing less than 50 kg or

renally impaired patients. However, no antidote is available and a long half-life also can be a disadvantage in the case of bleeding complications. Fondaparinux is renally excreted and should not be used in patients with kidney failure and should be avoided in patients undergoing neuraxial anesthesia, as there is the potential for epidural hematoma formation.

There are a variety of agents available for the prevention of VTE in patients undergoing general surgery. No single agent is optimal for all patients. Different agents should be used in patients at different levels of risk and patient characteristics and comorbid conditions can make one agent more appropriate than another in a certain patient. The stratification of general surgery patients by risk for VTE can guide surgeons in their selection of appropriate VTE prophylaxis.

RISK STRATIFICATION

The risk for VTE ranges from low to very high in patients undergoing general surgery. Risk category placement is dependent upon the presence of factors that influence the risk for VTE, including type of surgery, age, immobilization, and comorbidities. It has been demonstrated that up to 36% of general surgical patients had three or more risk factors, placing them in the high or highest risk groups.⁹⁸ These are groups in which pharmacologic VTE prophylaxis is strongly recommended. The number of factors that can influence the risk of VTE and the variety of agents available for VTE prophylaxis can make risk assessment and management difficult.

Risk stratification has been suggested as a means of determining the risk for VTE in patients undergoing surgery and of guiding the selection of appropriate prophylactic measures. Risk assessment models, like the one pictured in Figure 42.4, can be used to assign each patient a total risk factor score, which can then be used to categorize patients into one of four risk categories (low, moderate, high, and highest) (see Table 42.2).⁹⁹ An appropriate method of VTE prophylaxis can be chosen based on the patient's level of risk, taking into consideration any contraindications to prophylaxis that may be present.

The incidence of VTE in patients in the low-risk category (1 risk factor) is so low already (approximately 2%),¹⁴ that prophylactic measures would most likely not further reduce the risk. Thus, no measures above early ambulation are recommended in this patient population (see Table 42.2). The incidence of VTE ranges from 10 to 80% in the remaining groups;¹⁴ therefore, prophylactic measures are recommended in these groups. Elastic stockings and IPC reduce the incidence of DVT to 14% and 3% (see Figure 42.1), respectively, and can be used alone in moderate-risk patients (2 risk factors). Although IPC has been shown to reduce the

incidence of DVT to 3% following general surgery, it has not been extensively studied in general surgery and is not recommended as the sole method of prophylaxis in patients at greater than moderate risk for VTE.

Pharmacologic measures have been shown to produce lower incidences of DVT than mechanical methods of prophylaxis (see Figure 42.1) and therefore are recommended in patients at high and highest risk for VTE (see Table 42.2). Subcutaneous UFH (5000 UBID), LMWH (≤ 3400 UQD), or fondaparinux (2.5 mg QD) can be used in patients at high risk for VTE (3 to 4 risk factors). In patients at the highest risk for VTE (≥ 5 risk factors) higher doses of both subcutaneous UFH (5000 UTID) and LMWH (>3400 UQD) or fondaparinux (2.5 mg) should be used. Although fondaparinux has not been as extensively studied as UFH or LMWHs in general surgical patients, the results of PEGASUS (a 4.6% incidence of VTE)⁹⁴ suggest that fondaparinux is effective for VTE prophylaxis in this patient population and may be particularly effective in patients in the highest-risk category. In addition, for patients at highest risk for VTE, mechanical prophylaxis combined with pharmacologic prophylaxis can be more effective than pharmacologic prophylaxis alone. The recent APOLLO trial results emphasize the value of combined prophylaxis because, in that trial, the incidence of venographically positive DVT was 1.7% in moderate- and high-risk general surgical patients.⁶⁰

As an alternative to a risk assessment model, it has been suggested that appropriate thromboprophylactic measures be used in all but very low-risk general surgical patients. At a minimum, it has been suggested that the use of elastic stockings, sequential compression devices, and LMWHs should be considered in all patients undergoing cancer surgery, a group considered to be at high risk for VTE. In a recent editorial comment, Goldhaber suggests using pharmacologic methods of prophylaxis for all hospitalized patients, according to easily implemented protocols. For those patients with contraindications to pharmacologic prophylaxis, mechanical methods should be used. Patients at very high risk for VTE should receive a combination of both pharmacologic and mechanical measures.¹⁰⁰

CONCLUSION

Although the development of VTE is relatively common in the postoperative setting and is a frequent cause of sudden postoperative death, VTE prophylaxis remains underutilized. Because VTE is often asymptomatic and, when present, symptoms are nonspecific, surgeons may feel that they do not often see VTE in their practice. However, signs of VTE include leg pain, leg swelling, chest pain, shortness of breath, transient orthostatic hypotension, narcotic excess, fainting spells, hypoxia, sudden death, postoperative stroke, suspected myocardial infarction, and postoperative

Thrombosis Risk Factor Assessment

Patient's Name: _____ Age: ____ Sex: ____ Wgt: ____ lbs

Joseph A. Caprini, MD, MS, FACS, RVT
 Louis W. Bieler Professor of Surgery,
 Northwestern University,
 The Feinberg School of Medicine,
 Professor of Biomedical Engineering,
 Northwestern University,
 Director of Surgical Research,
 Evanston Northwestern Healthcare
 Email: j-caprini@northwestern.edu
 Website: vteozdisease.com

Choose All That Apply

Each Risk Factor Represents 1 Point	<input type="checkbox"/> Age 41-60 years <input type="checkbox"/> Minor surgery planned <input type="checkbox"/> History of prior major surgery (< 1 month) <input type="checkbox"/> Varicose veins <input type="checkbox"/> History of inflammatory bowel disease <input type="checkbox"/> Swollen legs (current) <input type="checkbox"/> Obesity (BMI > 25) <input type="checkbox"/> Acute myocardial infarction <input type="checkbox"/> Congestive heart failure (< 1 month) <input type="checkbox"/> Sepsis (< 1 month) <input type="checkbox"/> Serious lung disease incl. pneumonia (< 1 month) <input type="checkbox"/> Abnormal pulmonary function (COPD) <input type="checkbox"/> Medical patient currently at bed rest <input type="checkbox"/> Other risk factors _____
Each Risk Factor Represents 2 Points	<input type="checkbox"/> Age 60-74 years <input type="checkbox"/> Arthroscopic surgery <input type="checkbox"/> Malignancy (present or previous) <input type="checkbox"/> Major surgery (> 45 minutes) <input type="checkbox"/> Laparoscopic surgery (> 45 minutes) <input type="checkbox"/> Patient confined to bed (> 72 hours) <input type="checkbox"/> Immobilizing plaster cast (< 1 month) <input type="checkbox"/> Central venous access
Each Risk Factor Represents 3 Points	<input type="checkbox"/> Age over 75 years <input type="checkbox"/> History of DVT/PE <input type="checkbox"/> Family history of thrombosis* <input type="checkbox"/> Positive Factor V Leiden <input type="checkbox"/> Positive Prothrombin 20210A <input type="checkbox"/> Elevated serum homocysteine <input type="checkbox"/> Positive Lupus anticoagulant <input type="checkbox"/> Elevated anticardiolipin antibodies <input type="checkbox"/> Heparin-induced thrombocytopenia (HIT) <input type="checkbox"/> Other congenital or acquired thrombophilia If yes: Type _____ *most frequently missed risk factor
Each Risk Factor Represents 5 Points	<input type="checkbox"/> Elective major lower extremity arthroplasty <input type="checkbox"/> Hip, pelvis or leg fracture (< 1 month) <input type="checkbox"/> Stroke (< 1 month) <input type="checkbox"/> Multiple trauma (< 1 month) <input type="checkbox"/> Acute spinal cord injury (paralysis)(< 1 month)
For Women Only (Each Represents 1 Point)	<input type="checkbox"/> Oral contraceptives or hormone replacement therapy <input type="checkbox"/> Pregnancy or postpartum (<1 month) <input type="checkbox"/> History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant
Total Risk Factor Score <input style="width: 50px; height: 20px; border: 1px solid black;" type="text"/>	

FIGURE 42.4 Thrombosis risk factor assessment scoring sheet.

pneumonia, and most surgeons would agree that many of these conditions are relatively common following surgery.

Due to the significant morbidity and mortality that is associated with VTE, the risk of VTE must be considered in all general surgical patients. In this population, nearly 40% of patients are at high or highest risk for VTE (≥ 3 risk factors) and, therefore, require pharmacologic VTE prophylaxis. Risk stratification schemes may help to guide the intensity of clot-preventing measures. Risk stratification schemes like the one in Figure 42.4 may be helpful for assessing VTE risk in general surgical patients. Together with the consideration of any contraindications or precautions, risk stratification can be used to guide surgeons in selection of the optimal prophylactic therapy for each patient.

Clinical data suggest that using nonpharmacologic measures, such as GCS and IPC, can be effective in low- and

moderate-risk patients and can further enhance protection against VTE in high-risk patients when used in combination with pharmacologic agents. Pharmacologic therapies, including UFH and LMWH, are recommended for use in all high-risk (≥ 3 risk factors) general surgical patients. In addition, fondaparinux is an important treatment option for higher risk patients undergoing abdominal surgery, especially for cancer. It has been demonstrated that extended pharmacologic prophylaxis (up to 4 weeks) can significantly reduce the incidence of VTE events compared with prophylaxis for one week. Based on this data, it is suggested that high risk patients receive extended pharmacologic prophylaxis.

UFH is the least expensive pharmacologic agent and is safe for use in patients with renal failure and those undergoing neuraxial anesthesia. However, it is associated with HIT and must be given three times daily in patients at high risk for VTE. LMWHs have been shown to be at least as safe

and effective as UFH, are associated with a lower incidence of HIT, can be given once or twice daily, and may improve survival in patients with cancer. LMWHs should be used with caution in patients with renal failure or in those undergoing neuraxial anesthesia. Prophylactic administration of a novel factor Xa inhibitor, fondaparinux, has been shown to be as safe and at least as effective as UFH and LMWH for the prevention of VTE after abdominal surgery (see Figure 42.1) and to be significantly more effective than LMWH in cancer surgical patients. In addition, fondaparinux has an apparent lack of association with HIT and it can be given once daily. Fondaparinux has a long half-life, allowing for once-daily dosing, but this can be a disadvantage in the event of bleeding complications. In patients undergoing neuraxial anesthesia, there is a recent trial indicating that fondaparinux may be used with a longer period between spinal tap and the first injection of fondaparinux.¹⁰¹ It cannot be used in patients with advanced renal failure.

There is no single method of VTE prophylaxis that is optimal for every patient. The benefits and risks of each agent should be considered for each patient so that the safest, most effective therapy is initiated. As yet, little is known about the appropriate duration of these measures; however, in selected patients at high risk for VTE, extended prophylaxis is recommended.

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