Venous Thromboembolism Prophylaxis in the Surgical Patient

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1. Elements of Risk

Appreciate the high incidence of VTE in selected surgical patients who do not receive prophylaxis. 

1.1 Understand that the risk for VTE differs based on the type of surgical procedure performed and the underlying patient comorbidities.

Recommendations
- Consider the type of surgical procedure and patient comorbidities to estimate the risk for VTE before choosing the type and duration of VTE prophylaxis.
- Understand that the highest-risk surgeries are hip and knee surgeries.
- Understand that the highest-risk patients are those with a history of prior VTE, active cancer, or prothrombotic states.
- See table Surgical Risk Stratification and Associated VTE Incidence.

Evidence
- A 2012 guideline from the American College of Chest Physicians evaluated pooled VTE prophylaxis data on surgical and trauma patients and provides recommendations on VTE prophylaxis (1).
- DVT and PE are common causes of morbidity and mortality in surgical patients. Rate of occurrence is dependent on the surgical procedure and patient risk factors. The asymptomatic event rate is much higher than symptomatic events, with a ratio of between 5 and 10 to 1 (2).

Rationale
- Surgical procedures are often associated with venous stasis, venous intimal injury, and activation of coagulation.
- The perioperative period may result in significant immobility.
- Each procedure is associated with the above factors to a different degree and needs to be considered in addition to patient-specific risk factors.
2. Whom and How to Assess

Identify clinical risk factors and comorbidities that increase the risk for postoperative VTE.

2.1 Estimate the risk for postoperative VTE by a careful review of risk factors.

Recommendations

- Determine the presence of patient-related risk factors that predict a higher risk for postoperative VTE. Major patient-related factors include:
  - Age
  - Prior history of VTE
  - Malignancy
  - Immobilization or trauma
  - Medical conditions such as HF, nephritic syndrome, IBD, or lupus
  - Known thrombophilia
  - Venous catheters
  - Estrogen or estrogen agonist therapy or pregnancy
- See table Risk Factors Associated with VTE.

Evidence

- A retrospective study utilized an administrative database to determine the risk factors for VTE in surgical patients. Patient age was associated with postoperative VTE, with odds ratio of 1.1 for every 5-year increment. Previous VTE was associated with an odds ratio of 6.2 [CI, 5.5 to 7.0] and malignancy was associated with an odds ratio of 1.7 [CI, 1.6 to 1.8]. Asian/Pacific Islander ethnicity was protective against VTE, with odds ratio of 0.5 [CI, 0.4 to 0.6] (3).
- In a cohort of 18,661 nursing home patients over a mean of 8 months, the incidence of VTE was 1.3 events per 100 person-years of observation (4).
- In a community population, recent hospitalization for surgery accounted for 24% of VTE events, recent hospitalization for medical illness accounted for 22%, and nursing home residence for 13%. All of these factors are associated with immobilization (5).
- In a prospective epidemiologic study to evaluate cardiovascular risk factors, subjects with a BMI >40 had an adjusted hazard ratio of 2.7 for the development of VTE compared with those with a BMI <25. The population was a random sample of 855 men all aged 50 at baseline. They were reevaluated again at age 54 and then followed periodically until age 80. Although not a surgical population, the findings support the general belief that obesity is an independent risk factor for VTE in any clinical setting (6).
- In a prospective study of patients after major trauma, DVT was found in 65 of the 129 patients (50%) with major injuries involving the face, chest, or abdomen; in 49 of the 98 patients (54%) with major head injuries; in 41 of the 66 patients with spinal injuries (62%); and in 126 of the 182 patients with lower extremity orthopedic injuries (69%). Thrombi were detected in 61 of the 100 patients with pelvic fractures (61%), in 59 of the 74 patients with femoral fractures (80%), and in 66 of the 86 patients with tibial fractures (77%) (7).
- Among patients with Crohn's disease in a population-based cohort study, the incidence rate of DVT was 31 per 10,000 person-years and for PE, 10 per 10,000 person-years. For ulcerative colitis, the incidence rates were 30 per 10,000 person-years for DVT and 19.8 per 10,000 person-years for PE (8).
- In a hospital-based study of pregnant patients both during pregnancy and in the postpartum period, the cumulative incidence of pregnancy-associated VTE was 1.3 cases per 1000 deliveries.
[CI, 0.9 to 1.2]. There was a predominance of VTE during the postpartum period (66%), and DVT occurred more frequently in the left leg (77%) (9).

- A group of 2763 postmenopausal women with coronary heart disease but no previous history of VTE was randomly assigned to either estrogen and progestin or placebo. During an average of 4.1 years of follow-up, 34 women in the hormone therapy group and 13 in the placebo group experienced VTE (hazard ratio, 2.7 [CI, 1.4 to 5]; \( P=0.003 \); excess risk, 3.9 per 1000 woman-years [CI, 1.4 to 6.4 per 1000 woman-years]; number needed to harm, 256 [CI, 157 to 692]). Postmenopausal therapy with estrogen plus progestin increases the risk for VTE in women with coronary heart disease (10).
- In a prospective study of 645 patients in Sweden going for hip or knee replacement, 14.1% had the APC-resistance mutation, of which 10% had a VTE, compared with only 2% of the patients without APC-resistance (RR, 5.0 [CI, 1.9 to 12.9]) (11).
- PE and DVT are recognized complications associated with tamoxifen and raloxifene. The National Surgical Adjuvant Breast and Bowel Project study of tamoxifen and raloxifene showed the average annual rates of thromboembolic events were 3.30 per 1000 for tamoxifen and 2.47 per 1000 for raloxifene (RR, 0.75 [95% CI, 0.60 to 0.93]) (12).
- Further evidence is described in the table Risk Factors Associated with VTE. Exact relative risk estimates for each risk factor are not available, but general estimates are given in the table.

Rationale
- Risk factors increase the risk for thrombosis by stasis, intimal injury, or hypercoagulability (Virchow's triad).

2.2 Understand that VTE rates vary based on the specific type of surgical procedures. ⬤

Recommendations
- Stratify VTE risk based on the specific surgical procedure.
- Understand that the highest-risk procedures and situations include:
  - Major surgery in patients over age 40 with history of VTE, cancer, or certain hypercoagulable states
  - Hip or knee arthroplasty
  - Hip fracture surgery
  - Major trauma
- See table Surgical Risk Stratification and Associated VTE Incidence.

Evidence
- A 2012 guideline from the American College of Chest Physicians evaluated pooled VTE prophylaxis data on surgical and trauma patients and provides recommendations on VTE prophylaxis (1).

Rationale
- Wide ranges of rates of DVT and PE exist in randomized controlled and retrospective studies.

Comments
- The VTE rate varied by surgical procedure. General surgery often includes pelvic, abdominal, and thoracic procedures as a collective group. Orthopedic surgery was presented by specific procedures.

2.3 Do not routinely perform preoperative laboratory testing. Perform targeted testing only in limited situations associated with VTE prophylaxis or for the monitoring of drug prophylaxis. ⬤

Recommendations
- Do not routinely perform pre-operative laboratory testing.
• In patients receiving drug prophylaxis for VTE, obtain the following tests at appropriate periodic intervals based on clinical factors:
  • Hemoglobin to establish baseline and to evaluate changes due to bleeding
  • Platelet count to establish baseline if the patient is receiving heparin or LMWH due to associated thrombocytopenia
  • PT (INR) to establish baseline, but only if the patient is receiving warfarin
  • APTT to establish baseline, but only if the patient is receiving adjusted-dose unfractionated heparin
  • Creatinine to establish baseline to make a dosing adjustment for LMWH in patients with renal impairment, although the exact threshold is not known

Evidence
• A consensus paper provides information on the approach to diagnosis and management of heparin-induced thrombocytopenia by experts in the field (13).
• A review of five clinical trials compared the difference in the pharmacokinetics of LMWH in nondialyzed patients with varying degrees of renal function. The use of a 30 mL/min creatinine clearance as a cutoff for the use of LMWH was not justified by these studies. The data show that LMWHs may differ in their pharmacokinetics and the degree of renal dysfunction (14).

Rationale
• Testing should be for clinical indications when the test result will alter management or prognosis based on current evidence and drug monitoring indications.

Comments
• It is reasonable to reduce the dose of LMWH when the creatinine clearance is <30 mL/min by 25% to 30%. This is a conservative recommendation and not based on pharmacokinetic data. Fondaparinux is contraindicated when the creatinine clearance is <30 mL/min.

2.4 Do not routinely perform a preoperative investigation of thrombophilia in patients scheduled for surgery.

Recommendations
• Consider testing for hereditary thrombophilias only if knowledge of the result will change patient management.
• If testing for thrombophilia is clinically indicated, begin with the most prevalent conditions (factor V Leiden and prothrombin gene mutation).
• Clinical situations which may warrant testing include:
  • History of previous DVT or PE before ages 40 to 50
  • Uncommon sites of thrombosis (e.g., sagittal, mesenteric, inferior vena cava, upper extremity)
  • Warfarin-induced skin necrosis (protein C, S deficiency)
  • History of spontaneous abortions, especially after the first trimester (antiphospholipid antibody syndrome)
  • Unexplained massive thrombosis

Evidence
• A review article shows that blood coagulation proteins and platelet defects are now known to account for up to 90% of unexplained VTE and up to 70% of unexplained arterial thrombotic or ischemic events (15).
• Currently, hypercoagulability disorders can be correctly diagnosed in approximately 80% to 90% of patients. This paper provides a logical approach to the identification and treatment of hypercoagulability syndromes (16).

Rationale
• If further investigation into a thrombophilia would be indicated as part of usual medical care, it may be reasonable to perform at the time of preoperative evaluation, but surgery should not be delayed pending this evaluation.
• Positive test results for hereditary thrombophilias may increase the aggressiveness of VTE prophylaxis and raise the suspicion for a VTE event if clinical signs or symptoms present.
• No evidence exists that knowing the results of testing before surgery will alter management or outcomes.
3. Interventions to Decrease Risk

Stratify patients as low, moderate, high, and very high risk for the development of postoperative DVT and PE, and implement appropriate VTE prophylaxis strategies.  

3.1 Take measures to prevent VTE in all surgical patients and choose a specific regimen based on risk stratification (low, moderate, high, or very high risk).  

**Recommendations**
- Consider both drug and mechanical measures in prescribing prophylactic regimens for all patients undergoing surgery.
- Base the choice of VTE prophylaxis on risk factors associated with the procedure, patient comorbidities, and bleeding risk.
- Closely monitor perioperative patients for complications of VTE prophylaxis.
- Determine the appropriate duration of VTE prophylaxis.
- See table [VTE Prophylaxis Regimens by Surgical Procedure](#).

**Evidence**
- A 2012 guideline from the American College of Chest Physicians provides evidence-based guidelines for the assessment of risk and the use of VTE prophylaxis (1).
- See table [VTE Prophylaxis Regimens by Surgical Procedure](#) for detailed references.

**Rationale**
- DVT and PE are common causes of morbidity and mortality in surgical patients.
- Incidence of DVT and PE are dependent on the surgical patient and patient risk factors.
- Mechanical and drug measures have been shown to be effective in preventing VTE.
- With careful monitoring, the benefits of VTE prophylaxis outweigh the risks for complications.

3.2 Recommend that pneumatic compression devices and elastic stockings be worn continuously during and after the surgical procedure.  

**Recommendations**
- When indicated, apply intermittent pneumatic compression sleeves, foot pumps, or gradient elastic stockings before surgery or as soon as the patient becomes nonambulatory.
- Consider using these devices for the prevention of VTE during and after any surgical procedure, though in high- and very high-risk groups, combine them with drug prophylaxis.
- Place pneumatic compression devices on the patient in the preoperative area and ensure that they are worn continuously during surgery.
- Maintain IPC devices and elastic stockings until the risk for bleeding is low, at which time conversion to drug therapy can be accomplished.
- Alternatively, continue non-drug devices until the patient is ambulatory and the risk for VTE has been decreased.

**Evidence**
- A prospective randomized trial of 177 patients undergoing total hip or knee arthroplasty compared the use of above- and below-knee graded compression stockings in the prevention of DVT. Patients who had total hip replacement and wore below-knee stockings had a significantly higher rate of proximal or major calf DVT. This pattern was reversed in patients with total knee replacement who developed a significantly lower rate of proximal or major calf DVT with below-knee stockings (17).
- Eighty-nine consecutive patients undergoing total hip or knee replacement were enrolled in a trial evaluating the efficacy of graded compression stockings. The pressure gradient generated by the
stockings was evaluated in all patients, and 98% of the stockings failed to produce the ideal pressure gradient. A reversed gradient was observed in 54%, and this resulted in a higher incidence of DVT. The overall rate of DVT was 16.7% by venography (18).

- Investigators compared the effectiveness of calf-thigh sequential pneumatic compression devices with the effectiveness of plantar venous IPC devices (foot pumps) in the prevention of VTE after major trauma. Thirteen patients randomly assigned to foot pumps (21%) and 4 patients randomly assigned to calf-thigh sequential pneumatic compression (6.5%) developed DVT. Seven of 13 patients with DVT after prophylaxis with foot pumps had bilateral DVT, whereas all 4 patients with DVT after prophylaxis with calf-thigh sequential pneumatic compression had unilateral DVT. (19).

- A clinical trial used a step-wise approach to VTE prophylaxis in patients at risk for bleeding complications. Other clinical trial data are limited. The double-blind trial of 150 patients undergoing craniotomy for brain tumor randomly assigned patients to enoxaparin, 40 mg sc qd, or heparin, 5000 IU sc q12h. All patients wore graduated compression stockings plus IPC sleeves and had compression ultrasound to evaluate VTE at the time of discharge. The overall rate of asymptomatic VTE was 9.3% (20).

Rationale

- Pneumatic compression devices and elastic stockings reduce stasis and may prevent thrombus formation.

- Elastic stockings have proven efficacy in many low-risk surgical groups (e.g., general and gynecologic surgeries) and in some moderate-risk groups (e.g., urologic surgery); however, for most moderate- and all high- and very high-risk groups they are not adequate prophylaxis alone and should be replaced by or combined with drug methods or IPC devices.

- Elastic stockings can increase the risk for DVT if not fitted properly, due to the formation of reverse gradients, as has been shown in hip and knee arthroplasty patients.

- For pneumatic compression devices, both calf-thigh sleeves and foot pumps have proven efficacy, primarily in orthopedic populations; they are considered adequate prophylaxis for low- and moderate-risk surgical groups, and for high-risk gynecologic surgery patients.

- Pneumatic compression devices, both calf-thigh sleeves and foot pumps, should not be used as the sole method of prophylaxis in patients without a high risk for bleeding who are undergoing major orthopedic surgery, including elective hip replacement, elective knee replacement, and hip fracture surgery.

- At any point where the risks for bleeding outweigh the benefits of drug prophylaxis, it is recommended that non-drug modalities be used until the bleeding risk is minimized.

Comments

- IPC devices are contraindicated in patients with known acute DVT.

- All mechanical prophylaxis devices must be properly fitted, and careful attention paid to patient adherence nearly 24 hours a day.

- Most studies show that adherence with mechanical prophylaxis devices is poor.

- Direct comparisons between calf-thigh sleeves and foot pumps are limited. In one study comparing their efficacy in trauma patients, the calf-thigh devices were superior to prevent DVT (19).

- In hospitalized high-risk patients requiring high-risk surgery and who have not received adequate or any DVT and PE prophylaxis, it may be reasonable to perform lower extremity noninvasive venous CUS testing before applying IPC devices. Although there are no clinical trial data or cost-effective analyses to support this, the theoretical risk is that the compression device may dislodge a preexisting thrombus if one is present. This would only be reasonable if the pretest probability of DVT were relatively high based on symptoms and physical examination, because Doppler ultrasound has a lower sensitivity in asymptomatic patients than in patients with symptoms suggesting DVT.

- The use of non-drug interventions is based on physician choice for clinical situations where the postoperative risk for bleeding associated with the use of drug agents is considered to be high. For example, radical prostatectomy is a procedure with high risk for VTE and the postoperative bleeding is significant. The use of IPC sleeves intra- and postoperatively for 24 to 48 hours before
adding LMWH or UFH would be appropriate. This multimodal approach might also be effective in neurosurgery.

- IPC devices may limit mobilization because the patient cannot ambulate with them on.
- The original studies used IPC devices continually for up to 7 straight days except for bathroom and bathing. The median number of hours in most studies was about 15 hours per day. With the shortening of hospital stay and early mobilization, the use of IPC becomes limited.

### 3.3 Consider placement of an inferior vena caval filter only in patients with a VTE event less than 1 to 3 months prior to surgery in whom anticoagulation will be interrupted in the perioperative period.

#### Recommendations

- Consider placement of an IVC filter in patients at very high risk for a fatal PE, such as patients who have experienced a VTE in the last 3 months and especially if the VTE was in the last month.
- Do not otherwise recommend prophylactic IVC filters in high-risk groups (e.g., neurosurgery, orthopedic joint surgery, gynecologic or oncologic surgery).
- If the indication for an IVC filter is less than 1 month, consider the placement of a temporary retrievable filter such as the Günther Tulip® or Celect™ (Cook Inc., Bloomington, IN), Tempofilter® (B. Braun Celsa, Chasseneuil Cedex, France) or OPTEASE® (Cordis, Johnson & Johnson, Bridgewater, NJ).

#### Evidence

- A cohort study of patients receiving a retrievable IVC filter found that among 95 patients receiving filters, retrieval was attempted in 58 and was successful in 56 (96.6%). Among the patients in whom retrieval was not attempted, 18 died and 14 had filters after 12 month follow-up. Of note, no filters in the study were placed for surgical prophylaxis (21).
- A study of 27 patients with retrievable filters observed that retrieval was successful in all 21 patients in whom it was attempted (22).
- A study determined the 1-year cumulative incidence of rehospitalization for VTE among patients with VTE treated with a vena cava filter compared with the incidence in a control population with VTE. Insertion of a vena cava filter was not associated with a significant reduction in the 1-year incidence of rehospitalization for PE. Use of a filter was associated with a higher incidence of rehospitalization for VTE (23).
- Accepted indications for IVC filters include a recent proximal DVT plus an absolute contraindication to anticoagulation or life-threatening hemorrhage on anticoagulation and failure of adequate anticoagulation (24). Prophylactic placement, even in high-risk surgical groups, is not recommended.
- A multicenter study evaluated the Tempofilter, designed to be implanted for up to 6 weeks. A total of 66 patients were enrolled in the study with a mean duration of implantation of 29.9 days. There were no PEs during the implantation period. Filter migration occurred in 7.5% of patients (25).
- A collected Canadian Registry of Günther Tulip Retrievable Filters showed a broad range of utility; it can be used as a permanent filter or retrieved after implantation periods of 15 days and possibly longer. Indications for retrieval require further study, as does the maximum implantation time (26).

#### Rationale

- Use of IVC filters might prevent fatal PE in patients at very high risk for VTE.
- No randomized prospective trials exist of preoperative prophylactic filter placement.

#### Comments

- This approach to management could also be used in patients with multiple VTE events despite anticoagulation or patients who develop DVT or PE after short periods off anticoagulation.
3.4 Consider beginning prophylactic anticoagulants before surgery with UFH or LMWH. 

**Recommendations**
- Consider using UFH, 5000 IU sc, 2 hours before surgery, then every 8 to 12 hours postoperatively, or LMWH, 2 hours before surgery sc, in a dose depending upon the specific agent chosen.
- Alternatively, consider using warfarin, 5 mg po the evening before surgery, then adjust the dose postoperatively to achieve an INR of 2 to 3.

**Evidence**
- A meta-analysis of studies from 1984 to 1991 compared LMWH with UFH for VTE prophylaxis in general and for orthopedic surgery. There was no improvement in the benefit-to-risk ratio for LMWH compared with UFH. In orthopedic surgery the absolute risk reduction for VTE was significant for LMWH vs. UFH (27).
- The American Society of Regional Anesthesia and Pain Medicine has recommendations for the use of anticoagulation with epidural and spinal anesthesia (28).
- A review discusses the use of LMWH and regional anesthesia (29).

**Rationale**
- UFH use before surgery reduces the risk for thrombus formation during surgery.
- Preoperative warfarin administration reduces the risk for thrombus formation during surgery.

**Comments**
- Dosing warfarin the night before surgery has given way to the postoperative dosing schedule because of the higher use of neuraxial anesthesia and the potential risk for epidural hematoma. Warfarin is the most commonly used method of VTE prophylaxis reported by orthopedic surgeons. Also, it can be effectively used for 4 to 6 weeks into the postoperative period to reduce out-of-hospital VTE events.

3.5 Assure that all postoperative patients receive VTE prophylaxis unless contraindicated. 

**Recommendations**
- Use LMWH, heparin or fondaparinux for VTE prophylaxis in most eligible postoperative patients if not already begun preoperatively.
  - Administer enoxaparin, 40 mg sc qd or 30 mg sc q12h, beginning 12 to 24 hours postoperatively.
  - Administer dalteparin, 5000 IU sc q12h, beginning 12 to 24 hours postoperatively.
  - Administer fondaparinux, 2.5 mg sc, 6 hours postoperatively followed by once daily.
  - Maintain all prophylactic regimens for the duration of the patient's hospitalization.
  - In orthopedic surgery, maintain prophylaxis for at least 10 days, and consider continuing prophylaxis for up to 35 days.
  - Consider use of non-drug modalities until LMWH is initiated.
- In patients having hip or knee replacement, neurosurgery, or major abdominal or pelvic surgery, administer warfarin to reach a target INR of 1.8 to 3, or one of the following LMWH regimens:
  - Enoxaparin, 40 mg sc once daily
  - Dalteparin, 2500 U/d for abdominal surgery; 5000 U/d for high-risk patients
  - Danaparoid, 750 U sc q12h
  - Ardeparin, 50 U/kg sc q12h
- In patients undergoing hip or knee replacement, consider primary prophylaxis with rivaroxaban, 10 mg/d.
- Consider using fondaparinux as an alternative for VTE prophylaxis in orthopedic patients in the postoperative period.
Consider administering fondaparinux as first-line prophylaxis in patients undergoing orthopedic procedures.

Because fondaparinux is renally excreted, do not use it in patients with creatinine clearance <30 mL/min and in patients over age 75.

See table VTE Prophylaxis Regimens by Surgical Procedure.

Evidence

- In a systematic review of the relative efficacy and safety of the three LMWH regimens used to prevent VTE after total hip replacement, there was no convincing evidence that starting prophylaxis preoperatively is associated with a lower incidence of VTE than starting postoperatively. Perioperative regimens may lower the risk for postoperative thrombosis, but this positive effect is offset by an increase in postoperative major bleeding (30).
- A systematic review and meta-analysis demonstrated that among patients undergoing total hip or knee replacement, extended-duration prophylaxis (for 30 to 42 days) significantly reduces the frequency of symptomatic VTE. The reduction in risk is equivalent to about 20 symptomatic events per 1000 patients treated (31).
- A 2012 guideline from the American College of Chest Physicians recommends heparin, LMWH, or fondaparinux for prophylaxis of standard-risk surgical patients (1).
- A 2012 guideline from the American College of Chest Physicians recommends extending the prophylaxis up to 35 days in patients undergoing elective total hip replacement and hip fracture surgery, and suggests considering extending prophylaxis up to 35 days in patients undergoing elective total knee replacement (1).
- In patients undergoing elective hip replacement surgery, fondaparinux, 2.5 mg qd, was at least as effective as enoxaparin, 30 mg bid, in reducing the risk for VTE (32).
- In patients undergoing elective major knee surgery, postoperative prophylaxis with fondaparinux, 2.5 mg qd, was significantly more effective in preventing DVT than enoxaparin, 30 mg bid (33).
- In patients undergoing surgery for hip fracture, fondaparinux was more effective than enoxaparin in preventing VTE and was equally as safe (34).
- In a meta-analysis of four randomized trials, fondaparinux significantly reduced the incidence of VTE by day 11 (182 of 2682 = 6.8%) compared with enoxaparin (371 of 2703 = 13.7%) (OR, 0.552 [CI, 0.458 to 0.631; P<0.001]). Fondaparinux did not lower the rate of symptomatic VTE. This beneficial effect was consistent across all types of surgery and all subgroups. Major bleeding occurred more frequently in the fondaparinux-treated group, with number needed to harm of 100 (P=0.008) (35).

Rationale

- Some clinical trials initiated LMWH preoperatively, whereas others have initiated postoperatively.
- In a review of these approaches, there was no significant benefit noted in preoperative initiation, and bleeding was increased.
- This strategy prevents thrombus propagation after surgery.

Comments

- Of note, the daily use of LMWH (e.g., enoxaparin, 40 mg qd) is effective for most conditions and is more convenient and considerably less costly than every-12-hour dosing.
- LMWH with neuraxial anesthesia can be associated with spinal hematomas if the timing of dosing is not carefully monitored. Initiating LMWH postoperatively is a reasonable approach.
- Fondaparinux, a pentasaccharide, has a half-life of 17 to 21 hours, which is considerably longer than most LMWHs (4 to 8 hours) and has no reversibility with protamine, whereas enoxaparin and dalteparin are partially reversed with protamine.
- Rivaroxaban and dabigatran are undergoing FDA approval for VTE prophylaxis following total hip and knee replacement surgery. In several studies, rivaroxaban and dabigatran were found to be at least as effective in preventing VTE as enoxaparin, without an increase in major bleeding following total hip and knee replacement surgery (36; 37; 38; 39; 40).
3.6 Consider administering extended prophylaxis for 5 weeks following major orthopedic surgery or 4 weeks following high-risk general surgery to reduce the incidence of clinically important VTE.

Recommendations

- Consider extending prophylaxis up to 35 days following major orthopedic surgery; prophylaxis agents include warfarin adjusted to maintain an INR of 2 to 3 or LMWH.
- Consider extending prophylaxis up to 28 days in high-risk general surgery patients who have undergone major cancer-related surgery or have previously had VTE; prophylaxis agents include UFH or LMWH.

Evidence

- In a meta-analysis of patients undergoing total hip or knee replacement, extended duration prophylaxis significantly reduced the frequency of symptomatic VTE. The reduction in risk is equivalent to about 20 symptomatic events per 1000 patients treated (31).
- A subsequent meta-analysis found that these observed reductions in symptomatic VTE events were overestimated. Authors studied the absolute risk reduction of symptomatic VTE after discharge from hospital in controlled studies that avoided the potential bias of over-diagnosis. The absolute reduction in symptomatic VTE attributed to extended prophylaxis in some studies and meta-analysis did not reach significance (41).
- The American Society of Clinical Oncology guidelines for VTE prophylaxis and treatment in patients with cancer recommends that patients undergoing major surgical intervention should be considered for pharmacologic thromboprophylaxis unless contraindicated because of a high risk for bleeding or active bleeding. Prophylaxis should be continued for at least 7 to 10 days postoperatively. Prolonged prophylaxis for up to 4 weeks may be considered in patients undergoing major cancer-related surgery with other high-risk factors such as a previous history of VTE, residual malignant disease after surgery, and obesity (42).
- A 2012 guideline from the American College of Chest Physicians recommends continuing prophylaxis for 28 days in high-risk patients, including patients with cancer-related surgery, or patients with a history of previous VTE who are undergoing major general surgical procedures (1).

Rationale

- Clinical trials that have shown a benefit of out-of-hospital prophylaxis have primarily used venographic or Doppler ultrasound-proven DVT as the primary endpoint, and most have not been powered to detect a difference in symptomatic VTE.
- Some patients are still at high risk after discharge, and out-of-hospital prophylaxis may be indicated.

Comments

- It is critical to emphasize that all patients should have at least 7 to 10 days of prophylaxis initially.
- Posthospitalization prophylaxis should be considered in all patients, and the decision based upon the perceived VTE risk. For example, a patient after a total joint replacement who is going for inpatient rehabilitation and is not ambulatory at the time of discharge would warrant extended prophylaxis.
- Prolonged out-of-hospital treatment with elastic stockings, aspirin, or both has not been studied, but these methods are often used in clinical practice.

3.7 Understand the approach to reversing prophylactic anticoagulants in patients with postoperative bleeding.

Recommendations

- For patients on UFH:
  - Use protamine to reverse the anticoagulant activity of UFH if necessary.
Note that 1 mg of protamine reverses 90 IU of bovine lung derived-heparin sodium, 115 mg of porcine intestinal mucosa-derived heparin sodium, and 100 IU of porcine intestinal mucosa-derived heparin calcium.

If bleeding is life-threatening, administer protamine iv slowly over 10 to 30 minutes at a dose of 1 mg for every 100 IU of UFH, to a maximum of 100 mg.

Reduce the dose of protamine by 50% if the UFH was administered more than 30 minutes to 1 hour before protamine, and reduce to 25% if more than 2 hours have elapsed since the heparin dose.

Note that if UFH was administered sc, a portion of the dose of protamine (25 to 50 mg) may be administered initially iv over 10 to 30 minutes with the remainder of the dose administered as an iv infusion over 8 to 16 hours.

For patients on LMWH:

- Start with protamine, 1 mg/enoxaparin, 1 mg.
- If bleeding continues, administer a second dose of 0.5 mg protamine/100 anti-Xa units LMWH.
- Note that smaller doses are needed beyond 8 hours after LMWH administration.

For patients on warfarin use a reversal protocol based on INR value and clinical status:

- INR >3 and <5:
  - Omit or reduce next warfarin dose and resume at a lower dose
- INR 5 to 9, no bleeding:
  - Omit next 1 to 2 warfarin doses and resume at a lower dose
  - Vitamin K, 2.5 mg po × 1 may be given
- INR 10 to 19, no clinically significant bleeding:
  - Stop warfarin
  - Administer vitamin K, 5 mg po × 1
  - INR should decrease in 24 to 48 hours
  - Recheck INR and repeat, if needed
- INR >19, serious bleeding, requires urgent surgery, or major warfarin overdose:
  - Stop warfarin
  - Administer vitamin K, 10 mg in 50 mL normal saline iv over at least 30 minutes, 10 to 20 mL/kg
  - Unless INR is >19, serious bleeding occurs, the patient requires urgent surgery, or there is a major warfarin overdose, do not use iv vitamin K rather than oral vitamin K

Evidence

- A review describes the pharmacokinetics and pharmacodynamics of UFH and LMWH (43).
- The pharmacokinetics and pharmacodynamics of UFH and LMWH were reviewed. The recommendation for reversal of LMWH is consistent with package labeling but is clinically untested. Within 8 hours of administering LMWH, the dose of protamine is 1 mg/100 anti-Xa units for enoxaparin (1 mg = approximately 100 anti-Xa units) (43).
- The American College of Chest Physicians provides evidence-based guidelines on the pharmacology and management of the vitamin K antagonists (44).
- In a retrospective cohort study of 105 patients, intravenous phytonadione (vitamin K) proved to be safe and effective for semi-urgent correction of long-term oral anticoagulation therapy before surgery. In small doses, it does not prolong the patient's time to return to therapeutic anticoagulation (45).
- In a randomized trial of 51 patients, oral vitamin K lowered INR more rapidly than subcutaneous vitamin K in asymptomatic patients with supratherapeutic INR values while receiving warfarin (46).
- An uncontrolled case series evaluated the efficacy and safety of human recombinant factor VIIa concentrated in persons requiring reversal of the effects of warfarin. The study concluded that recombinant factor VIIa was safe, rapid, and effective in correcting critically prolonged INR and can avert or reverse bleeding associated with warfarin anticoagulation (47).

Rationale
• Protamine reverses the effects of UFH in a patient for whom bleeding complications require rapid decrease in the anticoagulation effect of heparin.
• Reverse the effect of LMWH in cases of life-threatening bleeding or if the patient requires invasive surgery and the surgeon is uncomfortable performing the procedure in the presence of the anticoagulant effect of LMWH.
• Vitamin K reverses the effect of warfarin when this is necessary to treat bleeding complications from anticoagulation.
• There are known risks to the use of iv vitamin K, including hypersensitivity reaction.

Comments
• Protamine may be associated with hypotension and bradycardia if administered too quickly or with hypersensitivity reactions in patients with a history of an allergy to fish or who have been sensitized to protamine.
• The decision to use protamine for reversing LMWH will also depend upon the timing of the last LMWH dose and how many half-lives of the drug have passed since dosing.
• Human factor VIIa concentrate has been used to reverse excessive anticoagulation with warfarin, but due to the extreme cost of this product and the fact that it is not proven to be superior to vitamin K, routine use of this product is not recommended for the reversal of warfarin.
• There may be difficulty in achievement of full anticoagulation for up to 1 week after administration of vitamin K, but this is minimized if smaller doses are given.
4. Patient Education

Advise patients about the risk for developing VTE in the postoperative period, and inform them of approaches to prevent it.

4.1 Inform patients of the incidence of VTE and the associated risks and benefits of VTE prophylaxis relevant to the planned procedure.

Recommendations

- Inform patients undergoing surgery about patient- and procedure-related risk for DVT.
- Explain benefits and harms of prophylactic regimens.
- Encourage early ambulation and adherence to use of mechanical devices to prevent VTE when they are required.

Evidence

- Consensus.

Rationale

- Educating patients may allow them to be more informed about their care and enable their cooperation in preventing postoperative complications of VTE.

Comments

- Patient education may be facilitated through the use of a specially created patient brochure for the procedure and by outlining the methods of prophylaxis with their associated risks and benefits.

4.2 Educate patients about the symptoms and signs of DVT and PE.

Recommendations

- Inform patients about the important symptoms and signs of DVT, including pain in the leg both at rest and with walking, increased warmth, redness of the skin, and leg swelling.
- Tell patients of the important symptoms and signs of PE including shortness of breath, pain on deep breathing, cough, bloody sputum, dizziness, feeling anxious, lightheadedness, or fainting.
- Instruct patients to report these alarm symptoms to their primary care provider, surgeon, or emergency department for further evaluation.

Evidence

- Consensus.

Rationale

- Educating patients may allow them to be more informed about their care and provide prompt recognition of complications after discharge.
5. Follow-up

Evaluate patients promptly who report signs or symptoms of DVT or PE and follow patients receiving extended DVT prophylaxis.

5.1 Understand the appropriate evaluation of suspected DVT in postoperative patients.

Recommendations
- When DVT is suspected, obtain a Doppler ultrasound as the noninvasive test of choice.
- Do not routinely obtain a Doppler ultrasound in asymptomatic postoperative patients with no clinical suspicion of DVT.
- See module Deep Venous Thrombosis.

Evidence
- A meta-analysis evaluated the accuracy of ultrasound screening for asymptomatic DVT in patients after orthopedic surgery. Ultrasound was found to have only a moderate sensitivity (62%) compared with venography when used to screen for DVT in asymptomatic patients after orthopedic surgery (48).

Rationale
- Noninvasive testing will prompt further investigation and treatment if indicated.

5.2 Understand the appropriate evaluation of suspected PE in postoperative patients.

Recommendations
- Perform lower extremity Doppler ultrasound, ventilation perfusion lung scanning, or spiral CT if postoperative PE is suspected.
- If DVT is identified, anticoagulation can be initiated without further evaluation for PE.
- See module Pulmonary Embolism.

Evidence
- A retrospective cohort study evaluated the safety of withholding anticoagulation in patients with suspected acute PE, negative CT results, and no other evidence of VTE, and found that the rate of DVT or PE over a 3-month follow-up period was 0.5% (CI, 0.5% to 1.0%). The number of postoperative patients included in the study is not clear (49).
- Investigators sought to determine the efficacy and safety of spiral CT of the pulmonary arteries as the primary diagnostic test in patients with suspected PE and found that it can be used safely as the primary diagnostic test to exclude PE. Serial CUS has limited additional value (50).

Rationale
- Shortness of breath with minimal activity or at rest should prompt further investigation by noninvasive testing.
- Spiral CT has replaced perfusion lung scanning in most institutions.
- It has been proven to be safe to withhold anticoagulation in patients with negative spiral CT scan results to exclude PE.

Comments
- It is recommended to discuss radiologic testing with the radiologist in order to obtain the optimal test based upon the clinical scenario.

5.3 Follow patients receiving extended VTE prophylaxis to assess for bleeding and other complications.
Recommendations
- Check INR in patients on warfarin every 1 to 2 weeks until therapeutic, then at least monthly, and assess for bleeding complications.
  - Goal INR is 2 to 3.
- Follow patients on LMWH for bleeding complications and difficulty with injections.
- Follow patients on UFH for bleeding complications and difficulty with injections and consider checking a platelet count in patients with borderline levels.
- Check CBC only if significant bleeding or thrombocytopenia is suspected.

Evidence
- Consensus

Rationale
- VTE prophylaxis carries bleeding risk.
- Heparin can cause thrombocytopenia.
Venous Thromboembolism Prophylaxis in the Surgical Patient

References


Glossary

ABG
arterial blood gas

APTT
activated partial thromboplastin time

ATIII
antithrombin III

bid
twice daily

BMI
body mass index

CBC
Complete blood count

CI
confidence interval

CNS
central nervous system

CT
computed tomography

CUS
compression ultrasonography

DVT
deep venous thrombosis

ECG
electrocardiography

HF
heart failure

iv
intravenous

IBD
inflammatory bowel disease

INR
international normalized ratio

IPC
intermittent pneumatic compression

IVC
inferior vena cava

LMWH
low-molecular-weight heparin

OCP
oral contraceptive pill

po
orally

PCP
primary care physician
Venous Thromboembolism Prophylaxis in the Surgical Patient

PE
pulmonary embolism

PT
prothrombin time

qd
every day

RR
risk ratio

sc
subcutaneous

SLE
systemic lupus erythematosus

UFH
unfractionated heparin

VTE
venous thromboembolism
### Tables

**Surgical Risk Stratification and Associated VTE Incidence**

<table>
<thead>
<tr>
<th>Patient Risk</th>
<th>Risk Factor Stratification</th>
<th>VTE Incidence Without Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Minor surgery in patients under age 40 with no additional risk factors</td>
<td>Calf vein DVT: 2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proximal vein DVT: 0.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical PE: 0.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatal PE: 0.002%</td>
</tr>
<tr>
<td>Moderate</td>
<td>Nonmajor surgery in patients aged 40-60 with no clinical risk factors</td>
<td>Calf vein DVT: 10%-20%</td>
</tr>
<tr>
<td></td>
<td>Minor surgery lasting &lt;30 minutes in patients with clinical risk factors</td>
<td>Proximal DVT: 2%-4%</td>
</tr>
<tr>
<td></td>
<td>Major surgery in patients under age 40 with no clinical risk factors</td>
<td>Clinical PE: 1%-2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatal PE: 0.1%-0.4%</td>
</tr>
<tr>
<td>High</td>
<td>Nonmajor surgery in patients over age 60 or with clinical risk factors</td>
<td>Calf vein DVT: 20%-40%</td>
</tr>
<tr>
<td></td>
<td>Major surgery in patients over age 40 or with clinical risk factors</td>
<td>Proximal DVT: 4%-8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical PE: 2%-4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatal PE: 0.4%-1%</td>
</tr>
<tr>
<td>Very high</td>
<td>Major surgery in patients over age 40 with history of VTE, cancer, or certain hypercoagulable states</td>
<td>Calf vein DVT: 40%-80%</td>
</tr>
<tr>
<td></td>
<td>Hip or knee arthroplasty</td>
<td>Proximal DVT: 10%-20%</td>
</tr>
<tr>
<td></td>
<td>Hip fracture surgery</td>
<td>Clinical PE: 4%-10%</td>
</tr>
<tr>
<td></td>
<td>Major trauma</td>
<td>Fatal PE: 0.2%-5%</td>
</tr>
<tr>
<td></td>
<td>Spinal cord injury</td>
<td></td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
## Risk Factors Associated with VTE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>The incidence of postoperative VTE increases about 20% per decade with a leveling off after age 70. The odds ratio increases from 1.6 between ages 41-45 to 3.9 at ages 81-85 (3).</td>
<td>Exponential increase in risk with increasing age. Etiology is likely multifactorial, including changes in vascular, hematologic, and cardiac systems as well as immobility.</td>
</tr>
<tr>
<td><strong>Previous VTE</strong></td>
<td>The odds ratio of 6.2 (CI, 5.5-7.0) for previous VTE makes this the most powerful risk factor for postoperative VTE (3).</td>
<td>Three- to four-fold higher risk. May be related to the underlying etiology for the initial thrombosis or the patient may have developed chronic venous insufficiency with the increased risk for stasis due to damaged valves or varicose veins.</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>In one study, malignant neoplasm accounted for almost one fifth of all cases of VTE in the community (5). Cancer diagnosed at the same time as or within 1 year after an episode of VTE is associated with an advanced stage of cancer and a poor prognosis (51). Malignancy was associated with an almost 1.7-fold greater risk for developing VTE after surgery (3).</td>
<td>Two-fold higher risk. Specific malignancies have a greater disposition to thrombotic events (e.g., adenocarcinoma, breast, prostate, pancreatic, ovarian cancers) than others (e.g., skin, laryngeal). Chemotherapy may be an added risk in this patient population. Because of the added risk for multiple risk factors, previous VTE and malignancy place the patient at significant risk for VTE and should receive extended prophylaxis after a surgical procedure. Although no clinical studies have been specifically performed in this patient population, extrapolation from other studies suggests a benefit.</td>
</tr>
<tr>
<td><strong>Institutionalization (recent hospitalization or nursing home residence)</strong></td>
<td>Factors associated with institutionalization independently account for more than 50% of all cases of VTE in the community. Other recognized risk factors such as malignant neoplasm, trauma, HF, central venous catheter or pacemaker placement, neurologic disease with extremity paresis, and superficial vein thrombosis account for 25%. The remaining 25% are idiopathic (5). In a cohort of 18,661 nursing home patients over a mean of 8 months, the incidence of VTE was 1.3 events per 100 person-years of observation (4).</td>
<td>Up to eight-fold increased risk. Institutionalization may be a proxy for other comorbidities known to increase risk for VTE.</td>
</tr>
<tr>
<td><strong>Prolonged immobilization</strong></td>
<td>In a community population, recent hospitalization for surgery accounted for 24% of VTE events, recent hospitalization for medical illness accounted for 22%, and nursing home residence for 13%. All of these factors are associated with immobilization (3). In subjects traveling at least 8 hours, up to 10% developed a symptomatic calf DVT. Prolonged travel is just one form of transient immobilization (52).</td>
<td>Increased with duration of immobilization. Immobilization results in stasis, which increases the incidence of VTE.</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>In a study of the incidence of symptomatic VTE after different elective or urgent surgical procedures, Asian or Pacific Islanders were shown to have a two-fold lower incidence of postoperative VTE than other ethnic groups (3).</td>
<td>Asians have two- to three-fold lower risk. The etiology for ethnic variations in VTE rates is unknown.</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>Among patients who underwent total hip arthroplasty, a BMI of 25 or greater was associated with the risk for subsequent hospitalization for VTE (53). In a study of risk factors for VTE among middle-aged men, waist circumference &gt;100 cm (P=0.004) and smoking &gt;15 cigarettes per day (P=0.02) were independent risk factors for VTE during follow-up. No associations with surgery were made, but it supports the general belief that obesity is an independent risk factor for VTE.</td>
<td>Increased with increasing BMI. Risk attributable to obesity may be due to inflammation, reduced fibrinolysis, or associated immobilization.</td>
</tr>
</tbody>
</table>
### Venous Thromboembolism Prophylaxis in the Surgical Patient

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Risk Factors</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogen use</strong></td>
<td>A group of 2763 postmenopausal women with coronary heart disease but no previous history of VTE was randomly assigned to either estrogen and progestin or placebo. During an average of 4.1 years, estrogen use was associated with a 2.7-fold higher risk of VTE compared with placebo (95% CI, 1.2-5.4). There was a predominance of VTE during the postpartum period (66%), and DVT occurred more frequently in the left leg (77%) (9).</td>
<td>Estrogens affect the coagulation cascade in both pro- and antithrombotic ways, with a net prothrombotic effect. This predisposes patients to thrombosis in the postoperative period.</td>
<td></td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>In a hospital-based study of pregnant patients both during pregnancy and in the postpartum period, the cumulative incidence of pregnancy-associated VTE was 1.3 cases per 1000 deliveries (CI, 0.9-1.2). There was a predominance of VTE during the postpartum period (66%), and DVT occurred more frequently in the left leg (77%) (9).</td>
<td>Increased risk. Stasis secondary to decreased venous drainage from the expanding uterus. Hypercoagulability as pregnancy progresses (decreased protein S, increased factor VIII). Surgical patients who are pregnant appear to have a higher risk for VTE than nonpregnant patients, although specific epidemiologic data in surgical patients are lacking.</td>
<td></td>
</tr>
<tr>
<td><strong>Lupus</strong></td>
<td>Patients with lupus have an estimated 6% incidence of thrombophlebitis at some time during their illness and 2% incidence at the onset of the illness (58).</td>
<td>The lifetime incidence of any VTE is higher in lupus patients, and especially in patients with SLE who have the antiphospholipid antibodies.</td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory bowel disease</strong></td>
<td>Among patients with Crohn’s disease in a population-based cohort study, the incidence rate of DVT was 31/10,000 person-years and for PE was 10/10,000 person-years. For ulcerative colitis, the incidence rates were 30/10,000 person-years for DVT and 19.8/10,000 person-years for PE (8).</td>
<td>This may be secondary to an inflammatory process secondary to the underlying IBD. Patients with IBD have a three-fold higher risk for developing DVT or PE.</td>
<td></td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>Investigators randomly assigned 665 medical patients with heart failure or severe respiratory disease to enoxaparin or unfractionated heparin. In the primary efficacy analysis, 451 patients were evaluated. The incidence of VTE was 6.4% with enoxaparin (40 mg sc qd) and 10.4% with unfractionated heparin (5000 IU sc q8h). This study highlights the fact that even with prophylaxis VTE is still a frequent occurrence in patients with HF (55).</td>
<td>Risk associated with severity of HF. Stasis and immobility secondary to cardiac dysfunction are likely mechanisms for an increased risk due to HF. This risk factor has been documented in medically ill hospitalized patients and would be similarly applicable to the surgical patient. No direct evidence for the additive risk for HF in surgical patients exists.</td>
<td></td>
</tr>
<tr>
<td><strong>Nephrotic syndrome</strong></td>
<td>Children with nephrotic syndrome compared with controls had lower ATIII levels, higher levels of protein C, and similar protein S levels. Higher fibrinogen and cholesterol levels were also found in nephrotic patients. Sample size was too small to make definitive statements about the causes leading to VTE (56). In a study of nephrotic patients, ATIII levels were depressed. There was no association between nephrotic syndrome, protein S levels, and VTE (57).</td>
<td>Reductions in ATIII, and possibly protein C and S, have been reported in patients with nephrotic syndrome.</td>
<td></td>
</tr>
<tr>
<td><strong>Trauma</strong></td>
<td>In a prospective study of patients after major trauma, DVT was found in 65 of the 129 patients (50%) with major injuries involving the face, chest, or abdomen; in 49 of the 98 patients (54%) with major head injuries; in 41 of the 66 with spinal injuries (62%); and in 126 of the 182 with lower extremity orthopedic injuries (69%). Thrombi were detected in 61 of the 100 patients with pelvic fractures (61%), in 59 of the 74 with femoral fractures (80%), and in 66 of the 86 with tibial fractures (77%) (2).</td>
<td>Increase related to location and extent of injury, especially pelvis, hip, and legs. Direct endothelial injury is the most likely etiology, with subsequent immobilization playing an important role.</td>
<td></td>
</tr>
</tbody>
</table>
### Venous Thromboembolism Prophylaxis in the Surgical Patient

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Evidence</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicose veins</td>
<td>No epidemiologic evidence exists to support this widely held opinion</td>
<td></td>
<td>Stasis in the varicose veins is the presumed risk factor</td>
</tr>
<tr>
<td>Indwelling central venous catheters</td>
<td>Two kinds of catheter-related thrombi may develop: sleeve thrombi, developing on the outside of intravascular catheters, and occlusive DVT. The prevalence of PE in patients with upper extremity thrombosis is close to that observed with lower extremity thrombosis. Cancer patients have a higher risk for developing a catheter-related thrombus than patients without cancer.</td>
<td>In a meta-analysis, current estrogen use was associated with an increased risk for VTE (RR, 2.14 [CI, 1.64-2.81]).</td>
<td>Intimal injury with associated stasis may lead to the increased risk. This risk is particularly high in cancer patients who require central venous catheters.</td>
</tr>
<tr>
<td>Acquired or congenital thrombophilias</td>
<td>A review outlined the mechanisms of thrombosis and gives general guidelines for treatment and prophylaxis for these patients, although not explicitly related to surgery.</td>
<td>Acquired or congenital thrombophilias include factor V Leiden mutation (activated protein C resistance), prothrombin gene mutation 20210, antiphospholipid antibody syndrome, elevated levels of factor VIII, IX, or XI, ATIII deficiency, protein C deficiency, protein S deficiency, homozygous homocystinuria or hyperhomocysteinemia, heparin-induced thrombocytopenia. Although little explicit evidence exists regarding the implications of these risk factors in surgical patients, they should be identified as additional risk factors for VTE.</td>
<td></td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agents</td>
<td>Patients undergoing spine surgery were randomly assigned to epoetin alpha or standard care in an open label study. The incidence of Doppler-detected DVT was 4.7% in the epoetin group and 2.1% in the non-epoetin group, though differences were not statistically significant.</td>
<td>Other patient populations such as those with cancer or chronic kidney disease may be receiving epoetin alpha or darbepoetin alpha agents. This would place them at risk for VTE should they require surgical procedures that also carry high VTE risk.</td>
<td></td>
</tr>
<tr>
<td>Selective estrogen receptor modulators</td>
<td>DVT are recognized complications associated with tamoxifen and raloxifene. The National Surgical Adjunct Breast and Bowel Project study of tamoxifen and raloxifene showed the average annual rates of thromboembolic events were 3.30 per 1000 for tamoxifen and 2.47 per 1000 for raloxifene (RR, 0.75 [95% CI 0.6-0.93]).</td>
<td>The proposed mechanism for the increased thromboembolic risk is a decrease in ATIII levels (12).</td>
<td></td>
</tr>
</tbody>
</table>

ATIII = antithrombin III; BMI = body mass index; CI = confidence interval; DVT = deep venous thrombosis; HF = heart failure; IBD = inflammatory bowel disease; OCP = oral contraceptive pill; PE = pulmonary embolism; qd = every day; RR = risk ratio; sc = subcutaneous; SLE = systemic lupus erythematosus; VTE = venous thromboembolism.

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ATIII = antithrombin III; BMI = body mass index; CI = confidence interval; DVT = deep venous thrombosis; HF = heart failure; IBD = inflammatory bowel disease; OCP = oral contraceptive pill; PE = pulmonary embolism; qd = every day; RR = risk ratio; sc = subcutaneous; SLE = systemic lupus erythematosus; VTE = venous thromboembolism.
# VTE Prophylaxis Regimens by Surgical Procedure

<table>
<thead>
<tr>
<th>General Surgery</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk (A)</strong></td>
<td></td>
</tr>
<tr>
<td>Early ambulation postoperatively (adequate for patients at very low risk)</td>
<td></td>
</tr>
<tr>
<td>IPC sleeves</td>
<td></td>
</tr>
<tr>
<td>Graduated elastic stockings</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate risk (A)</strong></td>
<td></td>
</tr>
<tr>
<td>Graduated elastic stockings</td>
<td></td>
</tr>
<tr>
<td>IPC sleeves (preferable), or</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin, 40 mg sc qd, or</td>
<td></td>
</tr>
<tr>
<td>Dalteparin, 5000 IU sc, or</td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin, 5000 IU sc q12h</td>
<td></td>
</tr>
<tr>
<td><strong>High risk (A)</strong></td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin, 5000 IU sc q8h, or</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin, 40 mg sc qd, or</td>
<td></td>
</tr>
<tr>
<td>Dalteparin, 5000 IU sc qd</td>
<td></td>
</tr>
<tr>
<td><strong>Very high risk (C)</strong></td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin, 5000 IU sc q8h, plus graduated elastic stockings and/or IPC sleeves or</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin, 40 mg sc qd (extended duration), plus graduated elastic stockings and/or IPC sleeves or</td>
<td></td>
</tr>
<tr>
<td>Dalteparin, 5000 IU sc qd (extended duration), plus graduated elastic stockings and/or IPC sleeves</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban, 10 mg po qd</td>
<td></td>
</tr>
</tbody>
</table>

**Comments**

- Intermittent compression sleeves alone are best reserved for patients at high risk for hemorrhage (e.g., trauma patients, patients undergoing procedures with a high incidence of bleeding such as radical prostatectomy, patients with factor deficiencies, craniotomy)

- Graduated elastic stockings and intermittent compression sleeves must be placed before surgery and worn continuously through the intraoperative and postoperative period until ambulatory

- The rate for symptomatic or asymptomatic total VTE in general surgery is ~25% without prophylaxis

**Evidence**

- A consensus-developed article provides guidance based on pooled VTE prophylaxis data on surgical and trauma patients (1; 66)

- Hip fracture patients who were repaired within 2 days of hospitalization and had more than 5 physical or occupational therapy sessions had a shorter length of stay, fewer medical complications, and were more likely to return to the community (67)

- A prospective randomized trial compared intermittent pneumatic calf compression with no treatment in patients undergoing major abdominal surgery. There was no difference in the incidence of VTE between the two groups (68)
In a review of VTE prophylaxis with unfractionated heparin in two specific surgical populations, unfractionated heparin was effective in reducing the incidence of fatal PE and proximal DVT (69).

A meta-analysis of studies from 1984 to 1991 compared LMWH vs. unfractionated heparin for postoperative VTE prophylaxis. Among general surgery patients there was no improvement in the benefit-to-risk ratio for LMWH compared with unfractionated heparin. In orthopedic surgery the absolute risk reduction for VTE was significant for LMWH vs. unfractionated heparin (27).

### Orthopedic Surgery

<table>
<thead>
<tr>
<th>Total hip or knee replacement (A) (treat for at least 10-14 days)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LMWH (preferred)</strong></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin, 30 mg sc q12h or 40 mg sc qd, or</td>
<td></td>
</tr>
<tr>
<td>Dalteparin, 5000 IU sc qd, or</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux, 2.5 mg qd</td>
<td></td>
</tr>
<tr>
<td>Warfarin adjusted to a target INR of 2-3</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 10 mg, po qd&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Apixaban 2.5 mg bid&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110 mg qd&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Unfractionated heparin</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Aspirin (may be less effective than other options)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Adjuvant prophylaxis with IPC (with or without graduated elastic stockings) may provide additional benefit (C)</strong></td>
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</tbody>
</table>

### Hip fracture surgery

<table>
<thead>
<tr>
<th>LMWH</th>
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</thead>
<tbody>
<tr>
<td>Enoxaparin, 30 mg sc q12h (C), or</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux, 2.5 mg qd (A)</td>
<td></td>
</tr>
<tr>
<td><strong>Unfractionated heparin</strong></td>
<td></td>
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<tr>
<td>Warfarin adjusted to a target INR of 2-3</td>
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<tr>
<td>Aspirin (may be less effective than other options)</td>
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</tbody>
</table>

### Extended prophylaxis (A)

<table>
<thead>
<tr>
<th>LMWH (preferred)</th>
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<tbody>
<tr>
<td>Enoxaparin, 40 mg sc qd, or</td>
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<tr>
<td>Dalteparin, 5000 IU sc qd</td>
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<tr>
<td>Warfarin with a goal INR of 2-3</td>
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</tbody>
</table>

### Comments

Dextran or IPC alone are not recommended

Enoxaparin 40 mg qd has not been approved for prophylaxis for total knee replacement, but may be as effective and is less costly than 30 mg q12h.
Venous Thromboembolism Prophylaxis in the Surgical Patient

The risk for VTE extends beyond the hospital stay; extended prophylaxis for 4–6 weeks may reduce the incidence of clinically important VTE events

Without prophylaxis, the rates for symptomatic and asymptomatic VTE in total hip replacement include total DVT, 45%–57%; proximal DVT, 23%–36%; total PE, 0.7%–30%; and fatal PE, 0.1%–0.4%. In total knee replacement rates are total DVT, 40%–84%; proximal DVT, 9%–20%; total PE, 1.8%–7%; and fatal PE, 0.2%–0.7%. In hip fracture patients without prophylaxis, rates are total DVT, 36%–60%; proximal DVT, 17%–36%; total PE, 4.3%–24%; and fatal PE, 3.6%–12.9%

Evidence

The four RECORD trials (36; 37; 38; 70) evaluated the efficacy and safety of rivaroxaban compared with enoxaparin in over 12,000 patients undergoing hip or knee arthroplasty. In the RECORD 1 trial, which included 4541 patients undergoing hip arthroplasty, a 31- to 39-day course of rivaroxaban significantly reduced the total event rate compared with an equal duration of treatment with enoxaparin (1.1% and 3.7%, respectively; P<0.001) (38). In the RECORD 2 trial involving 2509 patients undergoing total hip arthroplasty, a 31- to 39-day course of rivaroxaban significantly reduced the total event rate compared with a 10- to 14-day course of enoxaparin followed by 21 to 25 days of placebo (2.0% and 9.3%, respectively; P<0.0001) (36). The RECORD 3 trial included 2531 patients undergoing knee arthroplasty. A 10- to 14-day course of treatment with rivaroxaban significantly reduced the total event rate compared with an equal duration of treatment with enoxaparin (9.6% and 18.9%, respectively; P=0.001) (37). Finally, in the RECORD 4 trial involving 3148 patients undergoing knee arthroplasty, a 10- to 14-day course of treatment with rivaroxaban significantly reduced the total event rate compared with an equal duration of enoxaparin at the higher 30 mg twice-daily dose (6.9% and 10.1%, respectively; P<0.012) (70). In both the RECORD 2 and 3 trials, rivaroxaban significantly reduced the incidence of symptomatic VTE compared with enoxaparin. Rivaroxaban did not increase major bleeding in any of the trials, but a pooled analysis of the four RECORD trials revealed a small but significant increase in major plus clinically relevant nonmajor bleeding with rivaroxaban.

A pooled analysis compared newer agents (apixaban, rivaroxaban and dabigatran) to enoxaparin for the prevention of VTE after total hip or knee replacement. The study found that rivaroxaban was superior to enoxaparin for the prevention of major VTE with RR, 0.32 [CI, 0.15–0.67] and that apixaban and dabigatran were equivalent. There were no statistically significant differences in major bleeding when comparing newer drugs to enoxaparin (71).

A meta-analysis of four randomized controlled trials found that fondaparinux significantly reduced the incidence of VTE by day 11 (182/2682 = 6.8%) compared with enoxaparin (371/2703 = 13.7%) with an odds ratio of 0 (CI, 0.458–0.631) P<0.001 among patients undergoing major orthopedic surgery. This beneficial effect was consistent across all types of surgery and all subgroups. Major bleeding occurred more frequently in the fondaparinux-treated group (2.7%) than in the enoxaparin group (1.7%) (P=0.008) (35).

Patients undergoing total hip replacement were randomly assigned to enoxaparin vs. placebo. Venography was the endpoint for DVT. Four patients (10.8%) receiving enoxaparin developed DVT, whereas 20 (51.3%) had DVT in the placebo group. The observed major bleeding rate was 4% in both groups. This showed the efficacy of enoxaparin for preventing DVT in this patient group (72).

Investigators compared enoxaparin and warfarin for the prevention of VTE after total hip arthroplasty. Inpatient programs providing treatment with either enoxaparin, 30 mg sc q12h, or adjusted-dose warfarin for a mean of 7.3 days afforded protection against VTE, with overall rates of morbidity and mortality of 3.7% and 0.6%, respectively, and a very low rate of major bleeding complications (0.9%) for 3 months after total hip arthroplasty. During the hospitalization, the patients managed with enoxaparin had a lower rate of VTE than those managed with adjusted-dose warfarin (P=0.008). This benefit was lost after the medication was discontinued, with no difference in the prevalence of VTE between the two groups at 3 months after discharge from hospital (73).

A large, randomized trial compared aspirin, 160 mg, vs. placebo until post-op day 35 in patients undergoing repair of fractured hips. The group assigned to aspirin had lower rates of VTE (DVT or PE), with number needed to treat of 111 after 35 days. Patients were allowed to have other forms of VTE prophylaxis, which makes the results difficult to interpret and apply (74).

In a survey of members in the American Association of Hip and Knee Surgeons, warfarin was the most common drug treatment used for total hip and total knee arthroplasties, followed by IPC sleeves and LMWH (75).

A systematic review and meta-analysis demonstrated that among patients undergoing total hip or knee replacement, extended-duration prophylaxis (for 3042 days) significantly reduced the frequency of VTE. The reduction in risk is equivalent to about 20 symptomatic events per 1000 patients treated (31).

A consecutive patient study of 360 patients undergoing total hip arthroplasty showed that continuing warfarin (0.5%) after discharge for 4 weeks was more effective than placebo (9.4%) in the incidence of VTE (76).

In another study of prolonged out-of-hospital prophylaxis after total hip replacement, the LMWH reviparin was compared with an adjusted dose oral anticoagulant (acenocoumarol). Symptomatic thromboembolic events occurred in 2.3% (15/643) of the reviparin group and 3.3% (21/636) of those receiving acenocoumarol. Major bleeding was reported in 1.4% (9/643) of the reviparin group and 3.7% (24/643) in those on the adjusted-dose oral therapy (77).

In a trial of 89 patients undergoing total hip or knee replacement, investigators evaluated the efficacy of graded compression stockings. All patients had the pressure gradient generated by the compression stockings evaluated, and 98% of the stockings failed to produce the ideal pressure gradient. Reversed gradient was observed in 54%, and this resulted in a higher incidence of DVT. The overall rate of DVT was 16.7% by venography (18).

A consensus-developed article evaluated pooled VTE prophylaxis data on surgical and trauma patients and provides recommendations on VTE prophylaxis (2).

Gynecologic Surgery
## Venous Thromboembolism Prophylaxis in the Surgical Patient

### Low risk (C)

Early mobilization alone is recommended for low-risk patients undergoing short procedures for benign disease.

### Moderate to high risk (surgery for benign disease without additional risk factors)

Unfractionated heparin, 5000 IU sc q12h (A), or

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Enoxaparin, 40 mg sq qd, or Dalteparin, 5000 IU sc qd (C)</th>
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<tbody>
<tr>
<td>IPC (C)</td>
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</table>

### Very high risk (malignancy) (C)

IPC and/or unfractionated heparin, 5000 IU sc q8h, or

<table>
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<tbody>
<tr>
<td>IPC (C)</td>
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</table>

**Comments**

IPC must be placed before surgery and worn continuously through the intraoperative period and postoperative period until ambulatory and may be combined with LMWH.

Extended prophylaxis after discharge may be considered for select very high-risk patients who are not ambulating or are considered to still be at risk for development of VTE. LMWH: Enoxaparin, 40 mg sc qd, dalteparin, 5000 IU sc qd, or warfarin (goal INR 2-3) are suggested but not studied in clinical trials in this patient population.

**Evidence**

LMWH and IPCs appear to be similarly effective in the postoperative prophylaxis of VTE in high-risk gynecologic-oncology patients. The use of LMWH is not associated with an increased risk for bleeding complications when compared with IPCs (78).

### Neurosurgery

**Craniotomy (A)**

IPC alone (preferred except in high-risk patients), or

<table>
<thead>
<tr>
<th>IPC plus</th>
<th>Unfractionated heparin, 5000 IU sc q12h, or enoxaparin, 40 mg sc qd</th>
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</table>

**Spinal cord injury (C)**

| IPC | Enoxaparin, 30 mg sc q12h, or Heparin, 5000 IU sc q8h for 2 weeks, then Enoxaparin, 40 mg sc qd, or warfarin (goal INR 2-3) continued during the rehabilitation phase |

**Comments**

The rate for symptomatic or asymptomatic total VTE in gynecologic surgery is ~16%.

LMWH and IPCs appear to be similarly effective in the postoperative prophylaxis of VTE in high-risk gynecologic-oncology patients. The use of LMWH is not associated with an increased risk for bleeding complications when compared with IPCs (78).

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*Note: The text and tables above are extracted from a medical document discussing venous thromboembolism prophylaxis in surgical patients.*
Continuing prophylaxis into the rehabilitation phase is indicated in spinal cord injury but the duration has not been established.

**Evidence**

A randomized, prospective, double-blind trial of 150 patients undergoing craniotomy for brain tumor compared enoxaparin, 40 mg sc qd, to unfractionated heparin, 5000 IU sc q12h. All patients wore graduated compression stockings plus IPCs and had CUS to evaluate VTE at discharge. The overall rate of asymptomatic VTE was 9.3% and there were no significant differences between the groups (20).

### Urologic Surgery

**Transurethral prostatectomy (C)**

Early ambulation alone is recommended for patients undergoing transurethral prostatectomy or other low-risk procedures.

**Moderate risk (major open urologic procedures, e.g., nephrectomy) (B)**

- Unfractionated heparin, 5000 IU sc q12h
- LMWH
  - Enoxaparin, 40 mg sc qd, or
  - Dalteparin, 5000 IU sc qd
- IPC

**Very high risk (e.g. radical prostatectomy) (C)**

- IPC and or graduated elastic stockings plus
  - Unfractionated heparin, 5000 IU q8h, or
  - Enoxaparin, 40 mg sc qd, or dalteparin, 5000 IU sc qd

**Evidence**

A review of VTE prophylaxis with unfractionated heparin in general, orthopedic, and urologic surgery found that it was effective in reducing the incidence of fatal PE and proximal DVT (69).

In a prospective study of 36 patients undergoing urologic surgery for malignancy, patients received dalteparin for 3-7 days and no clinically evident VTE developed (79).

A consensus-developed article evaluated pooled VTE prophylaxis data on surgical and trauma patients and provides recommendations on VTE prophylaxis (2).

### Major Trauma

**LMWH**

- Enoxaparin, 40 mg sc qd, or
- Dalteparin, 5000 IU sc qd, or
- Unfractionated heparin, 5000 IU q8h

**Patients at high risk for bleeding:**

- Initial IPC and ES followed by
- LMWH when possible (C)

**Comments**
Patients with clinical risk factors for VTE should receive prophylaxis, if possible (A)

Enoxaparin is preferred if no contraindication for use such as intracranial bleeding, incomplete spinal cord injury with paraspinal hematoma, continued uncontrolled bleeding, or coagulopathy

Continue prophylaxis until ambulatory

If VTE risk continues after discharge, consider extended prophylaxis with LMWH or warfarin

Evidence

Among 344 randomly assigned major trauma patients, 136 who received low-dose heparin (5000 IU sc q12h) and 129 who received enoxaparin (30 mg sc q12h) had venograms adequate for analysis. Sixty patients given heparin (44%) developed DVT, and 40 patients given enoxaparin (31%) had DVT. The rates of proximal DVT were 15% and 6%, respectively. LMWH was more effective than low-dose heparin in preventing VTE after major trauma (80)

*Letters in parentheses indicate strength of recommendation:

A = Strength of recommendation based on preponderance of data derived from level 1 studies, which meet all of the evidence criteria for that study type;
B = Strength of recommendation based on preponderance of data derived from level 2 studies, which meet all of the evidence criteria for that study type;
C = Strength of recommendation based on preponderance of data derived from level 3 studies, which meet all of the evidence criteria for that study type.

1US FDA approval for this indication pending

bid = twice daily; CI = confidence interval; CUS = compression ultrasonography; DVT = deep venous thrombosis; INR = international normalized ratio; IPC = intermittent pneumatic compression; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; qd = every day; sc = subcutaneous; VTE = venous thromboembolism.