The Prophylaxis of Venous Thrombosis in Patients With Cancer Undergoing Major Abdominal Surgery: Emerging Options

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Cancer is a risk factor for venous thromboembolism (VTE). This risk is amplified by treatment with chemotherapy, radiation, or surgery. Thus, patients with cancer undergoing major surgery should receive appropriate prophylaxis. Available agents include low-dose unfractionated heparin (LDUH), low-molecular-weight heparin (LMWH), and Factor Xa inhibitors. Recent data suggest that Factor Xa inhibitors are safe and effective for VTE prevention in patients with cancer undergoing abdominal surgery. Further study in this patient population is warranted.
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INTRODUCTION

Venous thromboembolism (VTE) is a spectrum of disease that includes deep venous thrombosis (DVT) and pulmonary embolism (PE). Both are associated with significant morbidity and mortality, even with treatment. Cancer is an important risk factor for VTE.

Cancer alone is associated with an approximately fourfold increase in risk of VTE and chemotherapy is estimated to increase the risk to sixfold [1]. The incidence of DVT following general surgery in patients with cancer is estimated to be 37%, in contrast to an estimated 20% in patients without cancer [2]. Conversely, it has been demonstrated that approximately 12% of patients with idiopathic VTE are subsequently diagnosed with cancer, most within 1 year of diagnosis of VTE [2–6]. Furthermore, thrombosis has been found to significantly increase the risk of death in patients with overt malignant disease [7].

Proposed mechanisms to explain the hypercoagulation associated with cancer include general factors related to the tumor and the host's response to the tumor (e.g., abnormal protein synthesis, tumor-mediated extrinsic vascular compression, inflammation, cell necrosis, and new hemodynamic arrangements) and more specific factors related to tumor-mediated hemostatic activities [8–10]. Tumor-related hemostatic abnormalities that can induce up-regulation of the coagulation cascade include release of procoagulants by tumor cells, increased platelet activation and aggregation, activation of endothelial cells (leading to the overexpression of plasminogen activator inhibitor-1, and decreased hepatic synthesis of anticoagulation proteins [9–13]. In addition to tumor-related mechanisms, hypercoagulation associated with cancer may also be a function of cancer treatments, including surgery, radiation, chemotherapy, and other antineoplastic agents [13–19]. Side effects and complications of treatment, such as major infection and extended immobility, can also increase the risk of VTE [13,14].

The diagnosis of VTE in patients with cancer is challenging, particularly because many patients with VTE are asymptomatic. This difficulty in diagnosing VTE has led to a focus on the importance of VTE prophylaxis in patients with cancer. VTE prophylaxis

may also be particularly important in these patients because the presence of VTE in patients with cancer has been associated with a significantly decreased survival rate [20]. In addition, VTE in patients with cancer is characterized by higher recurrence rates than in patients without cancer [21,22].

VTE risk assessment and prophylaxis are imperative in this high-risk patient population. The purpose of this article is to review VTE risk factors and the current and emerging treatment options for VTE prophylaxis in patients with cancer, particularly those undergoing major abdominal surgery.

RISK FACTORS FOR VTE

Risk factors for VTE can be surgical, medical, or hereditary (Table I). Surgical risk factors include major surgery involving the abdomen, pelvis, or lower extremity; trauma or fracture to the lower extremities; acute spinal cord injury; total hip replacement; or total knee replacement [23]. Medical risk factors include active cancer or history of cancer; advanced age (increased risk starting at age 40 years and increasing significantly with age >60 years); history of DVT/PE; family history of thrombosis; prolonged immobility; cardiovascular accident or paralysis; myocardial infarction; stroke; cardiac dysfunction; sepsis; serious lung disease, including chronic obstructive pulmonary disease (COPD); obesity; varicose veins; nephrotic syndrome; pregnancy or post-partum (<1 month); recurrent spontaneous abortion; and estrogen use [23]. Hereditary thrombophilic risk factors include Factor V Leiden, prothrombin variant 20210A, antiphospholipid/anticardiolipin antibodies, antithrombin dysfunction, positive lupus anticoagulant, protein C deficiency, protein S deficiency, heparin cofactor II deficiency, dysfibrinogenemia, decreased levels of plasminogen and plasmin activators, heparin-induced thrombocytopenia (HIT), hyperhomocysteinemia, polycythemia vera, and primary thrombocytosis [23].

Patients with a combination of risk factors have a cumulatively increased risk [23]. Thus, a patient with cancer undergoing major surgery is at very high risk for VTE. The overall incidence of DVT following general surgery is nearly double in patients with cancer compared with patients without cancer (37% with cancer vs. 20% without) [2,24]. The risk of fatal PE in patients with cancer is nearly triple [14]. The prevalence of DVT in patients with cancer undergoing abdominal surgery appears to be particularly high. A DVT prevalence of 66% in 1375 evaluable patients with cancer who had undergone major abdominal surgery was reported in one study [25]. This is of particular concern because the first-line treatment of many cancers is surgery. Further compounding the risk of VTE in cancer patients undergoing surgery is the fact that thrombogenicity may be increased if surgery is performed during a time when the patient is also receiving chemotherapy [13–19].

TABLE I. VTE Risk Factors [23]

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	

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; HIT, heparin-induced thrombocytopenia.

PREVENTION OF VTE IN PATIENTS WITH CANCER UNDERGOING MAJOR ABDOMINAL SURGERY

Low-dose Unfractionated Heparin and Low-molecular-weight Heparin

According to the evidence-based 2004 American College of Chest Physicians (ACCP) recommendations for the prevention of VTE, surgery in a patient with cancer places that patient at high risk for VTE (Table II) [14]. The ACCP strongly recommends the use of low-dose unfractionated heparin (LDUH; 5000 units [U] TID) or low-molecular-weight heparin (LMWH; >3400 anti-Xa U [XaU] QD) in high-risk and highest-risk patients. In patients at highest risk (those undergoing major surgery with multiple risk factors), graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) are recommended in addition to pharmacologic prophylaxis [14].

The VTE Disease Panel for the National Comprehensive Cancer Network (NCCN) recently issued Clinical Practice Guidelines in Oncology that included the recommendation that adult patients with a diagnosis or suspicion of cancer, without a specific contraindication, should receive anticoagulation prophylaxis with or without mechanical compression. This recommendation carried the highest weight and reflected uniform NCCN consensus based on the highest level of clinical evidence. With regard to specific prophylactic agents, guideline recommendations for inpatient anticoagulation include LDUH and LMWH (Table III) [26].

In randomized controlled trials, both LDUH and LMWH similarly reduced the incidence of DVT and PE following major surgery in patients with cancer

TABLE III. NCCN Practice Guidelines in Oncology Recommendations for Prophylactic Anticoagulation Therapy in Surgical Patients With a Diagnosis or Suspicion of Cancer [26]

Anticoagulant[a]	Dosing Information
LDUH	5000 U subcutaneous TID
LMWH	
Enoxaparin	40 mg subcutaneous QD
Dalteparin	5000 U subcutaneous QD
Tinzaparin	4500 U or 75 U/kg subcutaneous QD
Pentasaccharide	
Fondaparinux	2.5 mg subcutaneous QD

Inpatient-administration in patients without specific contraindications to anticoagulant therapy. NCCN, National Comprehensive Cancer Network; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; U, units; QD, once daily; TID, three times daily.

[14,27,28]. In the ENOXACAN study (N = 631), the LMWH enoxaparin (40 mg QD) was as effective and safe as subcutaneous LDUH (5000 U TID) in patients who received thromboprophylaxis following major abdominal surgery for abdominal or pelvic malignancies [29]. The frequency of VTE was 18.2% with LDUH compared with 14.7% with LMWH (95% confidence interval [CI] of the difference: −9.2, 2.3) and there was no significant difference in the incidence of major bleeding (2.9% vs. 4.1%, respectively).

In the European Fraxiparin Study (N = 1896), nadroparin (7500 XaU QD) was compared with subcutaneous LDUH (5000 U TID) following abdominal surgery in patients with cancer [30]. Patients were stratified according to the presence or absence of cancer prior to randomization. The frequency of DVT was 4.2% in patients with cancer who received LMWH compared with 5.4% in patients who received LDUH. Bleeding

TABLE II. Stratification of VTE Risk in Surgical Patients [14]

Level of Risk	Successful Prevention Strategies
Low risk	No specific prophylaxis; early and ''aggressive'' mobilization
Minor surgery in patients aged <40 years with no additional risk factors	
Moderate risk	LDUH (BID), LMWH (≤3400 U QD), GCS, or IPC
Minor surgery in patients aged <40 years with additional risk factors	
Surgery in patients aged 40–60 years with no additional risk factors	
High risk	LDUH (TID), LMWH (>3400 U QD), or IPC
Surgery in patients aged >60 years, or aged 40–60 years with additional risk factors (prior VTE, cancer, molecular hypercoagulability)	
Highest risk	LMWH (>3400 U QD), fondaparinux, oral VKAs (INR, 2–3), or IPC/GCS + LDUH/LMWH
Surgery in patients with multiple risk factors (aged >40 years, cancer, prior VTE)	
Hip or knee arthroplasty, HFS	
Major trauma; SCI	

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VTE, venous thromboembolism; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparins; U, units; GCS, graduated compression stockings; IPC, intermittent pneumatic compression; VKAs, vitamin K antagonists; INR, international normalized ratio; QD, once daily; BID, twice daily; TID, three times daily; HFS, hip fracture surgery; SCI, spinal cord injury.

rates were similar between groups. The incidence of postoperative bleeding in patients with cancer was 16.1% with LMWH and 15.8% with LDUH; 29.9% of patients with cancer treated with LMWH required a postoperative blood transfusion compared with 30.7% treated with LDUH. In patients without cancer, the frequency of DVT was 2% with LMWH and 3.9% with LDUH. Bleeding rates were also similar between these treatment groups, but were lower than those reported in patients with cancer.

Higher doses of LMWH ($>$3400 XaU [27], 5000 XaU vs. 2500 XaU with dalteparin [31], and $>$20 mg QD with enoxaparin [32]) appear to be more effective in preventing thrombotic events in cancer patients. In a subset of patients with cancer (66.4% of 2097 patients) in a study of VTE prophylaxis with dalteparin (2500 XaU vs. 5000 XaU) following major abdominal surgery, the incidence of DVT was 14.9% with 2500 XaU vs. 8.5% with 5000 XaU ($P <$.001), with no difference in major bleeding between the two doses (3.6% vs. 4.6%, respectively) [31]. Although dalteparin is the LMWH associated with the lowest incidence of VTE following abdominal surgery in patients with cancer (8.5%) [31], no direct comparison study between any LMWH has been conducted and; therefore, no conclusions about superiority for any single agent can be drawn.

Emerging data suggest that VTE prophylaxis for patients with cancer should extend beyond the period of hospitalization. A prospective, randomized, open-label study compared prophylaxis with the LMWH dalteparin (5000 XaU once daily) for 7 vs. 28 postoperative days in patients who had undergone abdominal surgery for malignancy [33,34]. After 28 days, a DVT was observed in 16.5% of patients in the standard duration group (7 days) compared with 7.3% of patients who received extended prophylaxis ($P =$.012, relative risk reduction [RRR] = 55%). In addition, the incidence of proximal DVT was reduced from 16% (standard duration therapy) to 0% by extending the administration of prophylaxis to 28 days ($P <$.005) [33]. Similarly, the ENOXACAN II trial assessed VTE outcomes in patients with cancer who had undergone abdominal or pelvic surgery who received the LMWH enoxaparin (40 mg daily) for 1 week vs. 4 weeks [35]. Significant reductions in DVT rates were observed in those patients who received extended VTE prophylaxis compared with those who received standard prophylaxis (4.8% vs. 12 %, RRR = 60%, $P =$.02). Based on these data, clinical guidelines have recommended extended VTE prophylaxis in selected high-risk general surgery patients, specifically those undergoing major cancer surgery [14].

There are several practical advantages with LMWH over LDUH. With LMWH there is a lower risk of HIT, an immune-mediated reaction to heparin that may lead to PE

and death, and there is no need for therapeutic monitoring [36]. In addition, LMWH exhibits a predictable anti-coagulant response, has a longer half-life allowing for once- or twice-daily dosing, and demonstrates improved bioavailability [36]. LMWH may be self-administered, which can translate into decreased hospital length of stay and decreased cost [36]. However, unlike LDUH, LMWH is primarily eliminated by the kidneys and requires dose adjustment in patients with severe renal impairment [36].

Results of several clinical studies that evaluated LMWH as a treatment for advanced cancer suggest a possible association of LMWH therapy with improved survival in patients with cancer [37–41]. In one study where patients with advanced cancer were treated with the LMWH dalteparin or placebo for 1 year (in addition to their regular cancer treatment), 3-year Kaplan–Meier survival estimates were 21% with LMWH versus 12% with placebo ($P =$ 19) [40]. In a subset of patients with a better prognosis, Kaplan–Meier survival estimates were significantly higher with LMWH at 2 and 3 years (78% vs. 55% and 60% vs. 36%, $P =$.03). In contrast, a recent, small (N = 141), open-label clinical trial failed to find a survival benefit with LMWH in patients with advanced cancer [42].

A prospective, randomized study of 187 women with previously untreated breast or pelvic cancer compared the LMWH certoparin with LDUH for thromboprophylaxis following surgery (7 days postoperatively). The risk of mortality was significantly lower with LMWH than with LDUH at 650 days after surgery (5.7% vs. 15.6%, respectively; $P =$.005) but not at 1050 days after surgery (11.4% with LMWH vs. 18.4% with LDUH, $P =$.136) [43]. Subgroup analysis by type of cancer revealed that mortality rates were significantly lower at 650 days with LMWH compared with LDUH only in patients with pelvic cancer (8.7% vs. 28.6%, respectively; $P =$.0139) although at 1050 days the difference was still no longer significant (15.2% vs. 28.6%, respectively; $P =$.101). Thus, different tumor types in different stages of disease might have different responses to prophylactic treatment with LMWH.

The conflicting results reported with LMWH in the treatment of advanced cancer and the data indicating that a survival benefit may only exist in certain types of cancer and may not be significant in the long term suggest that further study is necessary before conclusions can be drawn regarding LMWH in the treatment of advanced cancer.

Factor Xa Inhibitors

Fondaparinux, the first selective Factor Xa inhibitor, represents another option for VTE prophylaxis in patients with cancer who undergo major abdominal surgery. In the ACCP evidence-based guidelines, fondaparinux is

recommended for use in patients who have undergone surgery who are at the highest risk for VTE, such as those with multiple risk factors (>40 years of age, prior VTE, or cancer), those who have undergone hip or knee arthroplasty or hip fracture surgery, or who have experienced a major trauma or spinal cord injury (Table II) [14]. Recently published NCCN guidelines recommended fondaparinux for inpatient anticoagulation therapy in surgical patients with cancer or a suspicion of cancer (Table III) [26]. Although the use of Factor Xa inhibitors in patients with cancer following abdominal surgery has not been well studied in a randomized controlled trial, the results of two recent studies, PEGASUS and APOLLO, suggest that fondaparinux has an excellent safety and efficacy profile for the prevention of VTE in this patient population.

The PEGASUS trial compared once-daily fondaparinux (2.5 mg QD) with the LMWH dalteparin (5000 XaU QD) in patients (N = 2927) who had undergone major abdominal surgery who were at high risk for VTE (aged >60 years or >40 years with 1 or more additional risk factors) [44]. Overall, the two agents demonstrated similar efficacy in the prevention of VTE following major abdominal surgery ($P = .144$, Table IV). The incidence of major bleeding during the treatment period was also similar ($P = .122$, Table IV). In a subgroup of patients with cancer, Factor Xa inhibitor was more effective than LMWH. Surgery for cancer was performed in 1408 (68.8%) evaluable patients. The rate of VTE at 10 days in these patients was 4.7% (33/696) with Factor Xa inhibitor vs. 7.7% (55/712) with LMWH, a RRR of 38.6% (95% CI: 6.7, 59.7; Table IV). The rate of VTE at 10 days following noncancer surgery was 4.2% (14/331) with Factor Xa inhibitor vs. 2.3% (7/309) with LMWH, a RRR of −86.7% (−356.5, 23.6) [45]. The incidence of major bleeding during the treatment period was similar between groups; 3.4% with Factor Xa inhibitor vs. 2.5% with LMWH in cancer surgery ($P = .355$; 95% CI of difference: −0.7, 2.3) and 3.5% with Factor Xa inhibitor vs. 2.1% with LMWH in noncancer surgery (95% CI of difference: −0.6, 3.6) [44,45]. These results suggest that Factor Xa inhibitors may be useful agents for preventing VTE in patients who have undergone abdominal surgery who are at highest risk, including those with cancer. Based on these data, fondaparinux was recently approved by the United States Food and Drug Administration for the prophylaxis of DVT, which may lead to PE, in patients undergoing abdominal surgery who are at risk for thromboembolic complications.

In the APOLLO study, once-daily fondaparinux (2.5 mg QD) plus IPC was compared with IPC alone for VTE prophylaxis in patients who had undergone major abdominal surgery [46]. Patients (N = 1309) were >40 years of age with intermediate to high risk for VTE, but not so high as to require pharmacologic prophylaxis in conjunction with IPC (Table II) [14]. The incidence of VTE at 10 days was significantly reduced with Factor Xa inhibitor plus IPC ($P = .004$, Table V). The incidence of major bleeding was higher with drug plus IPC (1.6% vs. 0.2%, $P = .006$). Forty percent of evaluable patients in APOLLO underwent cancer surgery. Additional analysis of this subset of patients demonstrated that the incidence of VTE at 10 days was also reduced with Factor Xa inhibitor; from 6.7% (12/180) with IPC alone to 2.5% (4/160) with Factor Xa inhibitor plus IPC for a RRR of 62.5% (95% CI: −13.9, 87.7). In the noncancer subset of patients, the incidence of VTE at 10 days was 4.2% (10/238) with IPC alone vs. 1.1% (3/264) with Factor Xa inhibitor plus IPC, a RRR of 73% (95% CI: 2.9, 92.5). The incidence of major bleeding was 0% with IPC alone vs. 2% with Factor Xa inhibitor plus IPC in cancer surgery (95% CI of difference: 0.3, 3.8) and 0.3% with IPC alone vs. 1.3% with Factor Xa inhibitor plus IPC in noncancer surgery (95% CI of difference: −0.2, 2.3). Although the bleeding risk in APOLLO was increased with Factor Xa inhibitor plus IPC compared with IPC

TABLE IV. Efficacy and Safety of Fondaparinux vs. Dalteparin in PEGASUS [44]

	Fondaparinux	Dalteparin	% Relative Risk Reduction (95% CI)
Overall			
VTE[a]	4.6% (47/1027)	6.1% (62/1021)	24.6 (−9.0, 47.9)
Major bleeding	3.4% (49/1433)	2.4% (34/1425)	—
Cancer surgery			
VTE[a]	4.7% (33/696)	7.7% (55/712)	38.6 (6.7, 59.7)
Major bleeding	3.4% (32/954)	2.5% (25/987)	—
Noncancer surgery			
VTE[a]	4.2% (14/331)	2.3% (7/309)	−86.7 (−356.5, 23.6)
Major bleeding	3.5% (17/479)	2.1% (9/438)	—

[a]VTE events up to the first venogram or up to day 10, whichever occurred first. VTE, venous thromboembolism; CI, confidence interval.

TABLE V. Efficacy and Safety of Fondaparinux plus IPC vs. IPC Alone in APOLLO [46]

	Fondaparinux + IPC	IPC Alone	% Relative Risk Reduction (95% CI)
Overall			
VTE[a]	1.7% (7/424)	5.3% (22/418)	68.6 (26.8, 86.6)
Major bleeding	1.6% (10/635)	0.2% (1/650)	—
Cancer surgery			
VTE[*]	2.5% (4/160)	6.7% (12/180)	62.5 (−13.9, 87.7)
Major bleeding[†]	2%	0%	—
Noncancer surgery			
VTE[a]	1.1% (3/264)	4.2% (10/238)	73.0 (2.9, 92.5)
Major bleeding[†]	1.3% (5/389)	0.3% (1/388)	—

[a]VTE events up to the first venogram or up to day 10, whichever occurred first.
[†]No bleed was fatal or into a critical organ. IPC, intermittent pneumatic compression; VTE, venous thromboembolism; CI, confidence interval.

alone, the risk was low and was consistent with that observed in previous studies of pharmacologic VTE prophylaxis in surgical patients [28,29,32]. In addition, no bleed during the treatment period was fatal or into a critical organ.

Factor Xa inhibitors have several potential advantages over heparins. Unlike LDUH and LMWH, Factor Xa inhibitors have not been associated with HIT. It has been demonstrated that Factor Xa inhibitors do not cross-react in vitro with IgG antibodies against heparin/platelet factor-4 [47] or with sera from patients with clinically and serologically confirmed HIT [48]. These findings suggest that Factor Xa inhibitors would not provoke clinical thrombosis even in patients who had HIT antibodies because of previous exposure to heparins. Further, the Factor Xa inhibitor fondaparinux was recently used with good success as an alternative anticoagulant in HIT patients [49,50]. In patients who have developed HIT as a result of heparin exposure, the NCCN guidelines recommend discontinuing the use of LDUH or LMWH and administering a direct thrombin inhibitor (DTI; argatroban or lepirudin) or fondaparinux or bivalirudin in special situations (treatment of HIT is off label for both agents) [26]. The guidelines recommend initiating warfarin therapy when the patient's platelet count has recovered (>100–150,000/mcL) and overlapping warfarin with fondaparinux or a DTI for at least 5 days.

The Factor Xa inhibitor fondaparinux has a linear pharmacokinetic profile and a 17–21 h half-life, which allows for once-daily subcutaneous administration [51]. Consequently, fondaparinux can be administered on an outpatient basis, which can greatly reduce healthcare costs by minimizing hospitalization time. It also has a predictable anticoagulant response because it selectively binds to antithrombin III [51]; therefore, routine coagulation monitoring is not necessary. Because fondaparinux, like LMWH, is eliminated by the kidneys, it is contraindicated in patients with creatinine clearance

<30 mL/min [51]. However, unlike LDUH, LMWH and Factor Xa inhibitors lack complete reversal agents. Protamine, which completely reverses the anticoagulant effects of LDUH in the case of a bleeding event or complication, only partially neutralizes LMWH (~60%) and is ineffective in neutralizing the anti-Factor Xa activity of Factor Xa inhibitors [52].

Factor Xa inhibitors specifically catalyze the inhibition of Factor Xa, which results in effective and linear dose-dependent inhibition of thrombin generation, but does not inhibit thrombin itself [51]. In contrast, heparins inhibit thrombin as well as Factor Xa to varying relative degrees [53]. There is evidence that thrombin plays a role in wound healing; therefore, Factor Xa inhibitors may be less likely than heparins to interfere with wound healing [54]. Additionally, efficient inhibition of Factor Xa activity impairs the activation of the tissue factor/Factor VIIa complex leading to down-regulation of the pro-coagulant state, pro-angiogenesis, and pro-inflammatory factors [55,56]. This could potentially play a role in preventing tumor progression.

CONCLUSIONS

Cancer is a significant risk factor for VTE. Surgery, a first-line treatment of many cancers, is another significant risk factor for VTE. Patients undergoing major abdominal surgery are at particularly high risk. Because the presence of multiple VTE risk factors cumulatively increases risk, patients with cancer undergoing major abdominal surgery (common in patients with ovarian or pelvic cancer, colorectal cancer, or pancreatic cancer) should be considered at particularly high risk for VTE and should receive pharmacologic prophylaxis.

Available agents for VTE prophylaxis in these patients include LDUH, LMWH, and fondaparinux. Compared with LDUH, LMWH offers greater ease of administration, as these agents can be given subcutaneously by a

health professional, caregiver, or the patient, allowing use in both inpatient and outpatient settings. In addition, regular monitoring is not required and LMWH has increased bioavailability, a longer half-life, variability in the number of AT binding sites, and a higher anti-Xa/anti-IIa inhibitory ratio. In addition, a survival benefit in patients receiving VTE prophylaxis with LMWH has been proposed; however, this benefit may only exist in certain types of cancer and may not be significant in the long term.

Fondaparinux, a newer, more selective pharmacologic method of anticoagulation compared with heparins, has demonstrated significant reduction in relative risk of postoperative VTE in the general surgical patient, especially those at high risk such as patients with abdominal cancer. Significant reductions in relative risk were observed with fondaparinux compared with LMWH in a subset of patients with cancer in the PEGASUS trial. In addition, in the APOLLO trial, fondaparinux plus mechanical prophylaxis was shown to be superior to mechanical prophylaxis alone in the prevention of VTE in patients with or without cancer who had undergone abdominal surgery. Potential advantages of this agent over LDUH and/or LMWH include a fixed once-a-day dose, 17-h half-life without the need for aPTT or anti-Factor Xa monitoring, subcutaneous administration allowing for outpatient use, and absence of HIT reports. No studies evaluating a survival benefit of fondaparinux in patients with cancer have been conducted; however, the mechanism of action of fondaparinux could potentially affect tumor progression. Although further study is necessary, consideration may be given to the use of fondaparinux in abdominal surgery patients with cancer due to the VTE risk reduction and low incidence of postoperative bleeding in this patient population, low risk of developing HIT, and a favorable relative risk reduction similar to that observed for LMWH.

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