Abbreviations

THROMBOSIS: TREATMENT AND PREVENTION IN PATIENTS WITH CHRONIC ILLNESSES

Ann K Wittkowsky, Pharm.D., FCCP; and Edith A. Nutescu, Pharm.D.

Reviewed by Todd P. Semla, Pharm.D., FCCP, BCPS; and Daniel M. Witt, Pharm.D., FCCP, BCPS

Learning Objectives

1. Perform venous thromboembolism (VTE) risk assessment for acutely ill medical patients admitted to the hospital.
2. Devise VTE prevention plans for acutely ill medical patients, including selection of the best drug and treatment duration.
3. Based on current evidence, develop a VTE prevention strategy that includes the best anticoagulant drug and initiation time in relation to major orthopedic surgery.
4. Review guidelines for duration of prophylaxis after major orthopedic surgery and be able to identify the appropriate length of therapy in a given patient case.
5. Estimate the VTE risk associated with various hypercoagulable states and the influence of transient risk factors on overall VTE risk.
6. Assess the value of primary prophylaxis in patients with known hypercoagulable conditions.
7. Justify the role of low-molecular-weight heparins (LMWHs) versus unfractionated heparin (UFH) and warfarin for preventing and treating cancer-related thrombosis.
8. Judge the therapeutic benefit versus risks associated with chronic anticoagulation in patients with malignancy.
9. Highlight current controversies in anticoagulating patients with obesity and recommend appropriate management strategies.
10. Design an appropriate dosing and monitoring plan for the use of LMWHs in patients with renal impairment.
11. Distinguish patients who require bridge therapy with injectable anticoagulants from those in whom chronic oral anticoagulation simply can be withheld before interventional or surgical procedures.
12. Develop patient-specific bridge therapy plans.

Introduction

Venous thromboembolic disease represents both a source for and a complication of chronic illness. The reader is referred to relevant textbook chapters, review articles, and primary literature for a thorough background in the pathophysiology of thrombosis, the pharmacology of antithrombotic drugs, the diagnosis of thromboembolic disease, the general treatment and prevention of thrombosis, and the routine management of antithrombotic therapy. This chapter provides details regarding the use of anticoagulation in specific populations and disease states, and highlights contemporary and controversial topics in this field.

Clinicians play a vital role in the prevention and treatment of thrombosis and in the safe and effective use of antithrombotic drugs. Using available evidence, pharmacists should be able to develop care plans for managing thrombosis that follow current guidelines while accounting for patient-specific factors that might alter the choice of drug, dose, or therapy duration while remaining sensitive to cost considerations.

Preventing Venous Thromboembolism in Hospitalized Medically Ill Patients

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in hospitalized patients. It has been estimated that nearly 300,000 cases of VTE occur in the United States annually, with a mortality rate of up to 3.8% for deep vein thrombosis (DVT) and up to 38.9% for pulmonary embolism. Long-term complications of VTE

Abbreviations in this Chapter

CLOT	Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer
CrCl	Creatinine clearance
DVT	Deep vein thrombosis
ELATE	Extended Low-intensity Anticoagulation for Thromboembolism
ENOXACAN	Efficacy and Safety of Enoxaparin Versus Unfractionated Heparin for the Prevention of Deep Vein Thrombosis in Elective Cancer Surgery
ENOXACAN II	Duration of Prophylaxis Against Venous Thromboembolism with Enoxaparin After Surgery for Cancer
ESSENCE	Enoxaparin (low-molecular-weight heparin) Versus Unfractionated Heparin for Unstable Angina and Non-Q-Wave Myocardial Infarction
FRISC	Low-Molecular-Weight Heparin (Fragmin) During Instability in Coronary Artery Disease
INR	International normalized ratio
LDUH	Low-dose unfractionated heparin
LMWH	Low-molecular-weight heparin
PREVENT	Prevention of Recurrent Venous Thromboembolism
PRIME	Prospective Epidemiological Study of Myocardial Infarction
THE-PRINCE	The Thromboembolism-Prevention in Cardiac or Respiratory Disease with Enoxaparin
TIMI-11B	Thrombolysis in Myocardial Infarction
UFH	Unfractionated heparin
VTE	Venous thromboembolism

include recurrent VTE and the post-thrombotic syndrome, which occurs in up to 30% of patients with VTE and is associated with significant pain, lower extremity edema, and leg ulceration from vascular insufficiency.

Venous thromboembolism is common in hospitalized patients, most of whom have one or more risk factor for thrombosis (Table 1-1), and accounts for about 10% of all hospital deaths. Up to 75% of VTE episodes occur in medical patients, in whom the estimated risk of VTE is 10–20%. In addition to associated morbidity and mortality, the development of VTE in hospitalized patients adds to length of stay and increases costs associated with diagnosis and treatment.

Numerous randomized, clinical trials have provided solid evidence that thromboprophylaxis prevents DVT and pulmonary embolism in hospitalized medical patients. The National Quality Forum has included VTE risk assessment among its 30 Safe Hospital Practices, and the Agency for Healthcare Research and Quality has ranked VTE prophylaxis as the number one strategy to improve patient safety in hospitals. Nonetheless, several registries and hospital-based studies have found that VTE prophylaxis is not commonly used in hospitalized medically ill patients.

To improve the rate of prophylaxis, current guidelines from the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy recommend that all hospitalized patients be assessed systematically for VTE risk factors on admission and routinely throughout hospitalization, and that low-dose-unfractionated heparin (LDUH) or low-molecular-weight heparin (LMWH) be used as thromboprophylaxis in "acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors." The rationale for VTE prophylaxis is based on the high prevalence of VTE in hospitalized patients, the adverse consequences associated with the development of VTE, and clear evidence of the efficacy and cost-effectiveness of VTE prophylaxis. Mechanical prophylaxis with graduated compression stockings or intermittent pneumatic compression, although less effective than pharmacological options, is recommended for patients with significant risk factors for bleeding.

Several controversies regarding the frequency of dosing, drug selection, and the duration of therapy are not answered by current guidelines, but can be addressed by evaluating available literature.

The most common method of VTE prophylaxis is the use of LDUH 5000 units by subcutaneous injection. Older studies suggested benefit of LDUH 5000 units subcutaneously given 2 times/day compared with control, but more recent and better designed studies suggest limited or no benefit. A meta-analysis of VTE prophylaxis in surgical patients concluded that 2 times/day LDUH was inferior to 3 times/day administration. These data and additional evidence from comparisons to enoxaparin (see below) have led to the general conclusion that LDUH 5000 units 3 times/day is superior to 2 times/day administration for VTE prophylaxis in hospitalized medically ill patients.

Three randomized, clinical trials found that enoxaparin 40 mg subcutaneously once daily, dalteparin 5000 units subcutaneously once daily, and fondaparinux 2.5 mg subcutaneously once daily reduce the incidence of symptomatic VTE and asymptomatic DVT, assessed by venography or compression ultrasound, by about 50% compared to placebo. In these studies, thromboprophylaxis was continued for a maximum of 14 days, and the relative risk reduction observed at the end of the treatment period persisted at 3 months for enoxaparin and dalteparin, and at

Abbreviations

Table 1-1. Risk Factors for Venous Thromboembolism

Surgery	Trauma (major or lower extremity)
Immobility or paralysis	Cancer therapy (hormonal, chemotherapy, radiotherapy)
Malignancy	Previous VTE
Increasing age	Pregnancy and the post-partum period
Obesity	Smoking
Varicose veins	Central venous catheters
Hormone replacement therapy	Estrogen-containing oral contraceptives
Acute medical illness	Selective estrogen receptor modulators
Heart failure	Respiratory failure
Inflammatory bowel disease	Nephrotic syndrome
Myeloproliferative disorders	Paroxysmal nocturnal hemoglobinuria
Inherited or acquired hypercoagulable conditions	

VTE = venous thromboembolism.

1 month for fondaparinux. The choice of drug among these three options is most often dictated by formulary status, which in turn is frequently driven by cost considerations. Fondaparinux, although the most expensive of these three options, is not associated with heparin-induced thrombocytopenia, an advantage in patients with a history of this disorder. However, fondaparinux is contraindicated in patients with renal impairment, in whom enoxaparin dosing can be adjusted to 30 mg once daily to avoid an increased risk of bleeding associated with drug accumulation.

Perhaps most controversial is when to select one of these newer drugs rather than LDUH. Three times daily LDUH has been compared to enoxaparin 40 mg subcutaneously once daily in hospitalized medically ill patients in two trials, the Prospective Epidemiological Study of Mycocardial Infarction (PRIME) and the Thromboembolism-Prevention in Cardiac or Respiratory Disease with Enoxaparin (THE-PRINCE) study. Neither study found a significant difference in the rate of asymptomatic VTE for either treatment strategy. In patients with heart failure, a very high-risk population, THE PRIME study suggested that enoxaparin was more effective for VTE prevention than LDUH. A third study reached a similar conclusion in stroke patients, another very high-risk population. A recent pooled analysis of data from several trials involving acutely medically ill patients found that in comparison to LDUH 3 times/day, enoxaparin was associated with a lower risk of minor bleeding. In addition, LMWHs are associated with a lower rate of heparin-induced thrombocytopenia, and once daily administration requires less nursing time and may be associated with better patient acceptance than 3 times/day administration. Thus, enoxaparin 40 mg subcutaneously once daily offers some advantages over LDUH 5000 units 3 times/day, despite its higher cost, especially in high-risk patients such as those with heart failure or stroke. To date, neither dalteparin nor fondaparinux have been compared to LDUH for preventing VTE in medical patients.

Although it is common to continue VTE prophylaxis until hospital discharge, a growing body of evidence suggests that VTE risk does not disappear at the time of discharge and that extended prophylaxis may be appropriate for some patients. Venous thromboembolism prophylaxis extended to 30 days has successfully reduced the incidence of VTE in total hip replacement and hip fracture surgery. In medically ill patients, the enoxaparin, dalteparin, and fondaparinux placebo-controlled trials continued treatment for a median of 7 days, 14 days, and 6–14 days, respectively. An ongoing investigation is studying extended prophylaxis with enoxaparin 40 mg subcutaneously once daily or placebo, continued for 28 additional days, after initial prevention with enoxaparin for 10 days. Final results will help clarify the appropriate duration of VTE prophylaxis in hospitalized medically ill patients, which for now is unknown. Cost considerations may drive decisions related to therapy duration, as many third-party payers, including Medicare, will not pay for out-of-hospital injectable drugs.

Preventing VTE in Orthopedic Surgery

Major orthopedic surgery places patients in the highest risk category for VTE. Without active prophylaxis, the incidence of venographically confirmed DVT ranges from 40% to 80% with about 33% of these clots affecting the proximal deep veins. These proximal clots are more likely to embolize and lead to pulmonary embolism, a cause for major clinical concern as about 10% of hospital deaths are attributed to pulmonary embolism. The rate of fatal pulmonary embolism is extremely high (0.1–7.5%) in patients undergoing orthopedic surgery, especially hip fracture surgery.

Because of the high risk of VTE in this patient group, administering routine thromboprophylaxis has been the accepted standard of care for more than 15 years. Current clinical guidelines recommend the use of LMWH, fondaparinux, or warfarin at an international normalized ratio (INR) goal of 2.5 (range of 2–3) as the preferred method of prophylaxis. The use of aspirin and LDUH are not recommended. Mechanical devices as the sole method of prophylaxis also are not recommended, except in patients undergoing hip fracture surgery and where anticoagulant prophylaxis is contraindicated due to the high risk of bleeding. Various clinical questions such as the selection of the best thromboprophylactic drug, timing of initiation of prophylaxis, and the appropriate duration of prophylaxis are

Lechler E, Schramm W, Flosbach CW. Venous thromboembolic risk in non-surgical patients. Epidemiological data and efficacy/safety profile of a low molecular weight heparin (enoxaparin). The PRIME Study Group. Haemostasis 1996;26(suppl 2):49–56.

Kleber FX, Witt C, Vogel G, Koppenhagen K, Schomaker U, Flosbach CW; THE-PRINCE Study Group. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J 2003;145:614–21.

Alikhan R, Cohen AT. A safety analysis of thromboprophylaxis in acute medical illness. Thromb Haemost 2003;89:590–1.

Table 1-2. Pharmacological Prophylaxis Options for Orthopedic Surgery

Procedure	ACCP Recommendation	Additional Considerations for Drug Selection		
		Efficacy	Safety	Convenience
THR	Fondaparinux (1A) LMWH (1A) Warfarin (1A)	Fondaparinux ++ to +++ LMWH ++ Warfarin +	Fondaparinux + to ++ LMWH ++ Warfarin +++	Fondaparinux +++ LMWH ++ to +++ Warfarin +
TKR	Fondaparinux (1A) LMWH (1A) Warfarin (1A)	Fondaparinux +++ LMWH ++ Warfarin +	Fondaparinux + LMWH ++ to +++ Warfarin +++	Fondaparinux +++ LMWH ++ Warfarin +
HFS	Fondaparinux (1A) LMWH (1C+) LDUH (1B) Warfarin (2B)	Fondaparinux +++ LMWH + to ++ LDUH ++ Warfarin + to ++	Fondaparinux ++ LMWH ++ LDUH ++ Warfarin ++	Fondaparinux ++ LMWH +++ LDUH + Warfarin +

The convenience category considered administration, dosing, monitoring, and ease of use for a certain indication. The efficacy and safety categories considered reported differences between the various prophylactic options in the major published clinical trials.
+++ most preferred; + least preferred; ACCP = American College of Chest Physicians; 1A = clear risk-benefit from randomized, controlled trials without important limitations; 1B = clear risk-benefit, randomized, controlled trials with important limitations (inconsistent results, methodological flaws); 1C+ = clear risk-benefit, no randomized, controlled trials but strong randomized, controlled trial results can be unequivocally extrapolated, or overwhelming evidence from observational studies; 2B = unclear risk-benefit, randomized, controlled trials with important limitations (inconsistent results, methodological flaws); HFS = hip fracture surgery; LMWH = low-molecular-weight heparin; LDUH = low-dose unfractionated heparin; THR = total hip replacement; TKR = total knee replacement.

still causes for controversy in determining the proper management of patients undergoing orthopedic surgery.

Pharmacological Options and Comparative Outcomes

Despite some reported differences in efficacy and safety between the various prophylactic options, the Seventh American College of Chest Physicians guidelines do not make specific recommendations as to when a certain drug or class of drugs would be preferred over another. Clinicians often are faced with requests to select a preferred therapeutic option for hospital formularies, prophylaxis protocols or pathways, and in certain specific patient scenarios. A careful review of the literature will aid the clinician in being able to appropriately select certain prophylactic drugs based on the differences in their efficacy and safety profiles, convenience of use, and cost (Table 1-2).

Total Hip Replacement Surgery

The incidence of both asymptomatic and symptomatic VTE is high in patients undergoing total hip replacement, 40–60% and 2–5%, respectively. Fatal pulmonary embolism occurs in about 0.1–2.0% of patients undergoing total hip replacement. Although nonpharmacological prophylaxis methods such as graduated compression stockings, intermittent pneumatic compression, and venous foot pumps have been evaluated, they only provide a modest reduction in VTE rates and are inferior to pharmacological prophylaxis. In addition, assuring proper usage and compliance with these devices is challenging outside of a clinical trial setting.

Various pharmacological prophylactic regimens also have been evaluated for VTE prevention in total hip replacement surgery. Aspirin and LDUH are more effective than placebo; however, they are inferior to other pharmacological options and are therefore not recommended. In the United States, warfarin is the most common method of prophylaxis used in patients undergoing total hip replacement, whereas in Europe, LMWHs are used in the majority of these patients. If warfarin is used, the initial dose should be given the evening before or the evening after surgery, and doses should be titrated to attain an INR goal of 2.5 (range of 2–3). Although lower INR ranges may be advocated by some orthopedic surgeons, these are not supported by well-designed, large, randomized trials. However, some recent evidence from nonrandomized, cohort studies and indirect comparisons with literature cohorts suggests that symptomatic VTE rates in patients who receive lower intensity warfarin (INR = 1.5–2.5) may be comparable to VTE rates in patients receiving LMWH. Despite these limited reports in favor of lower intensity warfarin, at this time the routine use of these lower intensity regimens cannot be recommended until more data from properly designed studies are available. Due to its delayed onset of action, warfarin allows surgical hemostasis to develop and this is why many surgeons feel more comfortable using it over other drugs with a more rapid onset of anticoagulant effect. In addition, warfarin's availability in tablet form and lower acquisition cost make it an attractive alternative to some of the higher cost and more novel anticoagulants such as the LMWHs and fondaparinux. However, the use of warfarin also is plagued by many challenges making its use tedious. Both hospitalized patients and patients discharged to the home setting require well-designed, structured programs for warfarin dosing and monitoring. Health systems that do not have such programs in place should consider alternate prophylactic drugs with a more predictable anticoagulant effect that are less complex to use.

Low-molecular-weight heparins are highly effective and safe in the setting of total hip replacement. Although some initial trials found no difference in efficacy between LMWH and adjusted-dose warfarin, more recent and larger studies have demonstrated a benefit in favor of LMWHs not only

with regard to lower total and proximal DVT rates but also a lower incidence of symptomatic DVT. Pooled results of the major total hip replacement trials comparing LMWH with adjusted-dose warfarin also support lower event rates in LMWH-treated patients. (20.7% vs. 13.7% for all DVT; p=0.0002; and 4.8% vs. 3.4% for proximal DVT; p=0.08). Pooled major bleeding rates were numerically higher in the LMWH group than in the warfarin group (5.3% vs. 3.3%). Major bleeding rates varied in the individual trials, with some showing no difference between the LMWH and warfarin groups, and some showing trends toward higher bleeding complications in patients treated with LMWH. Dalteparin, enoxaparin, and tinzaparin have all been studied for this indication; however, only the first two have labeled indications approved by the Food and Drug Administration.

Fondaparinux, a synthetic factor-Xa inhibitor, also has demonstrated efficacy in patients undergoing total hip replacement compared to enoxaparin in one study. Fondaparinux 2.5 mg/day subcutaneously, initiated 4–8 hours after surgery, was found to be superior to enoxaparin 40 mg/day subcutaneously initiated 12 hours before surgery (overall VTE 4% vs. 9%; p<0.0001; proximal DVT 1% vs. 2%; p=0.002). A second study that used the same fondaparinux regimen found no difference in efficacy compared to a higher dose of enoxaparin 30 mg subcutaneously 2 times/day initiated 12–24 hours after surgery. Major bleeding complications were not significantly different between the two groups, though there was a trend of increased overall bleeding in the fondaparinux group.

The direct thrombin inhibitors, desirudin and melagatran/ximelagatran, also have been compared with LMWHs in patients undergoing total hip replacement with trials showing varied results, depending on the time of initiation and the specific doses of the various drugs. Desirudin is approved by the Food and Drug Administration for this indication but is not yet commercially available; melagatran/ximelagatran are neither indicated nor available in the United States.

These data suggest that LMWHs are more effective than warfarin, and fondaparinux is more effective than LMWH and likely warfarin based on indirect comparison. The efficacy benefit with the LMWHs and fondaparinux come with a trade-off of slightly higher bleeding rates, especially bleeding at the surgery site or wound hematoma. In addition to the efficacy of LMWHs, additional advantages of those and fondaparinux include their predictable anticoagulant effect and no need for dose adjustment and monitoring, providing for somewhat less complex and more convenient prophylactic regimens. Acquisition costs for LMWH and fondaparinux are higher than for warfarin, pharmacoeconomic studies suggest that when overall costs to the health care system are considered, the costs of these therapies are comparable. However, some patients without drug insurance coverage may find it difficult to pay out-of-pocket for these higher cost alternatives. In addition to the convenience of oral administration, its much lower acquisition cost is what still makes warfarin a frequently prescribed prophylactic alternative after major orthopedic surgery. Unlike LMWHs, fondaparinux has not been linked to heparin-induced thrombocytopenia. However, there are several issues that should be considered when using fondaparinux such as its long half-life (about 21 hours), lack of a drug to reverse its anticoagulant effect, and a lack of dosing guidelines in patients with renal impairment and in those with very low body weights. Fondaparinux is contraindicated in the latter two populations. An additional consideration in selecting the best prophylactic drug is the type of anesthesia used during the surgical procedure. Due to their shorter half-lives, LMWHs are easier to manipulate around catheter placement and removal times, whereas there are no data for fondaparinux in patients with indwelling epidural catheters. However, great caution also must be applied with the use of LMWH in patients who receive neuraxial anesthesia. In a 1997 public health advisory, the Food and Drug Administration reported 41 cases of perispinal hematoma in patients who received LMWH around the time of spinal/epidural anesthesia. The package inserts of LMWHs have a "boxed" warning cautioning the use of these drugs in patients undergoing neuraxial anesthesia. Subsequently, the American Society of Regional Anesthesia has developed guidelines for the use of anticoagulants in these patients. These guidelines take into account the half-lives and dosing regimens of various anticoagulants, and recommend catheter placement and removal at times when the various drugs are at trough concentrations. (For a more detailed discussion, the reader is referred to the American Society of Regional Anesthesia Recommendations.)

Total Knee Replacement Surgery

Although total knee replacement patients appear to develop lower rates of proximal DVT and symptomatic VTE, the rate of asymptomatic DVT documented by venography is higher than in patients undergoing total hip replacement. Nonpharmacological options for prophylaxis also have been studied in the setting of total knee replacement. Graduated compression stockings and venous foot pumps provide no or only limited VTE protection and, therefore, are not recommended. Data from a few small studies indicate that intermittent pneumatic compression devices may provide adequate benefit; however, as previously discussed, poor compliance and inappropriate use limits their utility. As in patients undergoing total hip replacement, aspirin and LDUH have limited efficacy and are not recommended. Several studies support the use of adjusted-dose warfarin in total knee replacement; however, despite its reported efficacy, a fairly high (25–50%) residual asymptomatic VTE rate is still documented with its use. Furthermore, the complexity of warfarin administration, as previously discussed, needs to be considered. Several studies support the efficacy and safety of LMWHs for this indication. Pooled DVT rates from six large trials that compared LMWH and warfarin in total knee replacement favor LMWHs (33% vs. 48%, respectively). In fact, the risk reduction attained with LMWH versus warfarin in patients

Hull RD, Pineo GF, Francis C, et al. Low-molecular weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial Investigators. Arch Intern Med 2000;160:2199–207.

undergoing total knee replacement is greater than that attained after total hip replacement. Major bleeding was not higher in the LMWH group; however, wound hematomas may be slightly increased if LMWH is initiated within 12 hours after surgery. Various LMWHs have been studied in the setting of total knee replacement; however, of the three drugs available in the United States, most data are available with enoxaparin and only limited data are available for tinzaparin or dalteparin. Compared to enoxaparin 30 mg subcutaneously 2 times/day initiated 12–24 hours after surgery, fondaparinux 2.5 mg subcutaneously once daily initiated about 6 hours after surgery demonstrated more than a 50% risk reduction in VTE. However, major bleeding was significantly higher in the fondaparinux group, a difference mainly driven by changes in the bleeding index, which takes into account the units of blood transfused and changes in the hemoglobin concentration.

The oral direct thrombin inhibitor ximelagatran also has been compared with adjusted-dose warfarin in three large trials. The efficacy results were dependent on the dose of ximelagatran, with the higher dosage (36 mg) given 2 times/day showing benefit over warfarin. The safety outcomes were similar between the groups. Oral ximelagatran and subcutaneous melagatran (the active metabolite of ximelagatran) are approved in various European countries for short-term prophylaxis after orthopedic surgery; however, the Food and Drug Administration denied approval of the drug indications in the United States due to safety concerns revolving around liver toxicity and with short-term use, a 3-fold higher incidence of acute myocardial infarction and coronary artery disease.

In patients undergoing total knee replacement, LMWHs are more effective than adjusted-dose warfarin (INR goal = 2.5, range of 2–3), and fondaparinux is more effective than LMWH and likely warfarin based on indirect comparison. Again, as in the case of total hip replacement, wound hematoma and bleeding appears to be slightly higher with LMWH compared to warfarin, and with fondaparinux compared to LMWH.

Hip Fracture Surgery

Although patients undergoing surgery for hip fracture are considered to be at a higher risk of VTE and fatal pulmonary embolism than patients undergoing total hip replacement or total knee replacement, to date there are fewer trials evaluating various prophylactic measures in these patients. Data with mechanical prophylactic devices are limited, and these devices should only be considered in patients who are undergoing surgery for hip fracture if anticoagulation is contraindicated. Aspirin alone is not an effective prophylactic measure and it is not recommended. Limited data suggest efficacy in this setting with LDUH (5000 units 3 times/day), LMWH, and adjusted-dose warfarin (goal INR = 2.5; range of 2–3); however, comparative trials between LMWH and warfarin are lacking. To date, the largest and one of the better designed studies in patients undergoing surgery for hip fracture compared fondaparinux (2.5 mg subcutaneously once daily initiated 4–8 hours after surgery) with enoxaparin (40 mg subcutaneously once daily initiated 12–24 hours after surgery). The VTE rates and proximal DVT rates were both significantly reduced in patients treated with fondaparinux compared to enoxaparin (8.3% vs. 19.1%; $p<0.001$; and 0.9% vs. 4.3%; $p<0.001$). Although major bleeding was not different, minor bleeding was higher in the fondaparinux-treated patients.

In patients undergoing hip fracture surgery, based on superior efficacy data, fondaparinux should be considered as the preferred first-line prophylactic drug. Low-molecular-weight heparin and adjusted-dose warfarin (target INR = 2.5, range of 2–3) can serve as alternatives. If the time of surgery is delayed, prophylaxis should be initiated in the preoperative period and short-acting drugs, such as LDUH or LMWH, are preferred as fondaparinux and warfarin (due to their longer half-lives) will take a longer time to wear off.

In summary, the final selection of the appropriate prophylactic regimen for patients undergoing major orthopedic surgery should be based on the balance of efficacy and safety data, convenience of use, and the cost of various alternatives. These decisions are best made at the institutional level with careful consideration of the discussed literature.

Timing of Prophylaxis Initiation

Two additional controversies in patients undergoing orthopedic surgery pertain to preoperative versus postoperative initiation of LMWH prophylaxis and the proper time after surgery that a prophylactic drug should be initiated. Currently, European prophylaxis regimens with LMWH typically are initiated 10–12 hours before surgery. In contrast, in the United States, LMWH is initiated 12–24 hours after surgery. Although previous meta-analysis data suggested that preoperative initiation of LMWH may be more effective than postoperative initiation, more recent trial data found no significant differences in efficacy between two regimens of dalteparin initiated either before or after surgery. There was a nonsignificant trend toward higher bleeding complications with the preoperative regimen. Therefore, initiating LMWH before surgery offers no advantage over initiating after surgery.

It has been suggested that initiating prophylaxis close to surgery time can improve efficacy. When LMWH is initiated in close proximity to surgery (less than 2 hours before or 6–8 hours after), VTE prevention is significantly improved compared to postoperative adjusted-dose warfarin; however, this is offset by an increase in bleeding complications. These observations also have been substantiated by studies conducted with fondaparinux and the direct thrombin inhibitors, melagatran/ximelagatran. Based on a meta-analysis of four large fondaparinux trials in orthopedic surgery, major bleeding was significantly higher

Eriksson BI, Bauer KA, Lassen MR, Turpie AG; Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001;345:1298–304.

Raskob GE, Hirsh J. Controversies in timing of the first dose of anticoagulant prophylaxis against venous thromboembolism after major orthopedic surgery. Chest 2003;124(6 suppl):379S–85S.

when the drug was initiated within 6 hours after surgery (3.2%) versus waiting more than 6 hours (2.1%). Therefore, the gain in efficacy with early postoperative dosing should be balanced with the trade-off on the safety side. In selecting a certain prophylactic drug, the efficacy and safety ratio in context with timing of drug administration needs to be balanced.

Prophylactic Therapy Duration

How long to administer a prophylactic drug after major orthopedic surgery is yet another controversial question. Several studies showed that the risk of VTE can persist for 1–3 months after total hip replacement. The majority of VTEs after major orthopedic surgery are diagnosed after hospital discharge, at an average of 7 days with total knee replacement and 17 days with total hip replacement. Various trials have demonstrated the benefit of both LMWH and adjusted-dose warfarin over placebo for extended prophylaxis (up to 35 days) after orthopedic surgery. Significant reductions in overall and symptomatic VTE rates have been reported with both treatment options with no increase in major bleeding complications with LMWHs. However, an increase in bleeding with vitamin K antagonists was found in one study. Fondaparinux also has demonstrated an 89% relative risk reduction in symptomatic VTE compared with placebo for extended prophylaxis in patients undergoing surgery for hip fracture and showed no difference in bleeding rates. Patients undergoing total hip replacement appear to benefit more (number needed to treat = 62) in preventing symptomatic VTE with extending the prophylaxis period compared to patients undergoing total knee replacement (number needed to treat = 250). The Seventh American College of Chest Physicians guidelines recommend prophylaxis for at least 10 days in patients undergoing total knee replacement, total hip replacement, and hip fracture surgery. However, extended prophylaxis (28–35 days) in patients undergoing total hip replacement and hip fracture surgery is recommended after surgery. Low-molecular-weight heparin, warfarin, and fondaparinux are all acceptable options for extended prophylaxis, but based on current efficacy and safety data, fondaparinux is preferred in hip fracture surgery and a LMWH is preferred in total hip replacement. Warfarin at an INR goal of 2.5 (range of 2–3) could serve as an alternative option to LMWHs; however, major bleeding may be increased with its use. Drug cost is always a major factor to consider when selecting the best drug for out-of-hospital prophylaxis because many insurers such as Medicare will not pay for outpatient injectable therapy.

Table 1-3. Hereditary Hypercoagulable Disorders

Thrombophilia	Prevalence in General Population	Prevalence in Patients with VTE	Relative Risk for VTE
Deficiency states			
Protein C deficiency	0.2%	3%	Heterozygous: moderate Homozygous: highest
Protein S deficiency	Unknown	1–2%	Heterozygous: moderate Homozygous: highest
Antithrombin deficiency	0.02%	1%	Heterozygous: moderate Homozygous: highest
Genetic mutations			
factor V Leiden	4–7%	20%	Heterozygous: low Homozygous: high
Prothrombin gene mutation	2%	6%	Heterozygous: low Homozygous: high
Coagulation factor abnormalities			
Elevated Factor VIII	10%	Unknown	Unknown
Other defects			
Hyperhomocysteinemia	5–10%	10%	Unknown
Dysfibrinogenemia	Unknown	Unknown	Unknown
Antiphospholipid antibodies	2%	5–10%	High

VTE = venous thromboembolism.

Preventing and Treating VTE in Patients with Hypercoagulable Conditions

Patients with hypercoagulable conditions are at increased risk of VTE. Several thrombophilias have been identified, and although these disorders occur rarely in the general population, they may be encountered in patients who present with VTE (Table 1-3). The clinical characteristics of patients with thrombophilia include a known family history of VTE, thrombosis at a young age (younger than 40 years), recurrent or idiopathic thrombosis, thrombosis at unusual sites (hepatic, renal, mesenteric, or cerebral veins), or thrombosis with minimal provocation from additional risk factors, including pregnancy, exogenous estrogen use, or travel-related stasis.

In patients with new-onset VTE who present with these clinical manifestations, it is important to screen for possible hypercoagulable conditions. Screening is costly, and testing is best done before initiating anticoagulant therapy, as the presence of warfarin and heparin can influence the results of some of the tests (Table 1-4). In some cases, testing may be targeted toward the most likely cause of VTE. For example, elderly patients presenting with a first idiopathic VTE are more likely to be diagnosed with an underlying malignancy than with a genetic hypercoagulable disorder. Because factor V Leiden and the prothrombin gene mutation are the most prevalent hypercoagulable conditions, testing for these

Kearon C. Duration of venous thromboembolism prophylaxis after surgery. Chest 2003;124(6 suppl):386S–92S.

Abbreviations

Table 1-4. Hypercoagulability Screening Tests

Test	Cost[a]	Influence of Warfarin	Influence of Heparins
Protein C activity[b]	$54.50	Reduced	None
Protein S activity[c]	$74.25	Reduced	None
Antithrombin concentration[c]	$46.50	None	Reduced
Factor V Leiden DNA screen	$151.50	None	None
Prothrombin DNA Screen	$151.50	None	None
Homocysteine concentration	$56.00	None	None
Antiphospholipid antibody panel[d]	$223.00	None	None

[a]Cost at University of Washington, January 2005.
[b]May be increased in pregnancy or with oral contraceptive use, but rarely outside the normal range.
[c]May be decreased in pregnancy or with oral contraceptive use, but rarely outside the normal range.
[d]Includes anticardiolipin immunoglobulin (Ig) G, IgM, and IgA; lupus inhibitor; and anti-β2 glycoprotein.
DNA = deoxyribonucleic acid.

mutations alone may be appropriate in some situations. Although screening test results will not alter the initial treatment of VTE, the known presence of a hypercoagulable state will impact the therapy duration, the need for future VTE prophylaxis, and the management of asymptomatic family members with suspected disorders.

Therapy Duration in Patients with Hypercoagulable Conditions

Patients with transient risk factors for thrombosis (surgery, trauma, and stasis) typically have a low rate of recurrent VTE compared to patients with persistent risks factors, including hypercoagulable conditions. Numerous observational studies have documented a relatively high rate of thromboembolic recurrence in patients with hypercoagulable conditions and in patients with idiopathic VTE once oral anticoagulation is discontinued. Clinical trials to support these observations typically have been conducted in patients with idiopathic VTE, many of whom are subsequently found to have a hypercoagulable condition. These trials typically have been designed to include a period of routine anticoagulation (3–6 months) followed by randomization to placebo or to continued treatment. Overall, these trials have consistently shown that long-term oral anticoagulation significantly reduces the risk of recurrent VTE in patients with idiopathic thrombosis. However, therapy duration must be balanced against patient-specific risk factors associated with chronic oral anticoagulation.

Current guidelines recommend that patients with a first episode of idiopathic VTE be treated for at least 6–12 months, and be considered for chronic therapy. Similar recommendations are suggested for patients with hypercoagulable conditions. The appropriate treatment duration should be tailored to the relative risk of recurrent VTE. For example, patients with heterozygous factor V Leiden have a relatively low risk of recurrence and, therefore, may be appropriately treated for 6–12 months; patients with homozygous protein C, protein S, or antithrombin deficiencies typically are treated chronically due to the very high risk of recurrent VTE. For patients with antiphospholipid antibody syndrome or who have two or more concurrent hypercoagulable conditions, initial treatment for 12 months is recommended, and chronic therapy is suggested. Finally, chronic therapy is suggested in any patient with a history of recurrent VTE.

Although the benefits of long-term oral anticoagulation in patients with hypercoagulable conditions have been confirmed, the bleeding risk associated with chronic anticoagulation may be unacceptable. Two trials, Prevention of Recurrent Venous Thromboembolism (PREVENT) and Extended Low-intensity Anticoagulation for Thromboembolism (ELATE), were designed to determine whether reducing the goal INR could provide acceptable prevention of recurrent VTE while minimizing the risk of major hemorrhage. In both trials, patients with idiopathic VTE, many of whom were later diagnosed with hypercoagulable conditions, were treated with warfarin to a goal INR of 2–3 for 3 months, and then randomized to one of two experimental arms for long-term treatment. PREVENT showed that continuing warfarin to a goal INR of 1.5–2.0 was more effective than placebo in reducing the risk of recurrent VTE, without increasing the risk of bleeding. But ELATE showed that continuing warfarin at standard intensity was more effective than reduced intensity warfarin, again without a significant increase in the risk of bleeding. Based on the results of these trials, current guidelines recommend that patients with idiopathic thrombosis or hypercoagulable conditions should receive long-term oral anticoagulation at standard intensity.

Primary Prophylaxis in Asymptomatic Carriers

After the diagnosis of a hereditary hypercoagulable condition, it is common for first-degree relatives to be screened for the abnormality, even if they have not had VTE in the past. Whether these asymptomatic carriers should receive anticoagulation as primary prophylaxis to prevent a first event has been controversial. Recent evidence from long-term follow-up of asymptomatic carriers of protein C, protein S, and antithrombin deficiencies and the factor V Leiden suggests that the annualized incidence of spontaneous VTE is comparable to that of noncarriers. In addition, the annualized incidence of a first VTE episode is considerably lower than the risk of bleeding associated with long-term oral anticoagulation. These observations do not support the need for continuous anticoagulant prophylaxis in asymptomatic patients with known hypercoagulable conditions. However, the incidence of VTE increases significantly when asymptomatic carriers undergo surgery,

Ridker PM, Goldhaber SZ, Danielson E, et al; PREVENT Investigators. Long term, low intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003;348:1425–34.

Kearon C, Ginsberg JS, Kovacs MJ, et al. Extended Low-Intensity Anticoagulation for Thrombo-Embolism Investigators. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003;349:631–9.

experience trauma or immobilization, become pregnant, or are exposed to oral contraceptives or hormone replacement therapy. Aggressive prophylaxis is indicated during periods of increased risk.

Oral Contraceptive Use in Patients with Thrombophilia

Oral contraceptive use is associated with an increased risk of VTE. Early oral contraceptive formulations containing more than the equivalent of 50 mcg of ethinyl estradiol and a high progestin content were associated with an increased risk of both venous and arterial thrombosis. The newer third-generation oral contraceptive products with an estrogen content equivalent to less than 50 mcg of ethinyl estradiol and one of the new progestins (gestodene, desogestrel, or norgestimate) also are highly thrombogenic. It has been suggested that second-generation oral contraceptive products, with low estrogen content similar to the third-generation products, but containing older progestins, may have a lower thrombogenic potential.

Oral contraceptive therapy typically should be avoided in women with hypercoagulable conditions. Counseling regarding alternative methods of contraception should be provided due to the high thromboembolic risk of unplanned pregnancy in women with thrombophilia. If oral contraceptive use is the only option for contraception, it should be used in conjunction with therapeutic oral anticoagulation as protection against the development of VTE.

Although oral contraceptive use should be avoided in patients with protein C, protein S, and antithrombin deficiencies, in whom the annualized risk of thrombosis is highest among the thrombophilic states, second-generation oral contraceptive use may be considered in women with factor V Leiden and the prothrombin gene mutation, as these abnormalities are associated with a relatively lower risk of VTE. Women treated in this manner should receive thorough education regarding the signs and symptoms of recurrent (or initial) VTE and instructed to seek immediate medical care should thrombosis be suspected.

Preventing and Treating VTE in Patients with a Malignancy

Malignancy is considered an acquired hypercoagulable condition and thrombosis is a common complication of malignancy. The annual incidence of VTE in patients with cancer is about 0.5%, and is most prevalent in colon, lung, and prostate cancer in men, and breast, lung, and ovarian cancer in women; these tumor types are the most prevalent in the general population. Compared to VTE patients without cancer, patients with cancer-related thrombosis have longer hospital stays and higher rates of recurrent thrombosis, anticoagulant-induced hemorrhage, hospital readmission, and mortality.

Thrombosis may be the first presentation of occult malignancy. In patients with idiopathic thrombosis, nearly 10% are diagnosed with cancer in the subsequent 2 years, and that figure increases to nearly 20% in patients with recurrent idiopathic thrombosis. The pathogenesis of cancer-related thrombosis includes the influences of chemotherapeutic drugs and central venous catheters on vascular endothelial cells, and venous stasis induced by prolonged bed rest and vascular invasion by tumor cells. In addition, numerous tumor cell activities and interactions with other cell types lead to hypercoagulability in patients with cancer (Figure 1-1). This complex pathophysiology may in part explain various observations regarding drug selection, dose, and duration of anticoagulation for preventing and treating cancer-related thrombosis.

VTE Prevention in Malignancy

Meta-analysis of trials comparing LDUH and LMWH in preventing VTE in patients undergoing surgical procedures has found both strategies equally effective and safe in the general population and in a subgroup of patients with cancer. However, according to comparative clinical trials in patients with cancer undergoing surgical procedures, LDUH 5000 units subcutaneously 3 times/day is more effective than if given 2 times/day, and dalteparin 5000 units subcutaneously once daily is more effective than dalteparin 2500 units subcutaneously once daily, without an increase in bleeding complications. In addition, the Efficacy and Safety of Enoxaparin Versus Unfractionated Heparin for the Prevention of Deep Vein Thrombosis in Elective Cancer Surgery (ENOXACAN) study evaluated enoxaparin 40 mg subcutaneously once daily versus LDUH 5000 units subcutaneously 3 times/day in 1115 patients with cancer undergoing abdominal or pelvic surgery. This study found a similar rate of VTE by venogram at 3 months (14.7% vs. 18.2%) and no difference in total bleeding complications (18.7% vs. 17.1%). Thus, it appears that in patients with cancer, 3 times/day of LDUH and once-daily LMWH are equivalent options for VTE prophylaxis. Low-molecular-weight heparins offer advantages over LDUH, as previously discussed, but at higher drug cost. Currently, no studies have been conducted to compare the cost-effectiveness of LMWH versus LDUH in patients with malignancy.

Like VTE prophylaxis in hospitalized medically ill patients, surgical prophylaxis typically is continued until the time of hospital discharge. However, there may be a role for extended prophylaxis in postoperative patients with cancer. In the Duration of Prophylaxis Against Venous Thromboembolism with Enoxaparin After Surgery for Cancer (ENOXACAN II) study, 332 patients with cancer undergoing abdominal or pelvic surgery received VTE prophylaxis with enoxaparin 40 mg subcutaneously once daily for 6–10 days, and were then randomized to continue either placebo or enoxaparin for an additional 3 weeks.

DiCicco M. The prothrombotic state in cancer: pathogenic mechanisms. Crit Rev Oncol Hematol 2004;50:187–96.

Bergqvist D, Agnelli G, Cohen AT, et al; ENOXACAN II Investigators. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002;346:975–80.

Extended prophylaxis reduced the incidence of total VTE by 60% at 1 month (4.8% vs. 12%; p=0.02) and at 3 months (5.5% vs. 13.8%; p=0.01) without a significant increase in bleeding. Current guidelines recommend extended prophylaxis for patients undergoing surgery for cancer.

Because malignancy is a risk factor for VTE, patients with cancer who are admitted to the hospital with acute medical illnesses and are bedridden should receive VTE prophylaxis similar to that of other hospitalized medically ill patients. However, in this population, clinical studies and current guidelines do not address the relative efficacy of 3 times/day LDUH versus LMWH, the role of ambulation on VTE risk while hospitalized, the effect of radiation- or chemotherapy-induced thrombocytopenia on bleeding risk, and the appropriate duration of VTE prophylaxis.

VTE Treatment in Malignancy

Current evidence-based guidelines recommend that patients with VTE be treated with warfarin and concurrent unfractionated heparin (UFH) or LMWH for a minimum of 5 days and until the INR exceeds 2.0. Many meta-analyses have concluded that UFH and LMWH are equally safe and

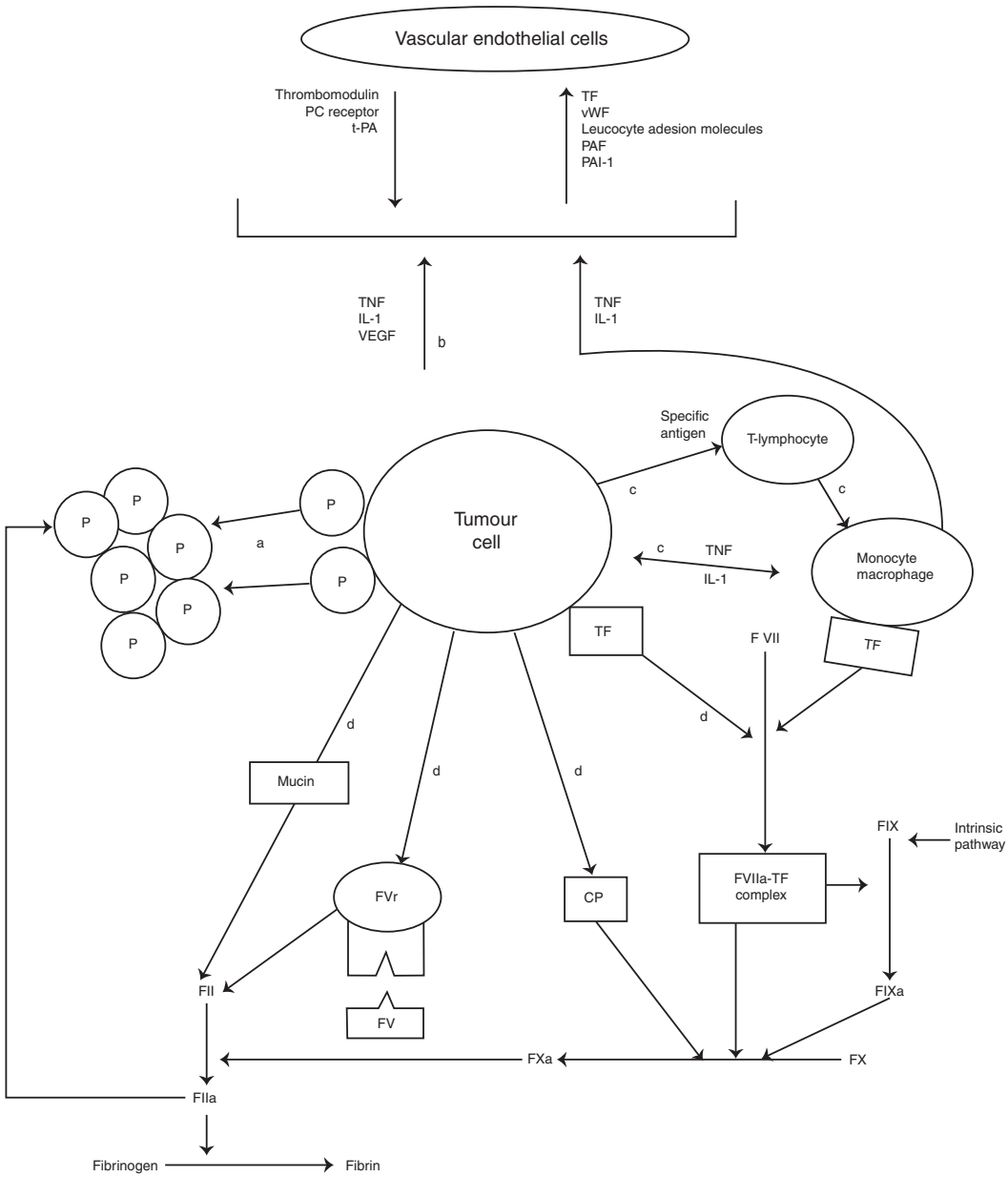

Figure 1-1. The central role of tumor cell in the pathogenesis of the prothrombotic state in patients with cancer.
(a) direct interaction with platelet (P) that induces aggregation; (b) interaction with vascular endothelial cells through tumor necrosis factor (TNF), interleukin-1 (IL-1) and vascular endothelial growth factor (VEGF), which induce the endothelial expression of tissue factor (TF), the release of von Willebrand's factor (vWF), leukocytes adhesion molecules, platelet activating factor (PAF), and plasminogen activator inhibitor type-1 (PAI-1), and down-regulate the expression of thrombomodulin, protein C (PC) receptor, tissue plasminogen activator (t-PA); (c) stimulation of the leukocytes to produce tissue factor (TF) and cytokines (TNF, IL-1); (d) direct expression of procoagulants: tissue factor (TF), cancer procoagulant (CP), factor V receptor (fVr), and mucin. Reprinted with permission from Elsevier. DiCicco M. The prothrombotic state in cancer: pathogenic mechanisms. Crit Rev Oncol Hematol 2004;50:187–96.

effective for the initial treatment of VTE, but that LMWHs may offer a small mortality benefit. In patients with malignancy, this mortality benefit appears to be magnified, according to analysis of subgroups of patients with cancer treated with UFH or LMWH. Thus, LMWH is preferred for the initial management of VTE. Tinzaparin 175 units/kg subcutaneously once daily, dalteparin 200 units/kg subcutaneously once daily, and enoxaparin 1 mg/kg subcutaneously 2 times/day have been effective for initial VTE treatment in patients with cancer. However, enoxaparin 1.5 mg/kg subcutaneously once daily does not appear to offer adequate prevention of recurrent VTE when used for the initial treatment of thrombosis in patients with cancer.

After initial treatment with an injectable anticoagulant, warfarin therapy typically is continued for 3 months to prevent recurrent VTE. In patients with cancer, oral anticoagulation is associated with significant complications compared to patients without malignancy. Higher rates of recurrent VTE and major hemorrhage have been observed, as well as more difficulty maintaining the INR within the therapeutic range, and rates of warfarin-associated emergency department visits and hospital admissions are higher in patients with cancer than in patients without malignancy.

Because of observed difficulties with oral anticoagulation in patients with cancer, several studies have evaluated long-term LMWH versus warfarin for preventing recurrent VTE after initial treatment with LMWH. Results of a small study with enoxaparin 1.5 mg/kg subcutaneously once daily versus warfarin dosed to an INR of 2–3 for 3 months showed that patients treated with enoxaparin had lower rates of major bleeding and a lower mortality rate than patients treated with warfarin. The study was underpowered to reveal statistically significant differences in these outcomes, and there were too few thromboembolic events to see a difference in this outcome. Nonetheless, this early study suggested a benefit of a LMWH over warfarin for treating VTE in patients with cancer. A subgroup analysis of a small group of patients with cancer with VTE randomized to tinzaparin 175 units/kg subcutaneously once daily or warfarin for 3 months found lower rates of recurrent thrombosis and major bleeding in patients treated with LMWH, but no difference in mortality.

The most conclusive data suggesting a benefit of LMWH over warfarin for long-term prevention of VTE in patients with cancer come from the Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) study. This trial randomized 672 patients with cancer who had new VTE to dalteparin 200 units/kg subcutaneously once daily for 30 days followed by 150 units/kg subcutaneously once daily for 5 months, or to dalteparin 200 units/kg subcutaneously once daily for 5–7 days followed by oral anticoagulation with a coumarin derivative (target INR of 2–3) for a total of 6 months. Symptomatic VTE recurred in 9% of patients treated with LMWH compared to 17% treated with oral anticoagulation (p=0.002). This study found no differences in bleeding or in mortality between the two groups, but a subsequent analysis found a significant difference in 12-month mortality in patients with nonmetastatic disease treated with dalteparin versus a coumarin (20% vs. 35%; p=0.03).

These studies indicate that LMWHs are superior to oral anticoagulation in preventing recurrent VTE in patients with cancer, and may provide benefits related to bleeding complications and mortality as well. The pharmacological basis for these benefits may be explained by the anti-inflammatory and antiangiogenic properties exhibited by LMWHs. These drugs also are easier to manage than warfarin because they can be administered at fixed doses without the need for routine coagulation monitoring, and with a relatively short offset of effect if therapy needs to be interrupted for invasive procedures or episodic thrombocytopenia. Platelet count should be monitored every 2–3 days for the first 2 weeks of LMWH therapy to evaluate the occurrence of heparin-induced thrombocytopenia, and periodically thereafter to assess the effects of chemotherapy and radiation. Serum creatinine should be monitored periodically to calculate creatinine clearance, in case adjustments in dosing need to be made because of worsening renal function.

The current American College of Chest Physicians guidelines recommend that patients with cancer-associated thrombosis receive LMWHs for at least 3–6 months. But because malignancy represents a persistent risk factor for thrombosis, it has been suggested that patients with malignancy who have had a first episode of VTE should be chronically anticoagulated to prevent recurrence. Chronic anticoagulation has not been evaluated in patients with malignancy, and LMWH has not been studied beyond 6 months. Even the use of a LMWH for 3–6 months has significant economic implications because of the high drug acquisition cost compared to warfarin, and difficulties with reimbursement. Therefore, the American College of Chest Physicians guidelines suggest that chronic anticoagulation with either warfarin or LMWH should be considered after the first 3–6 months of treatment with LMWH, as long as malignancy is present as a risk factor for thrombosis.

Anticoagulant Use in Special Populations

The variable anticoagulant response and the necessity for frequent monitoring and dose adjustment of traditional anticoagulants such as UFH and warfarin led to the development of novel drugs such as the LMWHs and synthetic factor Xa inhibitors. One of the major advantages of these novel anticoagulants is a wider therapeutic window and a predictable dose response with low interpatient variability allowing for fixed (for prophylaxis) and weight-based (for treatment) dosing without the need of routine

Lee AY, Levine MN, Baker RI, et al. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146–53.

coagulation monitoring. Although these drugs have been successfully administered without monitoring and dose adjustment in large numbers of the general population, this success has not been realized in certain special patient populations where dose-response may be more variable. Unfortunately, specific dose-finding studies with these newer anticoagulants have not been conducted in high-risk patients such as those with obesity and renal impairment. Therefore, specific dosing and monitoring guidelines are lacking for these patient groups. Clinicians often encounter these high-risk patients in clinical practice and are expected to make dosing and management recommendations. Traditional anticoagulants (UFH and warfarin) are usually the preferred first-line prophylactic and treatment options in these high-risk patients as their anticoagulant effect can be monitored and doses adjusted accordingly. However, there are clinical situations in which the traditional drugs are contraindicated or difficult to use and in those instances, the use of more convenient alternatives such as a LMWH can be considered.

Monitoring Considerations

Although routine laboratory monitoring of anticoagulant activity is not necessary for LMWHs, monitoring has been suggested to be useful in special patient circumstances such as obesity and renal impairment. The chromogenic anti-factor Xa assay has been advocated as a possible tool to guide dosing of LMWHs in high-risk patient populations. Although an absolute correlation between anti-factor Xa activity and patient outcomes has not been clearly established, the assay is considered the best biological marker to aid with LMWH dosing and it also is recommended by the College of the American Pathologists and the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy. Monitoring usually is initiated after steady-state is attained or after the third dose. Most available data support the measurement of peak concentrations, which occur about 4 hours after a subcutaneous dose. Trough concentrations are more useful to rule out drug accumulation, such as in patients with renal failure, and the concentrations typically are measured just before the next dose of the LMWH. Although there is some variation in the target concentrations reported in the literature, peak anti-factor Xa concentrations of 0.1–0.4 IU/ml are recommended for preventing VTE. For treating VTE, peak concentrations of 0.4–1.1 IU/ml with twice-daily dosing have been suggested, but a more conservative therapeutic range is from 0.5 to 1.0 IU/ml. With once daily dosing, as higher doses of drug are given per dose, peak concentrations of 1.0–2.0 IU/ml have been suggested, but this is less clear from available literature. Anti-Xa concentrations of greater than 1.0 IU/ml in venous indications and greater than 1.5 IU/ml in arterial indications have been associated with an increased risk of bleeding.

Obesity

Large randomized trials of LMWHs in the treatment of VTE have used weight-based dosing regimens without placing a maximum allowable dose (or "dose cap") in patients who are obese. Even though obese patients were not necessarily excluded, the number of patients who weigh more than 150 kg included in these studies is fairly limited. One of the most controversial questions that clinicians are faced with is whether similar dosing guidelines can be applied for LMWHs in obese and in nonobese patients.

Because it is primarily distributed in the intravascular space, the volume of distribution of LMWHs approximates the plasma volume. As total body weight does not have a linear relationship with plasma volume, theoretically the ideal body weight may be considered a better predictor of LMWH dosing than the total body weight. Pharmacokinetic studies with the various LMWH preparations have addressed this issue and results consistently suggest that anti-factor Xa activity is not significantly increased when these drugs are dosed in patients who are obese based on total body weight. Therefore, pharmacokinetic studies support the use of total body weight for dosing LMWHs, up to 144 kg (body mass index = 48 kg/m^2) for enoxaparin, 190 kg (body mass index = 58 kg/m^2) for dalteparin, and 165 kg (body mass index = 61 kg/m^2) for tinzaparin.

Unfortunately, clinical trials provide limited information on the impact of patient weight on clinical outcomes. The average weights reported in the VTE and acute coronary syndrome clinical studies were 70–80 kg, with the maximum weight reported at 159 kg for patients taking enoxaparin, 128 kg for patients taking dalteparin, and 88 kg for patients taking tinzaparin. A subgroup analysis from two large acute coronary syndrome trials of enoxaparin dosed at 1 mg/kg subcutaneously every 12 hours on total body weight showed a lower incidence of major bleeding in patients who were obese (n=921; body mass index = greater than 30 kg/m^2) compared to patients who were not obese, and the efficacy end point of combined death, myocardial infarction, and urgent revascularization was similar between the two groups.

These data suggest that full treatment doses of enoxaparin can be given safely based on total body weight at least up to a weight of 159 kg. In fact, underdosing LMWHs in patients who are obese with an acute thrombotic event appears to be of more concern than overdosing these drugs. The incidence of recurrent VTE doubled when enoxaparin 1.5 mg/kg subcutaneously once daily was compared to enoxaparin 1 mg/kg subcutaneously 2 times/day in patients who are obese with an acute VTE. Similar data have been reported with dalteparin in a subgroup analysis of the Low-Molecular-Weight Heparin (Fragmin) During Instability in Coronary Artery Disease (FRISC) study that showed a 3-fold higher incidence of recurrent events in patients who are obese versus patients who are not obese when dalteparin was dosed at 120 IU/kg given 2 times/day but "capped" at a maximum of 10,000 IU per dose. These

Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, Antman EM; ESSENCE and TIMI 11B Investigators. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J 2003;146:33–41.

data suggest that giving an appropriate amount of drug based on actual body weight may be the most important consideration in patients who are obese to minimize recurrent events.

For prophylaxis of VTE, the two LMWHs approved in the United States for this indication usually are given in fixed doses: dalteparin at 2500 IU/day or 5000 IU/day, or enoxaparin at 40 mg/day or 30 mg 2 times/day. As total body weight is a good predictor for LMWH dosing, the use of these fixed doses in patients who are obese can result in underdosing, raising the concern of potentially higher VTE rates. Data in surgical and in medical patients suggest a strong inverse relationship between total body weight and anti-factor Xa activity. Retrospective analysis in patients undergoing orthopedic surgery prophylaxed with fixed doses of enoxaparin 40 mg/day demonstrated a significantly higher risk of VTE in patients who are obese (body mass index = greater than 30 kg/m^2) compared to patients who are not obese. Another prospective, nonrandomized study in patients undergoing bariatric surgery showed a reduction in DVT rates with enoxaparin doses of 40 mg 2 times/day versus 30 mg 2 times/day (0.6% vs. 5.4% respectively; p=0.01). As the average patient weights in the major prophylaxis trials ranged from 70 kg to 80 kg, the fixed prophylactic doses of LMWHs used in these studies roughly correspond to 0.5 mg/kg per dose.

In summary, total body weight appears to be a good predictor of dosing LMWHs in patients who are obese. Setting a maximum dose (or dose "capping") is not recommended, and, in fact, it may result in underdosing of these patients with a potential increase in thrombotic complications. Monitoring of anti-factor Xa activity typically is not recommended; however, as only a limited number of patients with total body weight more than 150 kg have been included in the large treatment clinical trials, it is reasonable to consider anti-factor Xa measurement in these patients for the purposes of dose guiding. For prophylaxis, available data suggest that weight-based dosing might be preferable to fixed dosing. In the absence of clear dosing guidelines of LMWHs for prophylaxis in patients who are obese, a 25–30% dose increase or weight-based dosing of 0.5 mg/kg may be considered (Table 1-5).

Table 1-5. Dosing Considerations for LMWHs in Patients with Obesity

General considerations	TBW is recommended for dosing LMWH
Setting dose limits or "capping"	This practice is not recommended due to theoretical concern of underdosing
Dosing based on TBW	Pharmacokinetic studies support this practice for dalteparin, enoxaparin, and tinzaparin up to a maximum weight of 190 kg. Clinical studies support this practice for enoxaparin and tinzaparin up to a maximum weight 159 kg[a]
Anti-Xa monitoring	May be considered in patients greater than 150 kg
Treatment doses	Dalteparin and enoxaparin: 2 times/day dosing regimen preferred over once daily regimens Tinzaparin: Only data with once daily regimen are available
Prophylactic doses	Fixed doses are linked to higher event rates. A 25–30% dose increase or a weight-based dose of 0.5 mg/kg may be reasonable to consider in morbidly obese patients. Anti-factor Xa monitoring may be considered to guide dosing

[a]Dalteparin prescribing information suggests dosing in acute coronary syndromes using TBW (120 IU/kg/dose) but set a maximum allowable dose of 10,000 IU/dose or 20,000 IU/day. This dosing approach is acceptable in patients with average weights, but may be insufficient in obese patients. Higher event rates were observed in obese patients who received capped doses.
LMWH = low-molecular-weight heparin; TBW = total body weight.

Renal Impairment

The elimination of UFH is dose-dependent and due to its ability to be monitored and dose adjusted based on activated partial thromboplastin time test results, its use in patients with renal impairment has not been historically considered a major clinical challenge. In contrast, the LMWHs primarily are cleared through renal excretion and a wealth of pharmacokinetic data suggest that as renal function decreases to a creatinine clearance (CrCl) of less than 30 ml/minute, the half-life of LMWHs increases, and their clearance decreases. Reduced elimination can result in increased drug concentrations and an increased bleeding risk. The actual degree of accumulation is different for the various LMWHs as there are differences in their pharmacological profiles. With short-term use, the degree of enoxaparin accumulation is about 40% in patients with a CrCl of less than 30 ml/minute and 20% in patients with a CrCl of less than 40 ml/minute. In contrast, kinetic data suggest that the clearance of tinzaparin only decreases by about 20% in patients with a CrCl of less than 30 ml/minute. Furthermore, a small clinical study in 30 patients found no drug accumulation with full treatment doses of tinzaparin (175 IU/kg) when used in patients with a CrCl of 20–50 ml/minute. The pharmacokinetic profile of dalteparin is not as well characterized in patients with renal impairment as for enoxaparin and tinzaparin.

Because large clinical trials typically have excluded patients with renal impairment, efficacy and safety outcomes in these patients are not well documented, and clear dosing and monitoring guidelines are lacking. Dosing estimates can be at best inferred from the understanding of kinetic studies with the various LMWHs. With therapeutic unadjusted doses of LMWHs, the risk of bleeding complications increased in patients with renal insufficiency. A retrospective subgroup analysis from the Enoxaparin (low-molecular-weight heparin) Versus Unfractionated Heparin for Unstable Angina and Non-Q-Wave Myocardial Infarction (ESSENCE) and Thrombolysis in Myocardial Infarction (TIMI-11B) studies suggests that when enoxaparin is used at 1 mg/kg 2 times/day doses in patients with a CrCl of less than 30 ml/minute, the risk of bleeding complications significantly increases. However, this relationship also recently has been demonstrated with UFH, despite dose adjustment based on activated partial

Table 1-6. Dosing Considerations for LMWHs in Patients with Renal Impairment

CrCl less than 30 ml/minute	UFH is preferred over LMWH If LMWH is selected, then anti-factor Xa monitoring for dose guiding should be considered Specific Dosing Considerations: Dalteparin: No clear dosing guidelines Enoxaparin: Treatment doses: decrease to 1 mg/kg subcutaneously every 24 hours Prophylactic doses: decrease to 30 mg subcutaneously every 24 hours Tinzaparin: No clear dosing guidelines Accumulation seems to be about 20%
CrCl 30–60 ml/minute	No specific dosing adjustment recommended with initial doses Concern with prolonged use of more than 7–10 days due to potential accumulation Consider anti-factor Xa monitoring with extended use for dose guiding
CrCl greater than 60 ml/minute	No dose adjustment required

CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

thromboplastin time measurements. The data with prophylactic doses of LMWHs in patients with renal insufficiency also indicate a certain degree of drug accumulation; however, mean peak concentrations reported are less than 0.6 IU/ml and trough concentrations are less than 0.2 IU/ml with enoxaparin 40 mg/day.

The Seventh American College of Chest Physicians panel and many other experts still recommend the use of UFH to provide full therapeutic anticoagulation in patients with severe renal impairment (a CrCl of less than 30 ml/minute). If LMWH is used, then monitoring of anti-factor Xa activity should be considered in patients with a CrCl of less than 30 ml/minute or in patients with moderate renal impairment with a CrCl of 30–60 ml/minute if the LMWHs are used for extended periods of more than 7–10 days.

Current manufacturer recommendations for the three LMWHs available in the United States call for caution in dosing in renal insufficiency but specific dosing recommendations currently are only available for enoxaparin. In patients with a CrCl of less than 30 ml/minute, enoxaparin doses should be decreased to 1 mg/kg/day daily for VTE and acute coronary syndrome (treatment indications), and to 30 mg/day for prophylactic indications. As the degree of accumulation appears to be lower with tinzaparin, dosage reductions may not be necessary with short-term use; however, until more data are available, monitoring of anti-factor Xa activity may be prudent. Table 1-6 summarizes guidelines for dosing recommendations in patients with renal impairment.

Managing Anticoagulation in Patients Undergoing Invasive Procedures

Managing patients who require temporary interruption of anticoagulation therapy for surgical or invasive procedures presents a clinical challenge. The risk of thrombosis with discontinuing anticoagulant therapy has to be balanced against the risk of bleeding if anticoagulation is maintained during the procedure. Historically, intravenous UFH has been the gold standard used for anticoagulating or "bridging" patients in the perioperative period. The downside to this approach is the complexity of administration and the cost associated with hospitalizing patients for intravenous heparinization. The emergence of LMWHs provides an alternate and more convenient option to UFH as these drugs can be administered in the outpatient setting and without the need for routine coagulation monitoring. Currently, there is no consensus in the literature and/or clinical practice on the appropriate perioperative management of anticoagulation in patients receiving chronic warfarin therapy. This controversy is mainly spurred by the lack of well-designed studies to evaluate the efficacy and safety of various perioperative anticoagulant management strategies. Nonetheless, due to the potentially devastating effects of some thromboembolic events, some consensus groups and authorities, such as the American College of Chest Physicians and American College of Cardiology/American Heart Association, recommend anticoagulant bridging with either LMWH or UFH in many patients taking warfarin who require interruption of their therapy.

There are two major factors that every clinician needs to consider when coordinating periprocedural/perioperative anticoagulant management: 1) the risk of thromboembolism when anticoagulation therapy is discontinued, and 2) the risk of bleeding associated with the surgery or invasive procedure.

Evaluating Thrombosis Risk

Estimating the daily risk of thromboembolism while patients are off anticoagulant therapy is fairly difficult due to a general lack of data addressing this issue. Moreover, some reports suggest that a rebound hypercoagulable state may develop after abrupt discontinuation of warfarin therapy, further compounding the perioperative thrombotic risk. The estimated annualized thrombosis risk for the most common indications for anticoagulant therapy is summarized in Table 1-7. These include mechanical prosthetic valves, chronic atrial fibrillation, and venous thromboembolism. In addition to the indication for anticoagulant therapy, any additional risk factors predisposing patients to thrombosis and the potential consequences of a thromboembolic event also need to be

Thorevska N, Amoateng-Adjepong Y, Sabahi R, et al. Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin versus enoxaparin. Chest 2004;125:856–63.

considered when evaluating a patient's baseline thrombosis risk in preparation for a procedure.

The estimated incidence of a thromboembolic event in patients with a prosthetic heart valve without anticoagulation therapy is 9–22% per year. This incidence would correspond to an absolute thrombosis risk of 0.17–0.42% for a 6–8-day perioperative period. Although the estimated periprocedure thrombosis risk appears generally low, anecdotal evidence suggests that clots can form quickly (e.g., within 24 hours) in the absence of anticoagulation and in the presence of concurrent risk factors (e.g., major surgery or hypercoagulable conditions). In addition, most practitioners have difficulty calculating the daily or annual thrombosis risk in actual clinical practice; therefore, in these situations, a more conservative management approach may be preferred. Prosthetic mitral valves are more thrombogenic than aortic valves. Patients with a caged-ball valve or two prosthetic heart valves are in the highest risk category for a thromboembolic event.

In patients with atrial fibrillation, a history of stroke or a transient ischemic attack, or the presence of mitral valve stenosis places patients in the highest risk category for a recurrent event, with an annual incidence of 12–15%. The absolute risk of thromboembolism in patients with atrial fibrillation has been estimated at 0.28–0.38% in high-risk patients, 0.06–0.15% in moderate-risk patients, and 0.02–0.04% in low-risk patients.

In patients with VTE, the risk of recurrence is highest if anticoagulation therapy is interrupted within the first few weeks of diagnosis and treatment initiation. The risk of recurrence is higher if concurrent risk factors such as cancer or other hypercoagulable states are present. In addition, patients with idiopathic thrombosis have a 5-fold higher risk for a recurrent event compared with patients whose first event was triggered by a reversible risk factor. Table 1-8 provides a thromboembolic risk stratification scheme for patients with various indications for anticoagulation therapy.

Table 1-7. Annualized Risk of Thrombotic Complications in the Absence of Anticoagulant Therapy for Selected Indications

Condition	Annualized Thrombosis Risk, %
Lone atrial fibrillation	1
Average-risk atrial fibrillation	5
High-risk atrial fibrillation	12
Dual-leaflet (St. Jude) aortic valve prosthesis	10–12
Single-leaflet (Bjork-Shiley) aortic valve prosthesis	23
Dual-leaflet (St. Jude) mitral valve prosthesis	22
Multiple St. Jude prosthesis	91

Adapted with permission from Chest. Ansell JA, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:214S.

Evaluating Bleeding Risk

In addition to evaluating the risk of thrombosis as previously discussed, the risk of bleeding associated with the invasive procedure also has to be addressed to minimize the potential for bleeding complications if anticoagulant bridge therapy is administered. Anticoagulation after the procedure usually is initiated once hemostasis has been

Table 1-8. Recommendations for Risk Stratification and Anticoagulation Management in Patients Requiring Invasive Procedures

Risk of Thromboembolism	Patient Characteristics	Anticoagulant Management
High Risk	Any prosthetic valve plus recent (< 1 month) CVA/TIA Any mitral valve Caged ball or single-leaflet tilting disk aortic valve AF plus recent (< 1 month) CVA/TIA AF plus rheumatic mitral valvular heart disease Recent (< 3 weeks) VTE VTE plus active cancer, or APLA, or chronic cardiac, or pulmonary disease	Bridging anticoagulation strongly recommended pre- and post-procedure Use treatment doses of UFH/LMWH
Moderate Risk	Bileaflet tilting disk aortic valve and ≥ 2 RF[a] Chronic AF plus ≥ 2 RF[a] VTE < 6 months VTE occurring with previous interruption of warfarin therapy	Bridging anticoagulation should be considered/recommended pre- and post-procedure Use treatment or prophylactic doses of UFH/LMWH
Low Risk	Bileaflet tilting disk aortic valve and < 2 RF[a] Chronic AF plus < 2 RF[a] VTE > 6 months	Bridging anticoagulation optional Use prophylactic doses of UFH/LMWH Postoperative prophylaxis if procedure itself increases thrombosis risk

[a]Stroke risk factors: atrial fibrillation, previous stroke, transient ischemic attack or systemic embolism, left ventricular dysfunction, age greater than 75 years, hypertension, diabetes mellitus.
AF = atrial fibrillation; APLA = antiphospholipid antibody; CVA = cerebrovascular accident; LMWH = low-molecular-weight heparin; RF = risk factors; TIA = transient ischemic attack; UFH = unfractionated heparin; VTE = venous thromboembolism.
Adapted with permission from Elsevier. Douketis JD. Peri-operative anticoagulation management in patients who are receiving oral anticoagulant therapy: a practical guide for clinicians. Thromb Res 2003;108:3–13.

achieved. The assessment of hemostasis usually is evaluated by a series of subjective assessments such as bleeding at the surgery site and clinical features suggesting major bleeding. In most patients, hemostasis should be attained within 24–48 hours if hemostatic function was normal before surgery. However, there are certain surgical procedures that can cause a higher incidence of postoperative bleeding, including neurosurgical procedures, prostatectomy, bladder surgery, certain ophthalmologic procedures, renal biopsy, and bowel polypectomy. In the case of procedures with a high risk of bleeding, full-dose anticoagulation should be delayed for 48–72 hours after surgery, and lower prophylactic doses may be initiated once hemostasis has been achieved 24–48 hours after surgery.

Interruption of anticoagulant therapy is not recommended in uncomplicated dental procedures. The use of local measures such as tranexamic acid or aminocaproic acid mouthwash has been advocated to prevent bleeding complications in these situations.

Clinical and Practical Considerations in Designing a Bridge Therapy Plan

In preparation for a surgical procedure that is associated with a moderate to high bleeding risk, concurrent antiplatelet or anticoagulant therapy should be discontinued before the procedure to ensure normal hemostasis during surgery and to minimize bleeding complications. Antiplatelet drugs should be held at least 7 days before surgery. As a general guideline, warfarin should be discontinued 4–5 days before surgery when the INR goal is 2–3 or 5–6 days before surgery when the INR goal is 2.5–3.5 provided that the actual INRs are maintained within these goal ranges. However, there are several additional factors, including the INR level, the age of the patient, the daily or weekly warfarin dose, and the response to any history of withholding anticoagulant therapy for previous procedures, that clinicians should consider when determining what the best time frame to discontinue warfarin is before the planned procedure. If the INR is elevated above the desired goal range in the 1–2 weeks before the procedure, the INR will take longer to correct and the opposite is true for INRs that are below the desired goal range. Similarly, elderly patients may take a longer time for the warfarin to wear off; thus, a longer time frame is needed when planning the number of days to stop warfarin before the procedure. Patients taking low daily or weekly warfarin doses also require a longer time for the INR to return to baseline, whereas patients requiring high warfarin doses may have the anticoagulant effect of warfarin wear off more quickly. In addition, any history of stopping warfarin for previous procedures needs to be considered, as this information will help better plan the actual discontinuation date of the drug based on past patient response patterns.

International normalized ratio testing usually is performed at least 1 week before the procedure, but also the day before surgery to ensure that it is near normal (usually less than 1.4). If the INR is greater than 1.5 on the day before surgery, small doses of oral vitamin K (1–2.5 mg) will help lower the INR in 24 hours or by the time of surgery.

To date, several retrospective and prospective, cohort studies have indicated that LMWH can be used in bridging therapy and can serve as a suitable alternative to UFH, as it is at least as effective and more cost-effective. In addition, a recent systematic review also supports the use of LMWH as a feasible alternative to UFH for bridging therapy. The Seventh American College of Chest Physicians conference guidelines give recommendations for patient management, including both LMWH and UFH as appropriate periprocedure anticoagulant options. Specifically, in patients at low risk of thrombosis, no anticoagulant bridging therapy is recommended, unless the procedure itself increases the risk of thrombosis. In that case, a postoperative prophylactic anticoagulant regimen should be considered. In patients at moderate risk of thrombosis, preoperative and postoperative bridging anticoagulation is recommended using prophylactic doses. Some experts suggest treatment doses of anticoagulation as an alternative; most data from the available published studies would support the higher dose approach as actual trial data with prophylactic doses are limited. In patients at high risk of thrombosis, both pre- and postoperative bridging is recommended with full anticoagulant treatment doses (Table 1-8).

When bridging therapy with a LMWH is required, it usually is initiated 2 days after discontinuation of warfarin therapy, when the INR is expected to fall below the lower limit of the therapeutic range. The last dose of LMWH typically is given 12–24 hours before surgery, depending on whether a dosing regimen of 1 or 2 times/day is used. The time of the surgery is an important factor to consider when determining the timing of the last LMWH dose before the procedure. As the half-lives of the various LMWHs range between 3.5 and 4.5 hours, it may take an average of 17.5–22.5 hours for complete elimination of the anticoagulant effect. If an evening LMWH dose is administered before an early morning procedure, some residual anticoagulant effect will most likely be present, which can be problematic, especially in procedures with moderate to high bleeding risk. Therefore, in procedures with a high bleeding risk, and in patients with renal impairment in whom complete elimination of anti-factor Xa activity might not be achieved by the end of the 12-hour dosing interval, the last LMWH dose should be given 24 hours before surgery to eliminate the potential of any residual anticoagulant effect. Low-molecular-weight heparin usually is resumed after surgery once hemostasis is achieved. In addition, the bleeding risk of the procedure also is considered in timing the reinitiation of LMWH after surgery. In procedures with a high risk of bleeding, LMWH typically is initiated 24–48 hours after surgery at lower prophylactic doses, such as enoxaparin 40 mg/day or

Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized perprocedural anticoagulation regimen. Arch Intern Med 2004;164:1319–26.

Spyropoulos AC, Jenkins P, Bornikova L. A disease management protocol for outpatient perioperative bridge therapy with enoxaparin in patients requiring temporary interruption of long-term oral anticoagulation. Pharmacotherapy 2004;24:649–58.

Dunn AS, Turpie AG. Perioperative management of patients receiving oral anticoagulants: a systematic review. Arch Intern Med 2003;163:901–8.

dalteparin 5000 IU/day. In these cases, therapeutic doses of LMWH (such as enoxaparin 1 mg/kg subcutaneously every 12 hours or dalteparin 100 IU/kg subcutaneously every 12 hours) are best avoided for 48–72 hours after surgery. In surgeries with a low or moderate risk of bleeding, prophylactic dose LMWH is resumed on the evening of or the evening after surgery and subsequent doses can then be increased to a full therapeutic regimen if tolerated by the patient. Warfarin usually is reinitiated at the patient's usual maintenance dose on the evening after surgery, as it has a delayed onset of effect and it poses no immediate bleeding risk in proximity to surgery. A common alternative is to initiate a slightly higher warfarin dose for the first 2–3 days after the procedure, then resume the patient's regular maintenance dose. This method allows for reaching therapeutic INRs more quickly; because the patient's maintenance dose is already known, it is not perceived to predispose patients to over-anticoagulation to the same extent as when warfarin is being initiated in patients naïve to the drug. Low-molecular-weight heparin is continued until the INR reaches the lower limit of the therapeutic range and it is then discontinued. Table 1-9 provides a sample patient management algorithm for perioperative anticoagulation.

Table 1-9. Sample Perioperative Anticoagulation Patient Management Algorithm

Days Relative to Surgery	Anticoagulation Management
-10 to -7	Assess thrombosis and bleeding risk Determine appropriate bridging plan
-7	Stop aspirin or other antiplatelet therapy
-6 or -5	Stop Warfarin[a]; INR testing
-4 or -3	Start LMWH[b]
-2	LMWH
-1	LMWH; Last dose given 12–24 hours before surgery; INR and CBC count testing
0 = Surgery	Resume warfarin[c] at usual maintenance dose on evening of procedure
+ 1	Resume LMWH[d] Warfarin
+2 to +3	LMWH[d] Warfarin INR and CBC testing
+4 to +5	LMWH Warfarin INR and CBC testing
≥ +6	Stop LMWH once INR is therapeutic

[a]Warfarin stopped on day -5 if INR target is 2.0–3.0 or day -6 if INR target is 2.5–3.5.
[b]LMWH is initiated 2 days (36–48 hours) after warfarin is discontinued.
[c]Prophylactic dose LMWH may also be resumed in low bleeding risk procedures.
[d]Full (treatment) doses of LMWH can be resumed on days 1, 2, or 3 once hemostasis is adequate.
CBC = complete blood cell; INR = international normalized ratio; LMWH = low-molecular-weight heparin.
Adapted with permission from Elsevier. Douketis JD. Perioperative anticoagulation management in patients who are receiving oral anticoagulant therapy: A practical guide for clinicians. Thromb Res 2003;108:3–13.

Low-molecular-weight heparins are the preferred anticoagulant option for perioperative bridging in most patients because they allow outpatient administration and are more convenient to use. If UFH is used, then patients typically are hospitalized 3–4 days before and 3–4 days after the procedure for intravenous UFH administration and to optimize dosing. If UFH is given intravenously, the infusion typically is stopped 4–6 hours before the procedure to allow the activated partial thromboplastin time to return to normal. After the procedure, the UFH infusion is reinitiated after hemostasis is achieved and the risk of bleeding is minimized. When reinitiating UFH after the procedure, a loading dose typically is not recommended, especially after moderate to high bleeding risk procedures. Alternatively, outpatient treatment doses of subcutaneous UFH given 2 times/day can be used; however, mid-interval activated partial thromboplastin time monitoring is required with this approach and dosing, and attaining target activated partial thromboplastin time over such a short time course is fairly difficult. If this approach is selected, then the last dose of subcutaneous UFH typically is administered 12–24 hours before surgery and again reinitiated once hemostasis is achieved after the surgery as in the case of LMWHs.

In summary, the best periprocedure bridging approach for each patient is determined by balancing the risk of thrombosis, risk of bleeding, and the overall cost of therapy.

Conclusion

Venous thromboembolism is a major cause of morbidity and mortality in patients with chronic illness. Pharmacists play a vital role in the safe and effective use of antithrombotic drugs used for the prevention and treatment of VTE. Despite recent advances in the use of various anticoagulants to the prevent and treatment of thrombosis, many controversial areas still remain in daily clinical practice. This chapter has summarized contemporary issues of treating thrombosis in patients with chronic illnesses and highlighted various practice controversies in specific populations and disease states. Emphasis has been placed on patients who are medically ill, undergoing orthopedic surgery, with hypercoagulable conditions, malignancy, obesity, renal insufficiency, and patients undergoing invasive procedures. Based on available evidence, pharmacists should be able to design patient care plans to for thrombosis management that follow current practice guidelines, but also account for patient-specific circumstances.

Annotated Bibliography

1. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(suppl 3):339S–400S.

The American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy convenes every 2–3 years to review all available evidence related to the prevention and treatment of thromboembolism and to provide

graded recommendations based on level of evidence. In this chapter, the rationale for venous thromboembolism (VTE) prophylaxis is thoroughly examined, a comprehensive review of clinical trials is presented, and a standardized method for risk stratification is suggested. Guidelines for VTE prevention in a variety of clinical settings, including medically ill patients and patients undergoing orthopedic surgery using pharmacological and nonpharmacological methods, are recommended based on available evidence. However, the guidelines for VTE prevention in medically ill patients do not discuss the appropriate frequency of administration for unfractionated heparin (UFH), or differentiate situations in which UFH versus low-molecular-weight heparin (LMWH) might be more appropriate. In addition, the overall recommendations for orthopedic surgery do not differentiate between the various pharmacological prophylactic options based on specific efficacy and safety data.

2. Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(suppl 3):401S–28S.

   This chapter of the American College of Chest Physicians Guidelines includes a lengthy review of current literature suggesting that the duration of anticoagulation in patients with hypercoagulable conditions should be extended chronically because thrombophilia represents a chronic risk factor for thrombosis. It considers the risks of thrombosis in various hypercoagulable conditions, as well as the risks and benefits associated with chronic anticoagulation, including a discussion of a potential role for reduced intensity anticoagulation, as suggested in the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial. The authors also provide recommendations for intensity of anticoagulation in patients with antiphospholipid antibody syndrome based on a recent clinical trial, but without a critical review of this trial which would lead most readers to a conflicting conclusion.

3. Lee AY. Epidemiology and management of venous thromboembolism in patients with cancer. Thromb Res 2003;110:167–72.

   This article reviews available literature regarding the incidence of VTE in patients with cancer, the tumor types most strongly associated with VTE, the association between VTE and occult malignancy, and the expected prognosis of patients with cancer who have thrombosis. It also includes sections on prevention and treatment of cancer-related thrombosis. The author is the primary investigator of the Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) study, which compared LMWH and warfarin for secondary prevention of cancer-related thrombosis and, therefore, presents insights into how the results of this study influence treatment decisions. However, this review does not discuss the complex pathophysiology of thrombosis in malignancy. Readers are referred to other articles and textbooks for such information.

4. Howard PA. Low molecular weight heparins in special populations. J Infus Nurs 2003;26:304–10.

   This article reviews some of the most controversial areas for use of LMWHs, such as renal dysfunction, obesity, and pregnancy. The author reviews available pharmacokinetic and clinical studies and gives practical insights for dosing and monitoring considerations of the LMWHs in these high-risk patient groups. A detailed discussion on the clinical use of monitoring anti-factor Xa levels is included. In renal dysfunction, a dose decrease based on degree of drug accumulation is recommended by the author. In obesity, the use of total body weight is advocated. This is one of the more complete reviews of the currently available literature on the use of LMWHs in special populations.

5. Douketis JD. Perioperative anticoagulation management in patients who are receiving oral anticoagulant therapy: a practical guide for clinicians. Thromb Res 2003;108:3–13.

   This article is one of the better reviews in the literature that addresses practical aspects of managing patients who are receiving chronic anticoagulation and require an invasive procedure. The paper focuses on key areas that need to considered in perioperative anticoagulation management, such as assessing the risk of thromboembolism, when anticoagulant therapy is interrupted, and the risk of bleeding that is associated with the procedure. In addition, the author gives practical insights on how to develop a successful and practical “bridging” algorithm. A detailed case presentation illustrates the major practice considerations in patients on oral anticoagulation undergoing invasive procedures. Various tables throughout the manuscript summarize data on the use of thrombosis of various indications for anticoagulation and risk of bleeding of various invasive procedures.