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Prevention of venous thromboembolism in the cancer surgery patient

■ **ABSTRACT**

Cancer patients, especially those undergoing surgery for cancer, are at extremely high risk for developing venous thromboembolism (VTE), even with appropriate thromboprophylaxis. Anticoagulant prophylaxis in cancer surgery patients has reduced the incidence of VTE events by approximately one-half in placebo-controlled trials, and extended prophylaxis (for up to 1 month) has also significantly reduced out-of-hospital VTE events in clinical trials in this population. Clinical trials show no difference between low-molecular-weight heparin (LMWH) and unfractionated heparin in VTE prophylaxis efficacy or bleeding risk in this population, although the incidence of heparin-induced thrombocytopenia is lower with LMWH. The risk-benefit profile of low-dose anticoagulant prophylaxis appears to be favorable even in many cancer patients undergoing neurosurgery, for whom pharmacologic VTE prophylaxis has been controversial because of bleeding risks.

Venous thromboembolism (VTE) is a major complication of cancer, occurring in 4% to 20% of patients,[1] and is one of the leading causes of death in cancer patients, although these figures are believed to be underestimates, given the low autopsy rates among cancer patients.[2] In hospitalized cancer patients specifically, VTE is the second leading cause of death.[3,4] The risk of VTE in cancer patients undergoing surgery is three to five times greater than that in surgical patients without cancer.[4] Moreover, cancer patients with symptomatic deep vein thrombosis (DVT) exhibit a high risk of recurrent VTE that may persist for many years after the index event.[5]

■ **VTE PREVENTION POSES PARTICULAR CHALLENGES IN CANCER PATIENTS**

Until recently, data on VTE prevention specific to cancer patients have been sparse. Cancer patients have represented only a small subset (< 20%) of participants in most of the largest clinical trials of VTE prophylaxis. Until the past 2 or 3 years, clinicians largely have had to extrapolate their approach to VTE prophylaxis in cancer patients from data in patients without cancer, bearing in mind that cancer patients are among the populations at highest risk of developing VTE.

High rates of VTE, even with prophylaxis

What has been clear is that VTE prevention is a formidable challenge in this population, even when thromboprophylaxis is used. Despite thromboprophylaxis, cancer patients undergoing surgery have twice the risk of VTE and nonfatal pulmonary embolism (PE) and three times the risk of fatal PE compared with other surgical patients **(Table 1)**.[6,7]

Further insights have come from the @RISTOS project, a Web-based prospective registry of patients undergoing general, urologic, or gynecologic surgery for cancer at multiple centers in Italy.[8] Of the 2,372 patients tracked in this study, 82% received in-hospital VTE prophylaxis and 31% received prophylaxis following discharge. Despite this relatively high frequency of prophylaxis, however, the incidence of clinically overt VTE was 2.1% and the incidence of fatal VTE was 0.8%. Notably, most VTE events occurred after hospital discharge, and VTE was the most common cause of 30-day postoperative death in this registry.

■ **RISK FACTORS: CANCER TYPE AND TREATMENT LOOM LARGE**

Both the type and stage of a patient's cancer are important in assessing the risk of VTE. For men, cancers of the prostate, colon, brain, and lung have been associated with an increased risk of VTE. Among women, cancers of the breast, ovary, and lung have been especially implicated as risk factors for VTE.[9,10]

The type of cancer therapy also influences VTE risk:

• **Surgery.** Among patients who undergo cancer-related surgery, the rate of proximal DVT is 10% to 20%, the rate of clinically evident PE is 4% to 10%, and the incidence of fatal PE is 0.2% to 5%.[8,11]

TABLE 1
Event rates in surgical patients with and without cancer who received anticoagulant prophylaxis*

	Noncancer surgery (n = 16,954)	Cancer surgery (n = 6,124)	P for difference
Postoperative VTE	0.61%	1.26%	< .0001
Nonfatal PE	0.27%	0.54%	< .0003
Autopsy-confirmed PE	0.11%	0.41%	.0001
Death	0.71%	3.14%	.0001

* In an international multicenter randomized trial using VTE prophylaxis with either unfractionated heparin or low-molecular-weight heparin.[6,7]

VTE = venous thromboembolism; PE = pulmonary embolism

• **Systemic treatments**, including chemotherapy and hormone therapy, are also associated with an increased risk of VTE.[12–15]

• **Central venous catheters.** Approximately 4% of cancer patients who have central venous catheters placed develop clinically relevant VTE.[16,17]

In addition to the above risks related to cancer treatments, the following have been identified as risk factors for VTE in surgical oncology patients:

• Age greater than 40 years (risk also increases steeply after age 60 and again after age 75)
• Cancer procoagulants
• Thrombophilia
• Length and complications of cancer surgery (ie, often involving tissue trauma and immobilization)
• Debilitation and slow recovery.

Another risk factor worth noting is perioperative transfusion, as illustrated in a recent study of 14,104 adults undergoing colorectal cancer resection.[18] The overall incidence of VTE in these patients was 1.0%, and the risk of death was nearly four times as great in patients who developed VTE as in those who did not. Notably, the need for transfusion was a marker of increased risk of VTE, particularly in women: women who received perioperative transfusions had almost double the risk of developing VTE compared with women who did not receive transfusions (P = .004).

■ CLINICAL TRIALS OF PROPHYLAXIS IN CANCER SURGERY PATIENTS

LMWH vs UFH for in-hospital prophylaxis

Two large randomized, double-blind trials have compared low-molecular-weight heparin (LMWH) with low-dose unfractionated heparin (UFH) for VTE pro-

phylaxis in surgical patients with cancer—the Enoxaparin and Cancer (ENOXACAN) study[19] and the Canadian Colorectal Surgery DVT Prophylaxis Trial.[20] Patients in these studies underwent surgery for abdominal or pelvic cancer (mostly colorectal cancer). Both studies compared 40 mg of the LMWH enoxaparin given once daily with 5,000 U of UFH given three times daily for 7 to 10 days postoperatively. Outcome measures were the presence of DVT determined by venography on day 7 to 10 and the incidence of symptomatic VTE. Rates of VTE were statistically equivalent between the two treatment arms in both ENOXACAN (14.7% with LMWH vs 18.2% with UFH) and the Canadian Colorectal Surgery study (9.4% with both therapies), as were rates of major bleeding (4.1% with LMWH vs 2.9% with UFH in ENOXACAN; 2.7% with LMWH vs 1.5% with UFH in the Canadian study).

These findings are consistent with a 2001 meta-analysis by Mismetti et al of all available randomized trials comparing LMWH with placebo or with UFH for VTE prophylaxis in general surgery.[21] This analysis found no differences in rates of asymptomatic DVT, clinical PE, clinical thromboembolism, death, major hemorrhage, total hemorrhage, wound hematoma, or need for transfusion between LMWH and UFH in patients undergoing either cancer-related surgery or surgery not related to cancer.

Fondaparinux for in-hospital prophylaxis

Subgroup analysis of the large randomized trial known as PEGASUS[22] sheds some light on the efficacy of the factor Xa inhibitor fondaparinux relative to LMWH for thromboprophylaxis in cancer surgery patients. PEGASUS compared fondaparinux 2.5 mg once daily with the LMWH dalteparin 5,000 IU once daily for 5 to 9 days in patients undergoing high-risk abdominal surgery. Among the study's 1,408 patients undergoing surgery for cancer, rates of VTE were 4.7% in the fondaparinux group compared with 7.7% in the LMWH group, a relative risk reduction of 38.6% with fondaparinux (95% CI, 6.7% to 59.6%). In contrast, in the rest of the PEGASUS population (patients undergoing abdominal surgery for reasons other than cancer), LMWH was nonsignificantly more efficacious at preventing VTE than was fondaparinux. Rates of major bleeding in this cancer subgroup were comparable between the two treatments.

Extended prophylaxis

Two additional randomized trials have evaluated extended prophylaxis with LMWH in surgical cancer patients—ENOXACAN II[23] and the Fragmin After Major Abdominal Surgery (FAME) study.[24]

In ENOXACAN II, patients undergoing surgery for abdominal or pelvic cancer first received 6 to 10 days of prophylaxis with enoxaparin 40 mg once daily and then were randomized in a double-blind fashion to an additional 21 days of enoxaparin or placebo.[23] Among 332 patients in the intent-to-treat analysis, the rate of VTE at the end of the double-blind phase was reduced from 12.0% with placebo to 4.8% with extended-duration enoxaparin ($P = .02$), an effect that was maintained at 3-month follow-up ($P = .01$). There was no significant difference between the two groups in rates of major bleeding events or any bleeding events.

In FAME, patients received 5,000 IU of dalteparin once daily for 1 week following major abdominal surgery and then were randomized in open-label fashion to either placebo or extended prophylaxis with dalteparin for 3 more weeks; a subanalysis examined outcomes in the 198 FAME participants whose abdominal surgery was for cancer.[24] Among these 198 cancer surgery patients, the rate of venography-documented VTE at 4 weeks was reduced from 19.6% with placebo to 8.8% with extended-duration dalteparin, a relative reduction of 55% ($P = .03$). The rate of proximal DVT was reduced from 10.4% to 2.2% with extended prophylaxis, a relative reduction of 79% ($P = .02$).

The number needed to treat with extended LMWH prophylaxis to prevent one VTE event was 14 in ENOXACAN II[23] and 9 in the FAME subanalysis of cancer surgery patients.[24]

New systematic review of relevant trials

Leonardi et al recently published a systematic review of 26 randomized controlled trials of DVT prophylaxis in 7,639 cancer surgery patients.[25] They found the overall incidence of DVT to be 12.7% in those who received pharmacologic prophylaxis compared with 35.2% in controls. They also found high-dose LMWH therapy (> 3,400 U daily) to be associated with a significantly lower incidence of DVT than low-dose LMWH therapy ($\leq$ 3,400 U daily) (7.9% vs 14.5%, respectively; $P < .01$). No differences were demonstrated between LMWH and UFH in preventing DVT, DVT location, or bleeding. Bleeding complications requiring discontinuation of pharmacologic prophylaxis occurred in 3% of patients overall.

Implications of HIT

The sequelae of heparin-induced thrombocytopenia (HIT) can have major consequences for cancer surgery patients. The incidence of HIT is markedly lower with LMWH than with UFH, as demonstrated in a nested case-control study by Creekmore et al.[26] These researchers also found that the average cost of an admission during which HIT developed was nearly four times as great as the average cost of an admission during which UFH or LMWH was given without development of HIT ($56,364 vs $15,231; $P < .001$).

■ EVIDENCE IN SPECIFIC ONCOLOGIC POPULATIONS

Most of the patients in the trials reviewed above underwent abdominal surgery for malignancy. Although studies of VTE prophylaxis in patients undergoing nonabdominal cancer surgery are relatively few, some data are available for a few other specific oncologic populations, as reviewed below.

Surgery for gynecologic cancer

There is a paucity of randomized controlled trials or prospective observational studies on VTE and its prevention in the gynecologic cancer surgery population. Based on small historical studies, the postoperative risk of VTE in this population varies from 12% to 35%.[27,28] Twice-daily administration of UFH 5,000 U appears to be ineffective as VTE prophylaxis in this population, but increasing the frequency to three times daily reduces VTE risk by 50% to 60% compared with placebo. Once-daily LMWH is comparable to three-times-daily UFH in efficacy and safety in this population.

A systematic Cochrane review of eight randomized controlled trials in patients undergoing major gynecologic surgery revealed that heparin prophylaxis (either UFH or LMWH) reduces the risk of DVT by 70% compared with no prophylaxis, with an identical risk reduction specifically among women with malignancy (odds ratio, 0.30; 95% CI, 0.10 to 0.89).[29] This review found no evidence that anticoagulation reduces the risk of PE following major gynecologic surgery. LMWH and UFH were similar in efficacy for preventing DVT and had a comparable risk of bleeding complications.

Surgery for urologic cancer

The risk of VTE and the benefits of thromboprophylaxis also are poorly studied in patients undergoing surgery for urologic cancer.

The risk of VTE varies with the type of urologic surgery and the method used to diagnose VTE. For instance, patients undergoing radical retropubic prostatectomy have been reported to develop DVT at rates of 1% to 3%, PE at rates of 1% to 3%, and fatal PE at a rate of 0.6%, whereas the incidences of these events are somewhat higher in patients undergoing cystectomy: 8% for DVT, 2% to 4% for PE, and 2% for fatal PE. Radiologic diagnosis of thromboembolism in pelvic surgery patients has yielded higher incidences, with DVT rates of 21% to 51% and PE rates of 11% to 22%.[30]

Small studies suggest that prophylaxis with either

low-dose UFH or LMWH is both effective in reducing VTE risk and safe in urologic cancer surgery patients, although pharmacologic prophylaxis poses a possible increased risk of pelvic hematoma and lymphocele formation in this population.[30]

Neurosurgery

Most neurosurgical procedures are performed for malignancies. The risk of venography-confirmed VTE in patients undergoing neurosurgery is approximately 30% to 40%.[31,32] Likewise, the risks of intracranial or intraspinal hemorrhage in these patients are high. For this reason, mechanical methods of VTE prophylaxis are preferred in these patients. The use of anticoagulant prophylaxis remains controversial in this setting, although more recent data suggest that it might be safer than previously recognized.

A meta-analysis of studies of pharmacologic prophylaxis of VTE in neurosurgery included three randomized controlled trials that compared LMWH, with or without mechanical prophylaxis, to placebo plus mechanical prophylaxis or placebo alone in a total of 922 neurosurgery patients.[33] As detailed in **Table 2**, the analysis demonstrated statistically significant reductions in the risks of VTE and proximal DVT in favor of LMWH, with a statistically significant doubling in the risk of any bleeding and a nonsignificant 70% increase in the risk of major bleeding with LMWH therapy. The number needed to treat to prevent 1 proximal DVT was 16,

while the number needed to treat to cause 1 major bleeding event was 115. A risk-benefit analysis showed that the use of LMWH in neurosurgery patients was associated with 1 major nonfatal bleeding event for every 7 proximal DVTs prevented. When a fourth randomized trial was included in the analysis, comparing UFH 5,000 U three times daily with no prophylaxis, rates of VTE and bleeding events remained similar to those for the LMWH trials alone.

■ GUIDELINES FOR VTE PROPHYLAXIS IN THE CANCER SURGERY PATIENT

American College of Chest Physicians

The American College of Chest Physicians' Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy makes a number of recommendations regarding VTE prevention in patients undergoing surgery for cancer, as outlined in **Table 3**.[34]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) recently published clinical practice guidelines on venous thromboembolic disease in cancer patients.[35] The defined at-risk population for these guidelines is the adult cancer inpatient with a diagnosis of (or clinical suspicion for) cancer. The guidelines recommend prophylactic anticoagulation (category 1 recommendation) with or without a sequential compression device as initial prophylaxis, unless the patient has a relative contraindication to anticoagulation, in which case mechanical prophylaxis (sequential compression device or graduated compression stockings) is recommended. (A category 1 recommendation indicates "uniform NCCN consensus, based on high-level evidence.")

The NCCN guidelines include a specific recommended risk-factor assessment, which includes noting the patient's age (VTE risk increases beginning at age 40 and then steeply again at age 75), any prior VTE, the presence of familial thrombophilia or active cancer, the use of medications associated with increased VTE risk (chemotherapy, exogenous estrogen compounds, and thalidomide or lenalidomide), and a number of other risk factors for VTE as outlined in the prior two articles in this supplement. The NCCN guidelines explicitly call for assessment of modifiable risk factors for VTE (ie, smoking or other tobacco use, obesity, and a low level of activity or lack of exercise) and call for active patient education on these factors.

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO) recently released guidelines on VTE prevention and treatment in patients with cancer;[1] their key recom-

mendations for prevention are summarized in **Table 4**. Notable differences from the recommendations of the Seventh ACCP Conference are the ASCO guidelines' inclusion of fondaparinux among recommended prophylactic options for this population and more explicit recommendations on the prophylactic use of LMWH. Also, for treatment of cancer patients with *established* VTE, ASCO specifies that LMWH is the preferred anticoagulant for both initial and continuing treatment.

Our recommended algorithm

Drawing from the above formal society guidelines and the published literature, we recommend the algorithm in **Figure 1** as a practical approach to VTE prevention in patients undergoing major surgery for cancer.

■ LINGERING CHALLENGE OF UNDERUTILIZATION

Despite this consensus on ways to reduce thromboembolic risk in this population and the clear evidence of the benefit of VTE prophylaxis in patients with cancer, data from several registries confirm a persistently low utilization of prophylaxis in patients with cancer.[36–38] The global Fundamental Research in Oncology and Thrombosis (FRONTLINE) study surveyed 3,891 clinicians who treat cancer patients regarding their practices with respect to VTE in those patients.[36] The survey found that only 52% of respondents routinely used thromboprophylaxis for their surgical patients with cancer. More striking, however, was the finding that most respondents routinely considered thromboprophylaxis in only 5% of their medical oncology patients. These data are echoed by findings of other retrospective medical record reviews in patients undergoing major abdominal or abdominothoracic surgery (in many cases for cancer), with VTE prophylaxis rates ranging from 38% to 75%.[37,38]

■ SUMMARY

Patients undergoing surgery for cancer have an increased risk of VTE and fatal PE, even when thromboprophylaxis is used. Nevertheless, prophylaxis with either LMWH or UFH does reduce venographic VTE event rates in these patients. If UFH is chosen for prophylaxis, a three-times-daily regimen should be used
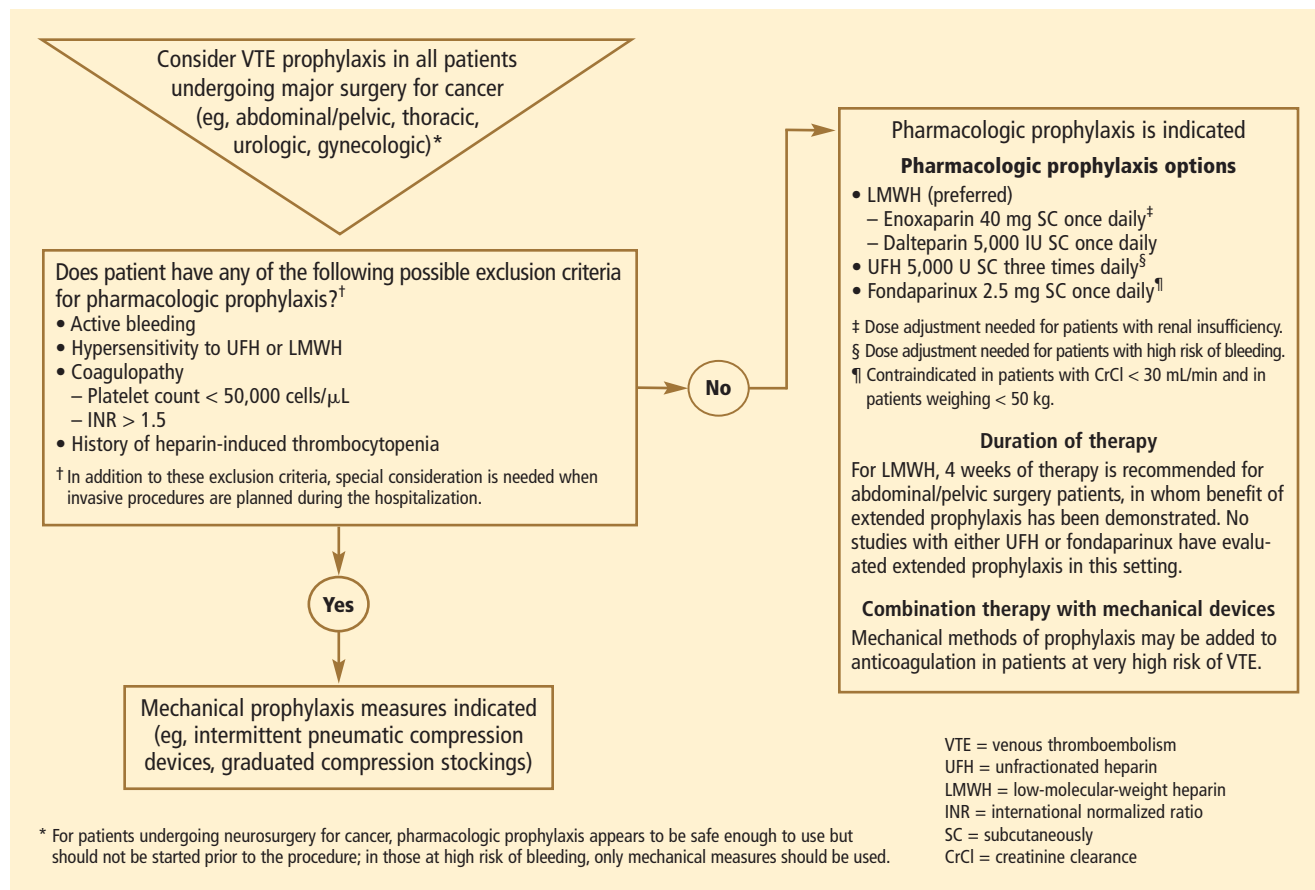
FIGURE 1. Algorithm for VTE prophylaxis in the patient undergoing major surgery for cancer.

in this population. In specific surgical cancer populations, especially those undergoing abdominal surgery, out-of-hospital prophylaxis with once-daily LMWH is warranted. Current registries reveal that compliance with established guidelines for VTE prophylaxis in this population is low.

■ DISCUSSION: ADDITIONAL PERSPECTIVES FROM THE AUTHORS

Dr. Jaffer: Dr. Amin, based on your study on thromboprophylaxis rates in US medical centers, will you comment on rates of prophylaxis for cancer surgery patients?

Dr. Amin: The overall study included approximately 200,000 medical patients and about 80,000 surgical patients enrolled over more than a 3-year period between 2002 and 2005.[39,40] Our goal was to assess rates of prophylaxis and, when it was provided, whether it was appropriate (in terms of type, dosage, and duration) based on the ACCP guidelines. A subanalysis assessed medical cancer patients and surgical cancer patients separately. Medical cancer patients

received thromboprophylaxis 56% of the time but received *appropriate* prophylaxis only 28% of the time. Among surgical cancer patients, appropriate prophylaxis was given only about 24% of the time for those undergoing gynecologic surgery and about 12% of the time for those undergoing neurosurgery. These percentages are consistent with data from other national registries, such as the IMPROVE registry, which documented prophylaxis rates on the order of 45% in medical patients with cancer.[41] We also analyzed the data according to individual practitioners and found that medical oncologists use prophylaxis about 25% of the time, which is relatively consistent with other providers, such as internists and surgeons.

So there is a huge opportunity to improve rates of prophylaxis for this group of patients that national guidelines say are at high risk. Why is prophylaxis so underutilized in the cancer population? One factor may be a misperception about the risk of bleeding with anticoagulants. Yet several studies have shown that the rate of bleeding from prophylaxis is extremely low, whether LMWH or UFH is used, so more aware-

ness of actual bleeding risk is needed. Another factor is the obvious focus among internists and oncologists on *treating* the patient, with perhaps a reduced consideration of prophylaxis and prevention. A third factor may be a concern about thrombocytopenia. However, in our study of prophylaxis rates in US medical centers, we excluded patients who had thrombocytopenia, yet rates of prophylaxis were still low. Nothing in the literature indicates that anticoagulants cannot be used in patients with platelet counts of 50,000 to 150,000 cells/μL or higher, so this suggests that we need to do more education.

Dr. Jaffer: Dr. Brotman, can you tell us more about how clinicians in practice should use prophylaxis in their neurosurgery patients, such as those undergoing craniotomy or spine surgery for cancer? What is the safest and most efficacious way to prevent DVT in these patients?

Dr. Brotman: First, it's important to recognize that some sort of prophylaxis needs to be used. Neurosurgery patients are at an extremely high risk for thromboembolic events, and such events are often fatal in these patients. Having said that, the jury is still out on whether the prophylaxis in these patients should be compression devices or anticoagulation. This gives physicians some latitude in their decisions. They can decide not to use pharmacologic prophylaxis so long as they use pneumatic compression devices consistently, perhaps even starting during the operation and certainly throughout hospitalization when the patient is immobilized.

Certainly, the concerns about using full-dose anticoagulation in the immediate postoperative setting in neurosurgery patients are valid. Yet these patients are at very high risk for thromboembolic events, and if we take too cautious an approach to prophylaxis in the immediate perioperative setting, more patients are going to have thromboembolic events, at which point management decisions become much more difficult. The risk of intracranial bleeding with anticoagulation to treat a patient who develops a DVT at postoperative day 10 will certainly be higher than it would have been with lower-dose perioperative prophylactic anticoagulation. Plus, if you put in a filter at that point, the outcomes tend to be poor. Therefore, I believe there is some degree of risk that we should be willing to take with regard to perioperative bleeding, even in neurosurgery patients.

Dr. McKean: I'd like to make a point about combination prophylaxis. At many institutions, compression stockings and sequential compression devices are used preoperatively and intraoperatively, and then pharmacologic prophylaxis—for example, twice-daily UFH—is used postoperatively. There is concern that these patients are hypercoagulable, and most clinicians believe that mechanical prophylaxis alone, even with sequential compression devices plus compression stockings, is not aggressive enough in these high-risk patients.

Dr. Jaffer: Dr. Spyropoulos, what is the optimal duration of pharmacologic prophylaxis for cancer surgery patients?

Dr. Spyropoulos: First let's consider in-hospital prophylaxis. The supportive data for in-hospital prophylaxis are strong, and the duration of therapy used in the major in-hospital prophylaxis trials was 7 to 10 days. With regard to extended prophylaxis, we have at least two moderately sized randomized controlled trials, ENOXACAN II[23] and the substudy of FAME,[24] that demonstrated that extending prophylaxis with LMWH at doses of 3,400 U once daily (5,000 IU of dalteparin; 40 mg of enoxaparin) reduces VTE risk at postoperative day 30. Also, recent data from the @RISTOS registry show that in cancer surgery patients, especially those having abdominal or pelvic procedures, the leading cause of 30-day mortality was VTE.[8] This registry also shows that despite prophylaxis, the rate of symptomatic VTE can be as high as 2%, with the rate of fatal VTE approaching 1%. Thus, in cancer patients undergoing abdominal or pelvic surgery, physicians should strongly consider prophylaxis of up to 30 days' duration.

Dr. Jaffer: One striking finding from the @RISTOS registry was that 40% of VTE events in these cancer surgery patients occurred after postoperative day 21. This really underscores the need to consider prophylaxis for at least 4 weeks in these patients in real-world practice.

Dr. Brotman: The other striking finding from that registry was that the in-hospital prophylaxis rate was quite high, about 80%, and the rate of extended prophylaxis approached 35%. These are rates that are rarely achieved in clinical practice. Yet despite these high levels of prophylaxis, patients in this registry still had a high incidence of morbidity and mortality from VTE. This suggests that we need to improve our out-of-hospital VTE prevention paradigms.

Dr. Jaffer: Dr. Deitelzweig, oncologists and internists are often unsure about whether their ambulatory cancer patients who are receiving chemotherapy should be on any form of prophylaxis. What is your opinion?

Dr. Deitelzweig: That question comes up regularly because these patients are encountered across many medical specialties. At this point, all of the large organizations, including ASCO and NCCN, are advocating that prophylaxis is not indicated for such patients.

Case studies in cancer surgery patients

■ CASE 1: SURGERY FOR OVARIAN CANCER

A 54-year-old woman is undergoing debulking surgery for ovarian adenocarcinoma. Her only comorbid condition is well-controlled hypertension, and she has no history of VTE. Her body mass index is 32.

True or false? *Pharmacologic prophylaxis with low-dose UFH has been proven superior to mechanical prophylaxis for the prevention of VTE in this setting.*

Strictly speaking, this is false, but that is not the end of the story. Not every specific patient population has been studied with adequate statistical power, so in some cases extrapolation from other patient populations is justified. This woman is at high risk for VTE despite her young age and not having a prior VTE. Her risk factors for VTE are obesity, an advanced malignancy (as evidenced by the need for a debulking procedure), and the risk of a hypercoagulable state from her adenocarcinoma.

In the ACCP guidelines,[34] intermittent pneumatic compression devices are considered acceptable prophylaxis in the setting of our case patient. This contrasts with other patients undergoing high-risk surgical procedures, such as orthopedic surgery patients.

The data to support this recommendation are sparse, however. There is one randomized trial that directly compared pneumatic compression devices with low-dose UFH.[42] Each arm of the study contained about 100 patients, and there were more thrombi in the low-dose UFH arm than in the pneumatic compression arm (7 vs 4, respectively), but this difference was not statistically significant, as there was only a handful of events. Low-dose UFH also was associated with higher rates of blood transfusion and increased volumes of retroperitoneal drainage, raising some concern over safety, but these complications did not lead to an increase in subsequent operations to decompress hematomas.

Although this study's sample size was inadequate for drawing conclusions, many gynecologic surgeons are relying on mechanical prophylaxis as a result of these data, citing concern that pharmacologic prophylaxis has not specifically been proven superior to pneumatic compression devices in these patients. We would caution, however, that absence of proof is not proof of absence. When examining a data set this small in the face of an abundance of data in other cancer surgeries and other types of surgeries indicating that LMWH and UFH

work very well in the prevention of VTE—and in some cases work better than pneumatic compression—perhaps we should not restrict ourselves to this single study to guide our decision-making.

True or false? *In studies demonstrating efficacy of LMWH and/or UFH for prevention of perioperative VTE in patients undergoing abdominal pelvic surgery for malignancy, therapy has generally been started preoperatively rather than postoperatively.*

This is true. In all major trials examining pharmacologic prophylaxis in patients undergoing abdominal pelvic surgery for malignancy, treatment was initiated preoperatively, often 2 hours before surgery.[43] This has also been the general timing of administration of anticoagulation in the general surgery population.

Nevertheless, clinical practice often differs from practices demonstrated in the literature to be effective. Data from randomized trials tell us that preoperative administration of LMWH and UFH, when used in prophylactic doses, is efficacious and adequately safe, yet reluctance to perform invasive procedures persists in patients who have received prophylactic doses of anticoagulation preoperatively.

True or false? *Mechanical measures for prophylaxis are widely used in patients like this, but no randomized trials have demonstrated their efficacy.*

This is false, but again the answer is compromised by the small sample size of relevant trials. One small study (N = 107) has documented the efficacy of sequential compression devices for 5 days in patients undergoing gynecologic cancer surgery.[44] In this study, 13% of patients who received the compression devices developed VTE compared with 35% of controls. Although this was a small study, the extremely high incidence of VTE in patients undergoing gynecologic cancer surgery is concerning. Even though these patients are not always elderly, they represent a very high-risk population that warrants prophylaxis as aggressive as what we use in our orthopedic surgery patients.

What should be recommended as perioperative prophylaxis in this patient?

Pharmacologic prophylaxis is the best-studied approach, and we would encourage its use in this case even though evidence from large randomized prospective trials in this specific population is lacking.

■ CASE 2: SURGERY FOR GLIOBLASTOMA

A 43-year-old previously healthy man undergoes neuro-imaging following a seizure and is found to have a large heterogeneous brain tumor invading the corpus callosum. Resection is planned.

True or false? *Prophylactic anticoagulation should be discouraged based on the risk of perioperative hemorrhage.*

This is false, but with a caveat. The consequences of an intracranial hemorrhage are often catastrophic. Despite this, researchers have studied systematically the use of pharmacologic prophylaxis in patients undergoing neurosurgery. In most of these studies, the anticoagulation was initiated the day after surgery rather than prior to surgery, in contrast to studies in patients undergoing abdominal pelvic surgery.

Agnelli et al conducted a study of 307 neurosurgical patients randomized to compression stockings alone or compression stockings plus enoxaparin.[31] Ninety-seven percent of patients underwent surgery for a tumor, and the procedure was intracranial in 85%. Enoxaparin 40 mg subcutaneously once daily (or matching placebo) was started the day after surgery.

Enoxaparin was associated with a 49% relative reduction ($P = .004$) in the incidence of VTE. Intracranial bleeding occurred in 4 placebo recipients and 3 enoxaparin recipients, illustrating that neurosurgery patients are at risk for intracranial hemorrhage but that prophylactic doses of anticoagulation are probably not the primary driver; instead, the surgery itself may be the main cause of hemorrhaging. There was a trend toward an increase in minor but not major bleeding with enoxaparin. Sixty-day mortality was no different between the groups, although 2 patients randomized to placebo died of autopsy-proven PE.[31]

Neurosurgery patients are at high risk for fatal thromboembolic disease, and even though intracranial hemorrhage is probably the most feared complication, it is not certain to cause death more often than VTE does. In this study, more patients died from fatal PE than from anticoagulation-associated intracranial hemorrhage, although the difference was not statistically significant.[31]

A meta-analysis examining the use of LMWH or UFH prophylaxis in neurosurgery patients found a 52% relative reduction in both proximal thromboembolic events and silent distal events with anticoagulant prophylaxis.[33] The number needed to treat to prevent one proximal VTE was 16, underscoring these patients' high risk of thrombosis. Among 1,022 patients evaluated for

safety, adjudicated bleeding deaths occurred in 2 controls and 2 treated patients. Among the treated patients, one hemorrhage started during surgery, prior to anticoagulant use, and the other occurred during full-dose anticoagulation and after confirmed VTE, which again suggests that intracranial bleeding may be more feared than real for most patients. Among the 827 patients evaluated for efficacy, fatal thromboembolic events occurred in 1 treated patient and 2 controls. Anticoagulant prophylaxis was associated with a statistically significant increase in minor bleeding but not major bleeding.

The surgeon agrees to use pharmacologic prophylaxis and also decides to use sequential compression devices. The surgery is successful, but on postoperative day 22 the patient presents from rehabilitation with swelling of the left leg. Ultrasonography confirms an acute left common femoral DVT.

True or false? *Given the risk of full-dose anticoagulation in this patient, an inferior vena cava (IVC) filter should be placed.*

This is false. Placement of an IVC filter is not recommended in this patient unless reoperation is anticipated, the patient already has had surgical bleeding complications, or the patient is at uniquely high bleeding risk for some other reason.

A study from the 1980s illustrates a favorable overall risk-benefit profile for anticoagulation in glioma surgery.[45] The study assessed postoperative treatment of documented VTE (not merely VTE prophylaxis) in 109 patients with glioma, 103 of whom were treated with anticoagulants. Of the 6 patients who were not treated with anticoagulants, 3 suffered a fatal PE. Among the 103 patients who received treatment with full-dose anticoagulation, 3 suffered intracranial hemorrhage. Thus, although full-dose anticoagulation did increase the risk of bleeding in neurosurgery patients with documented VTE, this risk clearly did not outweigh the benefit of treating VTE, as demonstrated by the 50% rate of fatal PE in the absence of treatment.

IVC filters are often used in patients who have had recent neurosurgery because these patients are believed to be at increased risk of intracranial hemorrhage with anticoagulation. Levin et al examined 42 cases in which an IVC filter was placed in patients with central nervous system tumors.[46] Despite the IVC filter, 12% of patients developed PE and 57% developed either IVC or filter thrombosis, recurrent DVT, or post-phlebitic syndrome. The authors concluded that the complication rate associated with an IVC filter in this population is higher than perceived and outweighs the risk of anticoagulation.

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