Venous Thromboembolism in Urologic Surgery: Prophylaxis, Diagnosis, and Treatment

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Venous thromboembolism (VTE) represents one of the most common and potentially devastating complications of urologic surgery. With VTE's rapid onset of symptoms, association with a precipitous clinical course, and high mortality rate, all urologists should be well versed in appropriate prophylaxis, prompt diagnosis, and expeditious treatment. A MEDLINE® search was performed for articles that examined the incidence, diagnosis, and treatment of VTE in urologic surgery. Additional articles were reviewed based on cited references. There is a paucity of prospective studies on VTE in the urologic literature with most recommendations for urologic surgery patients being extrapolated from other surgical disciplines. Retrospective studies place VTE incidence rates in major urologic surgeries among the highest reported—highlighting the importance of thromboprophylaxis. Conversely, VTE was rarely reported in association with endoscopic and laparoscopic procedures making mechanical thromboprophylaxis sufficient. Recent literature reveals delayed VTE occurring after hospital discharge to be a persistent threat despite inpatient preoperative prophylaxis. Computed tomographic angiography has emerged as the test of choice for diagnosing pulmonary embolism, whereas lower extremity duplex sonography is recommended for diagnosing deep venous thrombosis. Traditional angiography is rarely used. Treatment of VTE involves therapeutic anticoagulation for various lengths of time based on presence and reversibility of patient risk factors as well as number of events. Perioperative thromboprophylaxis should be considered in all major urologic surgeries. Urologists should be familiar with incidence rates, recommended prophylaxis, appropriate diagnosis, and treatment recommendations for VTE to minimize morbidity and mortality. The limited number of prospective, randomized, controlled trials evaluating the use of thromboprophylaxis in urologic surgery demonstrates the need for further research.
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Venous thromboembolism (VTE) is a term that refers to deep venous thrombosis (DVT) and/or pulmonary embolism (PE). In North America and Europe, the annual incidence of DVT and PE is 160 and 70, respectively, per 100,000 inhabitants.[1-3] The 1-week survival rate after PE is 71%. Moreover,

25% of cases present with sudden death.[4] The estimated cost of VTE in 1997 was estimated to be more than $4000 per episode and is obviously considerably higher today.[5] Most hospitalized patients possess at least 1 risk factor for VTE (Table 1).[3,6,7] Incidence of DVT without prophylaxis has been observed to range from 10% to 40% among medical and general surgical patients with higher rates still in orthopedic and neurosurgical patients.[8,9] PE accounts for approximately 10% of hospital deaths and is the most common form of preventable hospital mortality.[9] VTE is considered by many to be the most important nonsurgical complication in patients undergoing major urologic surgery, with PE being the most common cause of postoperative death.[10]

Over the last 30 years, multiple randomized, controlled studies have demonstrated the efficacy of thromboprophylaxis in preventing VTE.[11-15] Methods of thromboprophylaxis are typically divided into mechanical and pharmacologic modalities. Mechanical methods include graduated compression stockings (GCS) and intermittent pneumatic compression (IPC). Proven methods of pharmacologic prophylaxis in inpatients include low-dose unfractionated heparin (LDUH) and low molecular weight heparin (LMWH). Despite this evidence, many urologic surgeons are reluctant to place postoperative patients on pharmacologic prophylaxis due to the concern for postoperative bleeding and hematoma formation. Although there is some controversy in the literature regarding this risk, most randomized, controlled trials fail to demonstrate a significant increase in postoperative bleeding complications in patients receiving pharmacologic prophylaxis.[16-21]

Table 1
Risk Factors for VTE

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

VTE, venous thromboembolism.
Reproduced with permission from Geerts WH et al.[10]

Risk Factors for VTE

At the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy held in 2004, the factors listed in Table 1 were agreed on as placing patients at increased risk for developing VTE.[10] Virtually all of these factors may be found in the urologic population. However, surgery, malignancy, cancer therapy, and advanced age are pervasive in this population. Thus, VTE is a significant threat in the majority of patients undergoing major urologic surgery.

Methods of Thromboprophylaxis

Mechanical methods of thromboprophylaxis include GCS, IPC devices, and venous foot pumps (VFP). The mechanism of efficacy in these devices is likely due to reduction of venous stasis in the lower extremities and release of antithrombotic factors from leg muscles. Mechanical thromboprophylaxis is an attractive option for surgeons because it does not increase the risk for bleeding complications. However, although these devices have been demonstrated to decrease the incidence of DVT, they have not been shown to decrease risk of PE or death.[10]

Soderdahl and colleagues[22] evaluated the use of thigh versus calf length sequential compression devices in 90 patients undergoing urologic surgery. One patient in the calf-length group developed a DVT and 1 patient in the thigh-length group developed a

PE. Thus, the rate of VTE in both study groups was 2%. This study was not powered to demonstrate statistical equivalence. However, the authors also evaluated the relative cost and ease of use, both of which favored use of the calf-length sequential compression devices.[22]

Although aspirin and other antiplatelet drugs have been demonstrated to significantly reduce the incidence of major cardiovascular events related to atherosclerotic disease, they have not proven effective in preventing VTE.[23-27] Several studies in orthopedic patients have demonstrated significantly higher rates of VTE in patients receiving perioperative aspirin alone versus LMWH or VFP plus aspirin.[26,28] Furthermore, aspirin has been associated with an increased risk of major bleeding.[27,29] Therefore, the ACCP recommends against the use of aspirin alone for VTE prophylaxis.[10]

Pharmacologic thromboprophylaxis with subcutaneous (SC) heparin, oral warfarin, and, more recently, SC LMWH has been the most extensively studied area of VTE prevention. Most of the convincing evidence of the efficacy of pharmacologic prophylaxis in surgical patients comes from the general surgical literature. In a meta-analysis of 46 randomized clinical trials on general surgery patients, LDUH significantly reduced rates of DVT (22% vs 9%), symptomatic PE (2.0% vs 1.3%), and fatal PE (0.8% vs 0.3%). All-cause mortality was reduced from 4.2% in the control group to 3.2% in the LDUH group. In these trials, 5000 units of LDUH were administered SC 1 to 2 hours prior to surgery and continued 3 times daily or 2 times daily during the perioperative period. Twice-daily dosing was found to be more efficacious in preventing VTE without increasing bleeding risk. Overall, heparin prophylaxis increased bleeding risk from 3.8% to 5.9% versus placebo or no treatment (Figure 1).[15]

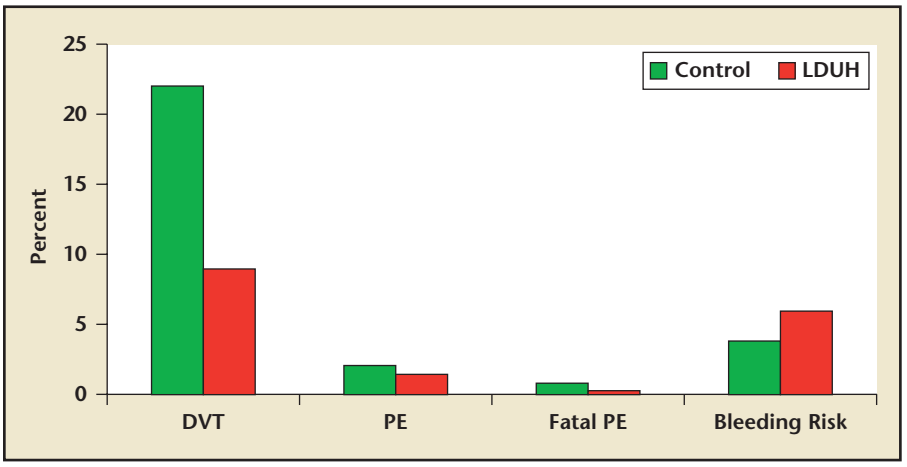

Figure 1. *Effect of low-dose unfractionated heparin (LDUH) on rates of postoperative venous thromboembolism and bleeding complications. DVT, deep venous thrombosis; PE, pulmonary embolism. Reproduced with permission from Collins R et al.*[15]

LMWHs are produced by depolymerization of LDUH into smaller molecules. This results in a molecular weight of 4000 to 6500 Da as compared with a molecular weight of approximately 15,000 Da for unfractionated heparin. These formulations have a more favorable pharmacokinetic profile including improved bioavailability, longer half-life allowing for 2 times or even 1 time daily dosing, and decreased interindividual variability in anticoagulant response, thus obviating the need for therapeutic monitoring in most patient populations.[30] Notable exceptions to this last rule include patients who are pregnant, have renal failure, or are morbidly obese. These patients should have anti-Xa levels measured 4 hours after drug administration and dosing should be titrated to a level of 0.6 to 1.0 IU/mL.[31] Additionally, LMWH has been associated with a significantly lower risk of heparin-induced thrombocytopenia.[32]

When compared with LDUH, LMWH demonstrates similar efficacy in the prevention of symptomatic VTE.[17,20,33,34] Although there has been controversy regarding its effect on bleeding complication rates, it appears that low-dose LMWH results in fewer bleeding complications than LDUH, whereas higher dose LMWH results in more bleeding complications than LDUH.[34] Thus, LDUH and LMWH should be regarded as equivalent choices for thromboprophylaxis in surgical patients. Postoperative outpatient prophylaxis may be more easily accomplished with LMWH due to less frequent dosing.

VTE in Cancer Patients

The association of malignancy and DVT was first described by Armand Trousseau (1801-1867), an achievement commemorated by the eponymous condition, Trousseau syndrome, which refers to migratory thrombophlebitis as the initial presenting symptom for occult malignancy. The relative risk of harboring occult malignancy is 3.2 in patients with spontaneous VTE when compared with the general population.[35] Patients with cancer have a 4.1-fold increase in the risk of VTE, and the addition of chemotherapy increases this risk to 6.5-fold.[35] The odds ratio for a cancer patient developing postoperative DVT is 2.2 compared with postsurgical patients without malignancy.[36]

The nature of the association between cancer and VTE is likely to be multifactorial, as patients with malignancy tend to have several other risk factors for VTE including advanced age, immobility, smoking history, chronic central venous catheterization, and exposure to chemotherapeutic agents. Additionally, there appears to be a procoagulant state associated specifically with malignancy. Proposed mechanisms for this effect include release of tissue thromboplastin from cancer cells, the expression of cancer procoagulant, a cysteine protease with direct factor X activation, the elaboration of a variety of fibrinolytic substances, and cancer cell–mediated endothelial injury.[37,38] The mechanism of chemotherapy-induced thrombosis is poorly understood, but has been proposed to result from decreased protein C,[39] increased production of fibrinopeptide A,[40] and increased endothelial cell activity.[41]

Among cancer patients, advanced stage,[42] central venous catheters,[43,44] and combination chemotherapy increase the risk of VTE.[45-47] The specific cancers that demonstrate the highest rates of VTE include pancreatic, ovarian, uterine, brain, kidney, and hematologic malignancies.[48-50] Regarding central venous catheters, several investigators have suggested routine use of fixed low-dose warfarin or heparin for prophylaxis in these patients.[43,44] However, the ACCP recommends against this practice.[10] Given these risk factors, it is recommended that inpatients with malignancy receive appropriate thromboprophylaxis. Even in the setting of adequate prophylaxis, cancer is an independent risk factor for VTE.[51]

VTE in Urologic Surgery

Multiple reports have identified VTE to be the most significant nonsurgical complication of major urologic procedures.[52-54] Approximately 1% to 5% of patients undergoing major urologic surgery experience symptomatic VTE. Furthermore, PE is believed to be the most common cause of postoperative death.[10]

In a review of 1,653,275 surgical cases entered into the California Patient Discharge Data Set between January 1, 1992, and September 30, 1996, White and associates found radical cystectomy to have an equal incidence of VTE to intracranial neurosurgery, occurring in 3.7% of cases performed.[36] This finding was the highest incidence reported for any surgery performed in all disciplines. Percutaneous nephrostomy performed in patients with malignancy demonstrated a 3.6% incidence of VTE. However, the incidence was only 0.8% in patients undergoing this procedure who were not cancer patients. Similarly, the incidence of VTE in patients undergoing nephrectomy for malignancy was 2.0% compared with a value of 0.4% in noncancer patients. The incidence in radical prostatectomy was 1.5%. Urologic procedures with a low incidence of VTE included transurethral resection of the prostate (TURP) and incontinence procedures.[36]

The increased incidence in cancer patients likely reflects increased age, longer operative times, more extensive dissection along vascular structures to achieve oncologic cure, immobility related to deconditioning, external compression of pelvic veins by tumor mass, and a primary prothrombotic effect of cancer.[36] The use of thromboprophylaxis was not available in this study. Therefore, it is difficult to compare rates of VTE in different procedures. However, the significant incidence of VTE in urologic procedures demonstrates the importance of thromboprophylaxis in the urologic patient.

In a more recent prospective, observational study of 685 patients undergoing various urologic procedures at 31 Italian hospitals, there were 10 cases of suspected symptomatic VTE.[55] Of these cases, 6 (0.87%) were adjudicated as VTE, of which 3 cases were fatal. By way of comparison, general surgery and gynecology patients observed over the same time period demonstrated VTE rates of 2.8% and 2.1%, respectively. The relatively low incidence of VTE in urologic patients was likely due to the fact that 61% of cases were endoscopic procedures (the incidence of VTE was 1.9% for open urologic procedures), with 32% of all urologic procedures performed being < 45 minutes in duration. Multivariate logistic regression analysis identified age ≥ 60 years, history of previous VTE, anesthesia lasting > 2 hours, advanced tumors, and postoperative bedrest ≥ 4 days as risk factors for perioperative symptomatic VTE. Postoperative bleeding occurred in 17.1% of patients receiving thromboprophylaxis and 5.7% of those receiving no prophylaxis (no *P* values provided), with 26.5% of these patients requiring transfusion. Risk factors for postoperative bleeding were anesthesia time ≥ 45 minutes, thromboprophylaxis, and endoscopic surgery.

Transurethral Surgery

As with the majority of urologic procedures discussed next, there are no randomized, controlled trials evaluating the use of pharmacologic thromboprophylaxis in transurethral surgery. However, the studies discussed in the preceding paragraph seem to indicate a very low incidence of VTE in patients undergoing these procedures. A retrospective analysis of 883 patients undergoing TURP revealed a 0.45% incidence of PE with the use of GCS compared with 0.55% incidence when data on thromboprophylaxis was absent.[56] The difficulty in quantifying blood loss during

transurethral procedures limits the evaluation of the effect of pharmacologic prophylaxis on this outcome. However, at least one study has (discussed in the previous paragraph) identified endoscopic surgery as an independent risk factor for postoperative bleeding.[55] The association of postoperative bleeding with transurethral procedures, along with the low incidence of VTE associated with endoscopic procedures, seems to indicate that the risks of thromboprophylaxis may outweigh the benefits in these cases.[55] The consensus at the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy was to recommend against specific prophylaxis other than early mobilization in patients undergoing transurethral surgery.[10] This recommendation was echoed in a Best Practice statement released by the American Urological Association (AUA).[57]

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The ACCP recommends routine prophylaxis with LDUH 2 to 3 times daily in major open urologic procedures. Alternatives include IPCs, GCSs, or SC LMWH.[10] The following section will discuss the incidence and prevention of VTE in individual, major, open urologic oncologic procedures.

Radical Retropubic Prostatectomy

Much of the available literature regarding VTE in urologic surgery examines the incidence in patients undergoing radical retropubic prostatectomy. Although early studies reported DVT rates of 6.9% to 12% and PE rates of 2% to 2.7%,[58-60] reported rates of DVT range from 0.2% to 7.8% and of PE range from 0% to 2.7% in more contemporary studies.[61-73] It should be noted that in the majority of these studies patients were not screened for VTE. Rather, diagnostic studies in these patients were prompted by symptoms concerning for VTE.

In a prospective study of 245 consecutive patients undergoing radical retropubic prostatectomy and pelvic lymphadenectomy, Leibovitch and colleagues examined lower extremity color flow Doppler screening examinations performed once during postoperative days 2 to 5. The rates of DVT and PE were 3.6% and 0.8%, respectively. Interestingly, just 2 of the 9 cases of DVT were detected on postoperative screening Doppler examinations performed during the inpatient stay. The remaining cases were diagnosed after discharge when patients presented 6 to 12 days postoperatively with symptoms concerning for DVT. The only parameters that correlated with development of VTE in this study were lymphocele and pelvic hematoma formation, with at least 1 of these factors being present in 50% of patients.[74]

Of particular concern is the use of pharmacologic thromboprophylaxis in patients undergoing pelvic lymph node dissection. Several studies have demonstrated a significant increased rate of pelvic lymphocele in patients receiving 5000 units of heparin SC immediately prior to surgery.[75-77] Bigg and Catalona demonstrated a significant increase in the incidence of prolonged lymphatic drainage into Jackson-Pratt drains after prostatectomy with pelvic lymph node dissection in patients who had received perioperative heparin when compared with those who had not. Whereas patients receiving perioperative heparin demonstrated increased estimated intraoperative blood loss and transfusion requirements, these increases were not statistically significant. Incidence of VTE was insignificantly decreased in the treatment group due to inadequate powering of the study.[66] A more recent and larger study performed by Sieber and associates demonstrated an insignificant increase in the incidence of pelvic lymphocele in patients treated with heparin compared with those who were not. Once again, there was a decreased rate of VTE in the heparinized group, but the difference was not statistically significant.[78]

Therefore, at the present time there is no definitive literature to support or refute the use of pharmacologic thromboprophylaxis after radical retropubic prostatectomy. IPC devices, GCSs, and early ambulation should be used in all patients undergoing this surgery. Surgeons should use their own judgement with regard to pharmacologic prophylaxis, perhaps administering perioperative pharmacologic thomboprophylaxis in patients who are thought to be at particularly high risk for VTE (eg, history of VTE, obesity).

Radical Cystectomy

Although there is a paucity of studies evaluating the incidence and treatment of VTE in patients undergoing cystectomy, the available data are impressive. As described previously, White's review of the California Patient Discharge Data Set revealed a postoperative VTE rate of 3.7%, the highest reported of any surgery in the database.[36] Similarly, in a review of 101 patients undergoing radical cystectomy for cancer, Rosario and colleagues found a symptomatic VTE

rate of 6%. There were 4 incidences of DVT and 2 of PE; none were fatal. No comment was made regarding what thromboprophylaxis modality, if any, was used.[79] No prospective, randomized, controlled trials regarding the use of pharmacologic thromboprophylaxis have been performed. However, these 2 studies reveal radical cystectomy to be an extremely high-risk procedure for VTE. This association is likely related to patient age, comorbid cardiopulmonary pathology, malignancy, smoking history, extensive pelvic dissection including lymphadenectomy, increasing use of adjuvant and neoadjuvant chemotherapy, central venous catheterization, and prolonged postoperative immobility/institutionalization.

In light of the high risk for and significant consequences of VTE, surgeons should strongly consider the use of perioperative pharmacologic thromboprophylaxis in patients undergoing radical cystectomy.

Nephrectomy

Several large-scale retrospective studies have demonstrated an increased risk of VTE in patients with renal malignancies relative to other cancers. However, incidence varies drastically from study to study and is likely a result of significant differences in disease stage depending on mode of retrospective examination. For example, in a retrospective study of incidence of VTE in patients with solid tumors, Sallah and associates reported a 22.6% incidence of VTE in patients with renal cell carcinoma. This was higher than that reported for pancreatic and brain tumors in the same study. The authors reviewed only patients referred to hematology/oncology services at 3 tertiary medical centers. In most cases, only patients who are not surgically cured of renal cell carcinoma (those with metastatic disease, vascular invasion, or local invasion) are referred to oncology. Thus, this extremely high incidence of VTE results from a selection bias for patients with stage III-IV disease.[49]

In a dated review of Medicare data from 1988-1990, Levitan and colleagues found a 0.8% incidence of VTE among patients admitted with an International Statistical Classification of Diseases and Related Health Problems, version 9, diagnosis of renal cancer. This finding placed renal cancer among the top 6 malignancies with regard to incidence of VTE. Once again, data regarding the nature of admission, stage of disease, and surgical treatment were not reported.[48] Although there is clearly an increased risk for VTE in patients with renal cell carcinoma, these studies offer little information with regard to determining the appropriateness of thromboprophylaxis in the perioperative setting.

In a recent retrospective study, Pettus and associates[80] reviewed the incidence of VTE in 2208 patients who had undergone any type of partial or radical nephrectomy at a single institution from January 1989 to July 2005. Thromboprophylaxis was provided by implantable cardioverter-defibrillators (ICD) only. The overall incidence of VTE was 1.5% with DVT and PE occurring in 0.6% and 0.9% of patients, respectively. Identifiable risk factors for DVT included increasing age, history of coronary artery disease, and nonorgan-confined disease. Increased intraoperative blood loss, history of DVT, and cardiac arrhythmia all significantly increased the risk for perioperative PE. Of note, procedure type (open, partial, laparoscopic) had no impact on incidence of VTE. The authors argued that this low incidence of perioperative VTE does not warrant the use of pharmacologic thromboprophylaxis with its associated bleeding complications as recommended by the ACCP. However, this study only captured incidences of VTE that occurred within 30 days of surgery. This fact, along with evidence from the prostate literature that inpatient ICD use only delays VTE, raises concern that a significant number of VTE events may have occurred after the 30-day window.[67]

Although there is conflicting evidence regarding the incidence of VTE in patients undergoing nephrectomy for malignancy, the routine use of pharmacologic prophylaxis in patients undergoing radical nephrectomy is recommended. Pharmacologic prophylaxis should not be used in patients undergoing partial nephrectomy due to high risk for renal parenchymal bleeding at the resection site.

Female Urologic Procedures

The majority of data on VTE as well as prophylaxis in female urologic procedures comes from the gynecologic literature. However, findings seem to mirror those just discussed. The risk of VTE appears to be higher in patients undergoing gynecologic procedures for malignancy.[10] In the AUA Best Practice Statement, early ambulation was recommended for low-risk patients undergoing minor procedures, mechanical or pharmacologic prophylaxis was recommended for moderate-risk patients undergoing higher-risk procedures, and both mechanical and pharmacologic prophylaxis was recommended for high- and highest-risk patients undergoing higher-risk procedures unless the risk of bleeding is unacceptably high.[57]

Laparoscopic Urologic Surgery

Relatively few studies have evaluated the use of thromboprophylaxis in urologic laparoscopic surgery. In a study of 344 patients undergoing urologic laparoscopic procedures randomly assigned to receive either fractionated heparin or sequential compression device (SCD) prophylaxis, Montgomery and Wolf found a

1.2% incidence of VTE in both groups. However, the rate of major hemorrhagic complications in the fractionated heparin group was 7.0% as compared with 2.9% in the SCD group. The fractionated heparin group also demonstrated increased rates of minor hemorrhagic complications, retroperitoneal hematoma, and port site hematoma. The study was not powered to demonstrate which laparoscopic procedures were associated with the greatest risk of VTE or hemorrhagic complications.[81]

In a large, multicenter study of 5951 patients undergoing traditional laparoscopic and robot-assisted laparoscopic prostatectomy, the rates of DVT and PE were 0.5% and 0.2%, respectively. Univariate analyses revealed history of DVT, current tobacco smoking, re-exploration, increased operating room time, longer hospital stay, and prostate volume > 100 cc to be associated with increased risk of VTE. Sixty-seven percent of patients received perioperative heparin. The use of preoperative heparin prophylaxis was associated with increased intraoperative estimated blood loss (300 vs 200 cc), longer hospital stay (3 vs 2 days), higher transfusion rates (4.2% vs 3.1%), and higher reoperation rates (1.6% vs 0.8%).[82]

Taken together, these 2 studies do not support the use of pharmacologic thromboprophylaxis in laparoscopic urologic surgery. However, specific laparoscopic procedures need to be examined in appropriately powered, prospective, randomized, controlled studies to definitively evaluate the safety and efficacy of pharmacologic thromboprophylaxis in laparoscopy. Patients still must be considered on an individual basis with appropriate measures being taken to minimize chances of VTE in high-risk patients. The Seventh ACCP Conference on Antithrombotic and Thrombolytic therapy did not recommend routine pharmacologic thromboprophylaxis in patients undergoing laparoscopic surgery unless patients have additional risk factors for VTE, in which case any combination of LDUH, LMWH, IPC, or GPS is appropriate.[10] The AUA Best Practice Statement confirmed these recommendations for this patient population.[57]

Lithotomy Position

In a review of 177 surgeries performed in the lithotomy position, the authors reported 4 cases (2.3%) of VTE. There were 3 cases of PE and 1 case of DVT. Of note, these patients had undergone urethral reconstruction and were placed on bedrest for 4 to 5 days postoperatively. Therefore, it is unclear if VTE was a function of operative positioning or lack of ambulation postoperatively.[83]

Timing of VTE

VTE has traditionally been considered a complication that occurs in the immediate postoperative period. However, recent studies have demonstrated that VTE often occurs after the immediate postoperative period. In many cases, VTE was diagnosed after the patient was discharged from the inpatient stay. As discussed, Leibovitch and colleagues found that 7 of the 9 patients who developed DVT after radical retropubic prostatectomy did so after discharge.[74] Dillioglugil and associates reported that 5 cases of symptomatic PE occurring after radical retropubic prostatectomy were diagnosed between 7 and 24 days postoperatively.[61] Cisek and Walsh found that patients not receiving thromboprophylaxis developed VTE an average of 11 days after prostatectomy compared with an average of 20 days postoperatively in patients who received perioperative implantable ICD prophylaxis.[67] Furthermore, patients receiving ICD prophylaxis demonstrated a trend toward increased VTE rates. This study indicates that inpatient thromboprophylaxis may delay postoperative VTE without decreasing overall incidence. Similarly, in the @RISTOS study on VTE after urologic surgery, Scarpa and colleagues reported 6 cases of PE, 3 of which were fatal, occurring between 4 and 22 days postoperatively.[55] All patients had received at least pharmacologic prophylaxis postoperatively, with 4 receiving pharmacologic prophylaxis when the event occurred.[55]

Delayed versus early postoperative VTE is increasingly recognized as the rule rather than the exception in all surgical disciplines. In a retrospective study of 5607 patients having undergone major hip or knee surgery, the total rate of VTE was 2.7%. Patients presented with DVT and PE at a median of 24 and 17 days after surgery for hip fracture, 21 and 34 days after total hip replacement, and 20 and 12 days after total knee replacement, respectively. Overall, 70% of the VTE cases developed after discharge.[84]

Recent studies have demonstrated that venous thromboembolism (VTE) often occurs after the immediate postoperative period. In many cases, VTE was diagnosed after the patient was discharged from the inpatient stay.

The propensity of VTE to occur after the immediate perioperative period has led some to examine the efficacy of prolonged postoperative regimens of pharmacologic prophylaxis. In a double-blind, multicenter, placebo-controlled trial, Bergqvist and colleagues evaluated extending daily use of enoxaparin 40 mg SC beyond the initial 6- to 10-day postoperative

period for an additional 21 days in patients undergoing surgery for cancer.[85] Patients were screened with bilateral venography between postoperative days 25 and 31 or sooner as clinically indicated. A total of 332 patients were evaluated. VTE rates were 12.0% and 4.8% in the placebo and treatment arms, respectively. There were no increases in major or minor bleeding complications in the treatment group. In another study, Bergqvist and Jönsson demonstrated similar efficacy as well as cost effectiveness of prolonged postoperative administration of enoxaparin following total hip replacement.[86] No such study has been performed specifically on urologic patients. However, the patient populations are similar and the results sufficiently convincing to warrant such a trial, if not application, in the urologic field.

Clinical Manifestations and Treatment of VTE

DVT

Patients who develop DVT may complain of pain, swelling, or discoloration of the affected extremity. Physical examination may reveal a palpable cord, edema, warmth, and/or superficial vein dilatation due to collateralization of venous return from deep to superficial systems. The classic physical examination finding of resistance to passive dorsiflexion or Homan's sign is neither sensitive nor specific and should not be used as a basis for clinical decision making. Phlegmasia cerulea dolens refers to massive ileofemoral thrombosis resulting in marked painful swelling of the lower extremities bilaterally. This serious medical condition can be complicated by compartment syndrome, arterial compromise, gangrene, shock, and death.

Initial evaluation for suspected DVT should include a complete blood count with platelet count and a coagulation panel. Diagnostic modalities include D-dimer, impedance plethysmography, compression ultrasonography, and contrast venography (traditional or computed tomographic). D-dimer is most useful in patients with a low pretest probability of DVT. Thus, it is of little or no use in postoperative urologic surgery patients.

Compression ultrasonography is the most appropriate imaging study to evaluate for DVT in a postoperative patient. This is due to its noninvasive nature and 95% positive predictive value.[87] Venography is the most sensitive and specific study for DVT, but it is invasive and usually unnecessary.

The Well's Score is a method designed to calculate pretest probability for DVT (Table 2).[88] A review of 15 studies evaluating the Well's score demonstrated that a low pretest probability has a 96% negative predictive value, which was further enhanced by a negative D-dimer. In contrast, the positive predictive value for DVT rarely exceeded 75% in patients with a high pretest probability.[89] This limits its applicability to postoperative urologic surgery patients.

DVT requires expeditious treatment to prevent early and late complications. Early complications include PE, extension of thrombosis, phlegmasia cerulea dolens, and venous gangrene. Late complications include postphlebitic syndrome, chronic venous insufficiency, and chronic thromboembolic pulmonary hypertension. Although treatment of all DVTs is required, it is most crucial in proximal lower extremity because 50% will result in PE if untreated.[90,91]

Compression ultrasonography is the most appropriate imaging study to evaluate for deep venous thrombosis (DVT) in a postoperative patient. This is due to its noninvasive nature and 95% positive predictive value.

Treatment according to the recommendations of the Seventh ACCP Consensus Conference on Antithrombotic and Thrombolytic Therapy and the American Heart Association/American College of Cardiology is as follows: Patients with DVT should be treated with LDUH intravenously (IV), LMWH or fondaparinux SC, or

Table 2
The Well's Criteria for Clinical Assessment of PE

Variable	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of deep veins)	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate is greater than 100	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the last 6 months or palliative)	1.0

Low clinical probability of PE: < 2 points; Moderate clinical probability of PE: 2-6 points; High clinical probability of PE: > 6 points.

DVT, deep venous thrombosis; PE, pulmonary embolism.

warfarin orally. The dose of IV LDUH should be adjusted for an activated partial thromboplastin time of 1.5 to 2.5 times the mean of the control value. LMWH dosing varies between specific medications. The dosing of enoxaparin is 1 mg/kg SC every 12 hours. Warfarin dosing should be adjusted for an international normalized ratio (INR) value of 2.5. When transitioning to warfarin for oral anticoagulation, the parenteral thromboprophylactic agent should be maintained at therapeutic levels until the INR has been therapeutic for at least 48 hours. An inferior vena cava filter is recommended when there is a contraindication to anticoagulation, complication on anticoagulation, or in cases of thromboembolism despite anticoagulation.[92,93]

The recommended duration of therapy for a patient diagnosed with DVT varies. Initial DVT in a patient with a temporary or reversible risk factor for VTE should be managed with 3 months' anticoagulation. Patients with idiopathic DVT without risk factors should be treated for 6 to 12 months. Patients with recurrent DVT, PE, or advanced malignancy in the setting of VTE should be anticoagulated indefinitely (Table 3).[92]

Patients with idiopathic DVT without risk factors should be treated for 6 to 12 months. Patients with recurrent DVT, pulmonary embolism, or advanced malignancy in the setting of VTE should be anticoagulated indefinitely.

PE

The evaluation of a patient with suspected PE must be performed with urgency given the propensity for rapid cardiopulmonary compromise and death.

Electrocardiography (ECG) should be performed in all patients with suspected PE, as tachycardia, dyspnea, syncope, and chest pain can be present in a variety of cardiac disorders. Although ECG abnormalities are common in patients with PE, they are very nonspecific and of little to no use in diagnosing PE.[94-96] The classic S1Q3T3 pattern indicating right heart strain and new incomplete right bundle branch block (RBBB) is uncommon in most PEs, but may be seen in patients with massive acute PE and cor pulmonale.[97,98] Atrial arrhythmias, RBBB, inferior Q waves, precordial T-wave inversion, and ST-segment changes have all been associated with worsened prognosis in patients with PE.[92,93]

A plain chest film is an expedient initial study that provides little information regarding the presence of PE. It may provide useful information regarding other cardiopulmonary pathology that may explain the patient's signs and symptoms such as atelectasis or pulmonary effusions. However, these findings are often seen in patients with PE and should not be assumed to explain signs and symptoms in a patient at high risk for PE.

Arterial blood gas (ABG) in the setting of PE should demonstrate hypoxemia, hypocapnia, respiratory alkalosis, and an elevated alveolar-arterial (A-a) gradient when compared with pulse oximetry. Although an ABG and A-a gradient were once thought to be a useful component of the initial diagnostic work-up in patients with suspected PE, their use has fallen out of favor in large part due to a pivotal study by Stein and colleagues published in 1996.[99] This study demonstrated a negative predictive value for PE of $<$ 69% for a normal ABG A-a gradient in patients without history of cardiopulmonary disease, a negative predictive value of 86% in patients with history of cardiopulmonary disease, a positive predictive value for PE of 40% for an abnormal ABG A-a gradient in patients without a history of cardiopulmonary disease, and a positive predictive value of 34% to 35% in patients with a history of cardiopulmonary disease. The sensitivity of an abnormal ABG or A-a gradient was 88% to 97%. However, the specificity was approximately 50%. In no case was an ABG value or an A-a gradient able to reliably exclude PE and, thus, alter further work-up or therapy. For this reason, use of ABG as a diagnostic tool for evaluation of suspected PE is no longer recommended. However, its utility remains with regard to management of a patient in respiratory distress.

Table 3
Recommended Duration of Anticoagulation for DVT

Clinical DVT History	Duration of Anticoagulation
First DVT with temporary reversible risk factor	3 mo
First DVT without identifiable risk factor	6-12 mo
First DVT with irreversible risk factor	6-12 mo; consider indefinite therapy
Recurrent DVT or first DVT with advanced malignancy	Indefinite therapy

DVT, deep venous thrombosis.

Although a D-dimer level has a high sensitivity and negative predictive value, it has very low specificity and positive predictive value. It is of little use in ruling out high-risk patients. D-dimer levels have been reported to be normal in 25% of patients without PE, a number that is likely significantly lower in postoperative patients.[100] Therefore, this laboratory test should not be used to rule out PE in postoperative urologic surgery patients.

A ventilation-perfusion (V/Q) scan is interpreted on the basis of pretest clinical probability. In patients with high clinical probability and high probability V/Q scan, a 95% positive predictive value has been reported. A 96% negative predictive value has been described in low probability patients. However, the combination of clinical and scan probability generally ranges from 15% to 86% for most patients. Therefore, further evaluation may be required in a large portion of patients who have undergone a V/Q scan.[101]

The rationale behind the use of lower extremity compression ultrasound in the evaluation of suspected PE is that a positive study will prompt essentially the same management as if PE were detected without subjecting patients to radiation, radiocontrast, or an invasive study. However, a negative study does not rule out PE and requires further evaluation for PE specifically. This phenomenon is particularly problematic because the rate of negative lower extremity ultrasounds in the setting of PE has been reported to be 71%.[102] Some have advocated complete lower extremity compression ultrasonography or serial exams for 2 weeks after suspected PE with low probability V/Q scans to decrease false-negative rates.[103-107] Although the results of these studies have been encouraging, it is the opinion of the authors that PE represents too dangerous a clinical entity to safely observe without instituting therapy except in the rare instance where anticoagulation poses more of a threat to the patient's health than PE.

The most widely used study for the definitive diagnosis of PE is spiral computed tomography scan. The advantages of this study include a high specificity, widespread availability, noninvasiveness, rapidity of the procedure, and ability to diagnose other pathologic processes potentially responsible for clinical presentation. Disadvantages are few, but include potential for contrast nephropathy as well as contraindication in renal insufficiency and in patients with contrast allergy. Reported sensitivity has varied drastically and seems to be related to experience of the interpreting radiologist as well as pretest probability. In the largest study to date, the use of the Well's Criteria to stratify patients into high, intermediate, and low clinical probability improved both positive and negative predictive values substantially. Accuracy appears to be equal to V/Q scan.[108,109]

Pulmonary angiography is the gold standard for diagnosis for PE. However, it is unnecessarily invasive and, in most cases, not required for definitive diagnosis.

The treatment recommendations for management of PE are very similar to those detailed for DVT. Patients should be therapeutically anticoagulated in the case of radiographically confirmed PE or if there is a high clinical suspicion. Once again, the efficacy of treatment hinges on the ability to reach therapeutic anticoagulation within the first 24 hours of treatment.[110,111] LMWH or IV LDUH can be used, but the former is preferred due to its more predictable ability to rapidly reach therapeutic levels using weight-based dosing. The indications for inferior vena cava filter are detailed in the DVT discussion above. In a large meta-analysis, 22 randomized, controlled trials demonstrated that LMWH decreased recurrent thrombosis and bleeding complications when compared with IV heparin; 12 randomized, controlled trials demonstrated that thrombus size reduction was more common with LMWH; and 18 randomized, controlled trials demonstrated that SC LMWH decreased mortality when compared with IV LDUH.[112] LMWH has also been demonstrated to be more cost effective with a $91,332 savings per 100 patients treated with LMWH versus IV LDUH.[113]

The indications for preferential use of IV LDUH in therapeutic anticoagulation include patients with massive PE and resultant persistent hypotension, severe renal failure (creatinine clearance $<$ 30 mL/h), or in postoperative patients where the threat of acute hemorrhage requires the ability for rapid reversal of anticoagulation. The efficacy of SC LMWH has not been evaluated in patients with massive PE and hypotension, because this group has been excluded from the clinical trials of LMWH.[114] LMWH should be avoided in patients with severe renal failure as anti-Xa activity must be monitored in these patients, which is not as readily available as partial thromboplastin time (PTT) in most institutions. As just discussed, weight-based dosing regimens are recommended with infusion rate adjusted to attain a PTT of 1.5 to 2.5 times the control value of the institution.

As in the treatment of DVT, warfarin should be started with a parenteral agent at PE diagnosis, or as soon as is considered safe in a postoperative patient. Dosing should be adjusted for an INR of 2.5 and parenteral anticoagulation should be continued for 48 hours once a therapeutic INR has been reached.[92]

The recommended duration of anticoagulation is similar to that for DVT. If it is the patient's first episode of VTE and there is a reversible risk factor (eg, surgery), the patient should be anticoagulated for 6 months. Attempts to decrease the duration to

< 3 months have demonstrated increased rates of recurrent thromboembolism.[115,116] If it is a patient's first episode of VTE, but there is no identifiable reversible risk factor (eg, idiopathic VTE), the patient should be anticoagulated for 6 to 12 months. In cases of a patient's first episode of VTE with an irreversible risk factor (eg, hypercoagulability, cancer), anticoagulation should be continued for 6 to 12 months and indefinite therapy should be considered, especially if there is more than one irreversible risk factor. When treating patients with cancer who experience an episode of VTE, urologists should consider anticoagulation with LMWH for the initial 3 to 6 months of treatment before transitioning to warfarin. This approach has demonstrated significant reduction of recurrent VTE rates without increasing rates of major bleeding complications. However, no improvement in mortality was demonstrated with this regimen. Patients with 2 or more episodes of PE should be therapeutically anticoagulated indefinitely (Table 4).[92]

Conclusions

VTE is a pervasive and dangerous pathologic entity in the field of urologic surgery. The propensity for PE to result in sudden postoperative death highlights the importance of prevention,

Table 4
Duration of Anticoagulation in Treatment of PE

Clinical PE History	Duration of Anticoagulation
First PE with temporary reversible risk factor	6 mo
First PE without identifiable risk factor	6-12 mo
First PE with irreversible risk factor	6-12 mo; consider indefinite therapy
PE with advanced malignancy	LMWH for first 3-6 mo prior to switch to warfarin
Recurrent PE	Indefinite therapy

LMWH, low molecular weight heparin; PE, pulmonary embolism.

Main Points

- Venous thromboembolism (VTE) is a pervasive and potentially devastating complication of urologic surgery. The propensity for pulmonary embolism (PE) to result in sudden postoperative death highlights the importance of prevention, rapid diagnosis, and expedited treatment of this condition. Urologists should be familiar with incidence rates, recommended prophylaxis, appropriate diagnosis, and treatment recommendations for VTE to minimize morbidity and mortality.
- The American Urological Association's Best Practice Statement states that early ambulation is indicated for low-risk patients undergoing minor procedures, mechanical or pharmacologic prophylaxis is suggested for moderate-risk patients undergoing higher-risk procedures, and both mechanical and pharmacologic prophylaxis is recommended for high-risk patients undergoing high-risk procedures—unless the risk of bleeding is unacceptably high.
- Treatment of VTE involves therapeutic anticoagulation for various lengths of time based on presence and reversibility of patient risk factors as well as number of events. Perioperative thromboprophylaxis should be considered in all major urologic surgeries.
- Studies have demonstrated the efficacy of thromboprophylaxis in preventing VTE. Methods are divided into 2 modalities: mechanical (eg, graduated compression stockings and intermittent pneumatic compression and pharmacologic (eg, low-dose unfractionated heparin [LDUH] and low molecular weight heparin [LMWH]). Despite the evidence, many urologic surgeons are reluctant to place postoperative patients on pharmacologic prophylaxis due to the concern for postoperative bleeding and hematoma formation.
- When compared with LDUH, LMWH demonstrates similar efficacy in the prevention of symptomatic VTE. Although there has been controversy regarding its effect on bleeding complication rates, it appears that low-dose LMWH results in fewer bleeding complications than LDUH, whereas higher dose LMWH results in more bleeding complications than LDUH. Thus, LDUH and LMWH should be regarded as equivalent choices for thromboprophylaxis in surgical patients.
- Treatment recommendations for the management of PE are very similar to those detailed for deep venous thrombosis (DVT). Patients should be therapeutically anticoagulated in the case of radiographically confirmed PE or if there is a high clinical suspicion. The efficacy of treatment hinges on the ability to reach therapeutic anticoagulation within the first 24 hours of treatment.
- Recent literature highlights that delayed VTE occurring after hospital discharge is a persistent threat despite inpatient preoperative prophylaxis. Computed tomographic angiography has emerged as the test of choice for diagnosing PE, whereas lower extremity duplex sonography is recommended for diagnosing DVT.

rapid diagnosis, and expedited treatment of this condition. Practicing urologists should have a thorough knowledge of the literature regarding prophylaxis against, as well as evaluation and treatment of, VTE so that they may use an evidence-based approach to management. The paucity of prospective clinical trials evaluating the safety and efficacy of pharmacologic prophylaxis in most major urologic surgeries forces us to extrapolate data from research in other surgical fields. This is obviously suboptimal and indicates a pressing need for further urologic clinical research in this area. ■

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