ASHP Therapeutic Position Statement on the Role of Pharmacotherapy in Preventing Venous Thromboembolism in Hospitalized Patients

Position

Hospitals should develop formal policies, guidelines, practices, and procedures to address the appropriate prevention of venous thromboembolism (VTE). In addition, all hospitalized patients should be assessed for risk for both VTE and bleeding to determine if pharmacologic, mechanical, or combination VTE prophylaxis should be initiated. Patients should also be reassessed following any pertinent clinical changes. In at-risk patients without contraindications (i.e., risk for bleeding, active bleeding, or allergy), pharmacologic thromboprophylaxis should be initiated as soon as possible and within the first 24 hours of arrival at the hospital. Mechanical methods should be used when pharmacologic prophylaxis is contraindicated. Active interdisciplinary, multifaceted VTE prevention programs, in contrast to passive strategies, should be used to improve appropriate VTE prophylaxis within hospitals. These programs should incorporate provider, staff, and patient education; audits and feedback; hospital guidelines and policies; clinical decision-support software; monitoring for appropriate anticoagulant use; and provider reminders. Guidelines and policies need to be individualized at the hospital level, depending on the degree to which pharmacy, providers, nursing, and other staff are involved. The National Quality Forum (NQF) and the Joint Commission recommend creating policies and guidelines regarding anticoagulation. This is also a key recommendation of the American College of Chest Physicians (ACCP). Pharmacy professionals should actively participate in the development, implementation, and monitoring of anticoagulation and VTE prophylaxis programs. In addition, because pharmacologic prophylaxis is the primary method to prevent VTE, pharmacy professionals should take a leadership role in these hospital programs.

Background

Burden of Disease and Pharmacologic Prophylaxis. VTE comprises pulmonary embolism (PE) and deep vein thrombosis (DVT). Despite a wealth of information regarding the mortality and morbidity associated with VTE, hospitals worldwide continue to do poorly at preventing VTE events for at-risk patients. Between 60,000[1] and 300,000[2] deaths occur annually in the United States from PE, and as many as 200,000 of those deaths occur in U.S. hospitals.[3] Approximately 70% of fatal PEs are first detected postmortem.[4,5] Furthermore, up to 2,000,000 new DVTs occur annually within the United States.[1] VTE occurs in approximately 64.4% of surgical patients and 41.5% of medical patients.[6] PE is the most preventable cause of death among all causes for patients; therefore, VTE prevention is the best strategy for improving patient safety in U.S. hospitals.[7,8] In the absence of thromboprophylaxis, 1 in 10 hospital deaths is attributed to PE.[9] Recurrent VTE occurs in 7% of patients at six months,[10] increasing to up to 30% at 8–10 years[11,12] for

patients despite treatment for the initial VTE. The risk of developing VTE rises sharply when the number of risk factors increases.[13] At 1 year after the initial VTE, the mortality rates associated with PE and DVT are particularly high in patients older than 65 years (39% and 21%, respectively).[14] The risk of recurrent VTE continues for up to 90 days after hospitalization.[15,16]

Approximately 60% of VTE events[17] and 75% of autopsy-confirmed fatal PE[18–21] occur in nonsurgical patients. More importantly, PE and proximal DVT are occurring more frequently in medical patients than in surgical patients.[22] This increase may be partially attributable to medical patients having historically lower rates of thromboprophylaxis compared with surgical patients. In addition, VTE prophylaxis for surgical patients has been studied for approximately 50 years, whereas well-designed studies for medical patients began surfacing in the mid-1990s. In placebo-controlled studies, VTE events have been reduced by 50–65% in acutely ill patients when prophylaxis was used.[23–25] Examples of avoided morbidity associated with VTE are recurrent VTE, postthrombotic syndrome (PTS), congestive heart failure, and pulmonary hypertension. PTS is the term used to describe signs and symptoms that may occur as a long-term complication of DVT and includes swelling, pain, edema, venous ectasia, and skin induration of the affected limb.[26] In severe PTS, patients may have painful, intractable leg ulcers, which decrease mobility and require additional medical care.[26] PTS is associated with an annualized cost as high as $11,667[27] and can lead to loss of quality of life and functional status. After a symptomatic DVT, the overall incidence of PTS is 20–50%, and severe PTS occurs in 5–10% of patients.[28] Within 2 years after the development of PE, chronic thromboembolic pulmonary hypertension occurs in approximately 3.8% of patients.[29] Results from clinical trials have shown that when pharmacologic prophylaxis is administered at appropriate doses and durations in medical patients, the breakthrough occurrence of VTE is clinically uncommon (2.8–5.6%).[23–25] The use of thromboprophylaxis has been shown to reduce mortality in both primary studies and meta-analyses.[25,30,31] This position statement focuses on key issues and guideline recommendations for the prevention of VTE in hospitalized patients augmented by health-system pharmacists.

Current Hospital Performance and Barriers. Globally, 41.5% of surgical patients and 60.5% of medical patients at risk for VTE do not receive appropriate prophylaxis therapy.[6] The concept of "appropriate VTE prophylaxis" has recently emerged and denotes appropriate drug, dose, and duration of therapy. Recent studies have demonstrated appropriate prophylaxis rates of only 13–33% in hundreds of U.S. hospitals.[32–35]

Barriers to VTE prophylaxis include concerns about bleeding complications; underestimation of the VTE risk; gaps in provider knowledge of VTE prevention; lack of

knowledge regarding recommendations and standards; heterogeneous patient populations; perceived difficulties in risk assessment; lack of familiarity, agreement, or confidence with guidelines; belief that implementing guidelines is ineffective in improving outcomes; resistance to changing established practice patterns; need for approval and funding to implement guidelines; and lack of clarity and ease of use of guidelines.[36–38]

National Impact and Readmissions. Currently, VTE has an estimated financial burden of $13.5 billion–$69.3 billion per year in the United States, with $4.5 billion–$39.3 billion of this being preventable with pharmacist-driven or other VTE prevention programs.[39,40] Because of the gravity of the problem and poor performance of U.S. hospitals, many of the leading U.S. organizations began to prioritize VTE as a top initiative for improvement within the last decade. Some of these organizations include NQF, the Agency for Healthcare Research and Quality, the Institute for Healthcare Improvement, the Joint Commission, the Centers for Disease Control and Prevention (CDC), and the Centers for Medicaid and Medicare Services (CMS).[41]

Interestingly, a 2007 study found that approximately 5.3% of patients previously hospitalized for a DVT or PE are readmitted within one year for VTE.[42] A clear trend of hospital readmission occurred within the first 30 days of the initial event for these patients, with 27.1% readmitted for a DVT and 44.3% readmitted for a PE.[42]

Guidelines and Quality Measures

Many national and international guidelines exist for appropriate, evidence-based treatment of VTE prophylaxis. These include the ACCP guidelines, which were last updated in 2012,[43–45] and the International Union of Angiology guidelines from June 2006.[46] Oncology-specific guidelines, such as those created by the American Society of Clinical Oncology (ASCO)[47] and the National Comprehensive Cancer Network (NCCN),[48] are also available and are very specific about contraindications for prophylaxis, which is helpful to the practicing clinician. ASCO and NCCN guidelines were updated in 2007 and 2011, respectively.

Both the Joint Commission and CMS have initiated quality measures to promote VTE prophylaxis in hospitalized patients. In 2008, the Joint Commission implemented a National Patient Safety Goal that focuses on anticoagulation management in the hospital setting for both medical and surgical patients.[49] CMS also added DVT and PE after total knee replacement (TKR) or total hip replacement (THR) procedures to a list of conditions whose associated costs will not be reimbursed if acquired during a hospital stay.[50] The Joint Commission collaborated with NQF on the development of these measures to promote VTE prophylaxis, which were piloted in U.S. hospitals and then endorsed by NQF in 2008.[51] In October 2009, the Joint Commission made available a core measure set for VTE (Table 1), focusing on prophylaxis, treatment, and one outcome measure of "preventable" VTE.[52] Hospitals may choose this VTE core measure set as one of four required core measure sets on which to report.[52] However, because these measures alone do not give detailed recommendations on VTE prophylaxis, hospitals should base their guidelines, policies, practices, and recommendations on the most recent edition of the ACCP guidelines. At this time, only 60 of approximately 5000 acute care hospitals are reporting on the VTE core measure set. Therefore, hospitals should also adopt the Joint Commission's VTE measure set for core measure reporting to aid in improving patient care and reduce health care costs.

Mechanical Methods of Prophylaxis in Hospitalized Patients. While the focus of this manuscript is pharmacologic prophylaxis, pharmacists should familiarize themselves with mechanical methods of prophylaxis to make appropriate recommendations for patients when a pharmacologic contraindication exists. Mechanical methods of prophylaxis may be dynamic, static, or a combination of the two. Dynamic methods include intermittent pneumatic compression (IPC) devices, sequential compression devices, and venous foot pumps. Static methods include graduated compression stockings, elastic stockings, and thromboembolic deterrent hose. Mechanical methods of prophylaxis have been shown to only reduce the rates of DVT, not PE or death, in contrast with pharmacologic prophylaxis.[8] A 2005 meta-analysis of IPC device use in surgical patients found a 60% risk reduction in DVT with no substantial reduction in PE risk, compared with no prophylaxis ($p < 0.001$).[53,54]

Inferior vena cava filters (IVCFs) are an alternative static method of mechanical prophylaxis. To date, IVCFs have been shown to reduce recurrent PE at the expense of an increased risk of DVT in the absence of anticoagulation.[55] Hospitals should use IVCFs for patients with confirmed proximal DVT who have an absolute contraindication to full-dose anticoagulation (e.g., patients with active bleeding) or who have not responded to standard anticoagulant regi-

Table 1.

The Joint Commission Venous Thromboembolism (VTE) National Hospital Inpatient Quality Measures[a]

Set Measure ID #	Measure Short Name
VTE-1	Venous thromboembolism prophylaxis
VTE-2	Intensive care unit venous thromboembolism prophylaxis
VTE-3	Venous thromboembolism patients with anticoagulant overlap therapy
VTE-4	Venous thromboembolism patients receiving unfractionated heparin therapy with dosages/platelet count monitoring by protocol
VTE-5	Venous thromboembolism discharge instructions
VTE-6	Incidence of potentially preventable venous thromboembolism

[a]Reprinted from the *Specifications Manual for National Hospital Inpatient Quality Measures,* version 4.1, March 2012, a collaborative work of the Centers for Medicare and Medicaid Services and the Joint Commission. This manual is periodically updated, and users of the manual must update their software and associated documentation based on the published manual production timelines.

mens (e.g., patients who developed recurrent thromboembolism despite full-dose anticoagulant therapy) or in high-risk patients who have major surgery planned in the very near future. Once the absolute contraindication to anticoagulation subsides or the major surgery is completed, treatment with an appropriate anticoagulant should be initiated or resumed, depending on the clinical scenario.[8]

The health care team should ensure patients' compliance with mechanical methods of VTE prophylaxis throughout their hospitalization, as compliance is the most important determinant of efficacy.[56] Most devices used for mechanical VTE prophylaxis should be used for a minimum of 20 hours per day to be effective. Because of these compliance issues, hospitals and physicians should attempt to use mobile, battery-powered IPC devices that have the ability to record and report the hours the devices are used.[8,43–45] Mechanical methods of prophylaxis should be reserved for patients who are actively bleeding or at high risk for bleeding, with inclusion of such documentation in the patient record, or possibly as an adjunct to pharmacologic methods of prophylaxis.[8] Studies have demonstrated greater reductions in VTE rates among certain groups of patients (i.e., trauma patients, patients with spinal cord injury, and high-risk patients undergoing TKR, THR, hip fracture surgery, neurosurgery, and elective spine surgery) receiving combination pharmacologic and mechanical VTE prophylaxis compared with pharmacologic prophylaxis alone.[8]

Health-system pharmacists should evaluate patients for potential contraindications to anticoagulation therapies. They should also familiarize themselves with the specific mechanical methods available at their institution, which could be used in patients with such contraindications.

Risk Stratification and Identification

Most hospitalized patients have at least one risk factor for VTE, and approximately 40% have multiple risk factors.[8] Common risk factors for VTE are listed in Table 2, and DVT rates among various patient groups are presented in Table 3.[57] Most critically ill patients have multiple risk factors for VTE. Risk factors that may precede admission to a critical care unit may include trauma, active infection (e.g., sepsis), recent surgery, active malignancy, stroke, advanced age, congestive heart failure, respiratory failure, history of VTE, and pregnancy. In addition, patients admitted to critical care units have an increased risk of developing VTE due to immobilization, placement of central venous lines, sepsis, pharmacologic paralysis, mechanical ventilation, vasopressor use, and the need for surgical procedures and dialysis.[8,58]

PE is the second most common cause of death in patients with cancer.[8] Patients with hematologic malignancies, lung cancer, and gastrointestinal cancer have the highest rates of VTE. Within the first three months after being diagnosed with cancer, patients have an approximate 50-fold increased risk of developing a VTE compared with patients with no cancer.[59] Even during therapeutic anticoagulation after a VTE, fatal PE outnumbers fatal bleeding events in an approximate 3:1 ratio.[60] Certain cancer treatments, including chemotherapy, hormonal manipulation, erythropoiesis, and the presence of a central venous catheter, are also risk factors for VTE.[8] Chemotherapy is associated with an approximate sixfold increased risk of VTE,[61–63] with specific drugs contributing to higher VTE rates, including tamoxifen, anastrozole, letrozole, exemestane, bevacizumab, thalidomide, and lenalidomide.[64–73] Tamoxifen is associated with a higher rate

Table 2.

Venous Thromboembolism (VTE) Risk Factors[8,57]

Risk Factor Category	Risk Factors
Common general risk factors	Previous VTE; surgery; trauma; thrombophilia; obesity (body mass index of >25 kg/m^2); acute hospitalization for medical illness; immobility or lower-extremity paresis; active or occult malignancy; cancer therapy, such as radiotherapy, hormonal therapy, chemotherapy, or angiogenesis inhibitors; venous compression from sources such as tumor, hematoma, or arterial abnormality; increasing age; pregnancy and the postpartum period; estrogen-containing oral contraceptives or hormone- replacement therapy; selective estrogen-receptor modulators; erythropoiesis-stimulating agents; inflammatory bowel disease; nephrotic syndrome; myeloproliferative disorders; paroxysmal nocturnal hemoglobinuria; central venous catheterization
Specific medical risk factors	
High risk	History of deep venous thrombosis or pulmonary embolism, family history of thrombosis, acute infection, active malignancy, age >75 yr, stroke, myocardial infarction, congestive heart failure, prolonged immobility (≥4 days), pregnancy or postpartum period, acute or chronic lung disease, acute inflammatory disease, inflammatory bowel disease, shock
Probable risk	High-dose estrogen therapy, obesity (body mass index of >25 kg/m^2), varicose veins, heparin-induced thrombocytopenia, congenital or acquired thrombophilia, antithrombin deficiency, positive lupus anticoagulant, antiphospholipid antibodies, protein S or C deficiency, positive factor V Leiden, elevated anticardiolipin antibodies, positive prothrombin gene mutation 20210A
Possible risk	Paraproteinemia, Behçet's disease, disorders of plasminogen and plasminogen activation, nephrotic syndrome, polycythemia, elevated serum homocysteine levels, dysfibrinogenemia, myeloproliferative disorders, age ≥ 41 yr, sepsis (<1 mo)

Table 3.

Frequency of DVT Associated with Various Patients Groups and Conditions in the Absence of Prophylaxis[8,57,a]

Patient Group or Condition	Frequency of DVT, %
General medical patients	10–26
Myocardial infarction	17–34
Stroke	11–75
Congestive heart failure	20–40
Medical intensive care	25–42
Critical care patients	10–80
General surgical patients	15–40
Major gynecological surgery	15–40
Major urologic surgery	15–40
Neurosurgery	15–40
Major orthopedic surgery of the hip or knee[b]	40–60
Trauma	40–80
Spinal cord injury	60–80

[a]DVT = deep venous thrombosis.
[b]Total knee or hip replacement or hip fracture surgery.

of VTE than the aromatase inhibitors anastrozole, letrozole, and exemestane.[74–77]

Furthermore, surgical patients with cancer have at least twice the risk of developing a postoperative DVT and three times the risk of developing a fatal PE as compared with patients with no cancer undergoing the same surgeries.[8] VTE recurrence rates are high both during anticoagulation and after anticoagulation has been discontinued.[78–81] Patients with cancer who develop a VTE have a substantial reduction in survival compared with cancer patients who do not develop a VTE.[82-84]

Research into other risk factors for VTE continues,[85–87] though validation of these risk factors will be needed. Risk-assessment models (RAMs) have been developed for the hospitalized patient and have proved useful in identifying patients at risk for VTE and bleeding.[8] The health-system pharmacist should take initiative and lead the collaborative implementation of RAMs within the hospital.

Several methods of risk assessment to reduce hospital-acquired VTE exist. Some methods may use one process or form for all patients being evaluated, while others may use specific processes or forms for specific patient groups. Both methods can be computerized (i.e., using electronic alerts) or completed manually. RAMs could also be based on a scoring system (i.e., positive points for specific risk factors and negative points for contraindications) or they could assess risk factors by patient groups based on guideline recommendations.[8]

Several RAMs have been proposed for hospitalized patients, incorporating both predisposing and exposing risk factors (e.g., major surgery,   acute medical illness).[88–92] For example, Caprini et al.[88] developed a RAM for both hospitalized surgical and medical patients, with the surgical RAM being validated in 2009,[90] and Cohen et al.[90] developed an algorithm-based RAM for medical patients.

Another recent, predictive, evidence-based, weighted-risk scoring system was developed from the large International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) database for medical patients.[92] The risk scores were derived from the hazard ratios of seven independent clinical risk factors for VTE. The Padua prediction score is another RAM that uses 11 risk factors to determine VTE risk in the medical patient and categorizes a patient's VTE risk as low or high.[93] For all patients, the risk of bleeding should be determined using a group-appropriate RAM or guideline-delineated risk factors. A clear advantage of the IMPROVE RAM is that its derivation is evidence based, whereas the Padua prediction score is not.[91] Collectively, these RAMs further validate the concept of weighted scoring, demonstrating that all VTE risk factors are not equally associated with VTE risk.

Because risk factors are not weighted equally, clinicians should carefully examine risk factors to determine the individual care needed for each patient. Furthermore, efforts should be made to maximize the number of risk factors assessed with the RAM, as this will capture a greater number of patients at risk for VTE and maximize the sensitivity of the model.[94]

Although a review of all risk-assessment programs to reduce VTE is beyond the scope of this position statement, several reviews reiterate key characteristics that are essential to such programs.[94–97] Risk-assessment programs should be multifaceted, and those involved in such programs should provide active interventions instead of merely handing out guidelines or placing incomplete risk-assessment forms in patient charts. These programs should also educate and remind health care providers about the need for VTE prophylaxis, educate patients, use audit and feedback for the program itself and for individuals ignoring alerts (i.e., alert fatigue), monitor for inappropriate use of thromboprophylaxis, and use clinical decision-support software, either electronically or manually.

Pharmacist-driven VTE programs have helped improve the care received by hospitalized patients.[39,98–102] The implementation of one such program led to a significant increase in appropriate type, dose, and duration of prophylaxis while also significantly reducing "preventable" VTE events (relative risk reduction = 74%, $p = 0.0006$).[39] Another pharmacist-driven program significantly increased optimal VTE prophylaxis among hospitalized nonsurgical patients from 11% to 44% ($p < 0.001$). The program consisted of presentations, newsletters, and VTE prophylaxis recommendations made during clinical pharmacy rounds.[98] In addition, a multidisciplinary program that included pharmacists in the surgical intensive care unit achieved substantial reductions in both hospital-acquired and preventable VTE.[103] Lastly, the use of a simple, nonscoring, three-tiered (low, moderate, or high) VTE RAM led to an 86% reduction in preventable hospital-acquired VTE over three years.[104] This RAM was modular and embedded into computerized provider-order-entry (CPOE) order sets but was not a pharmacist-driven program.

Efficacy of Antithrombotic Prophylaxis and Recommendations

Heparins and Fondaparinux. Three prospective, randomized, placebo-controlled studies have been conducted to evaluate the efficacy of low-molecular-weight heparins (LMWHs)

and fondaparinux for VTE prophylaxis in medical patients. These include the MEDENOX[23] (enoxaparin), PREVENT[24] (dalteparin), and ARTEMIS[25] (fondaparinux) trials. The number needed to treat to avoid a VTE ranged from 11 to 45 in these studies. Major bleeding rates were 1.7%, 0.49%, and 0.2% in the MEDENOX, PREVENT, and ARTEMIS trials, respectively. The three studies demonstrated significant relative risk reductions of 63%, 55%, and 49.5% for VTE, respectively, with no significant differences in major bleeding rates. In the United States, enoxaparin and dalteparin have Food and Drug Administration (FDA)-approved indications for VTE prophylaxis in acutely ill medical patients; fondaparinux does not. Fondaparinux does carry this indication in certain European Union countries. In the recent PROTECT trial, investigators randomized critical care patients to dalteparin 5000 units daily or unfractionated heparin (UFH) 5000 units twice daily and found no significant difference in the rate of proximal DVT, major bleeding, or inhospital death. However, there was a significant reduction in the occurrence of PE with dalteparin as compared with UFH.[105]

According to a recent systematic review conducted by the American College of Physicians (ACP), the use of heparin in medical patients to prevent VTE decreases the rate of pulmonary embolism but does not decrease mortality and leads to more bleeding complications.[106,107] No differences in risks or benefits were found between the types of heparin used, though there was a nonsignificant difference favoring LMWH over UFH for PE (odds ratio, 0.67; confidence interval [CI], 0.45–1.00; $p = 0.053$; $I^2 = 0\%$). The use of mechanical devices led to adverse outcomes and did not demonstrate any benefit. Therefore, in medical and stroke patients, ACP currently recommends assessing the risks of VTE and bleeding before starting VTE prevention and only using pharmacologic prophylaxis if the risk of VTE is greater than the risk of bleeding. In addition, ACP recommends against using mechanical devices to prevent VTE.[106–108] These recommendations are similar to those of ACCP, which recommends an LMWH, a UFH two or three times daily, or fondaparinux for patients not at risk of bleeding but at risk of VTE. However, ACCP does recommend mechanical means of prophylaxis, such as IPC devices and graduated compression stockings for patients at risk of bleeding and VTE. ACCP analyses did not note any substantial difference in bleeding, VTE, or heparin-induced thrombocytopenia between UFH two and three times daily.[43] Because ACCP guidelines are in their ninth edition and ACP guidelines are newly released, we recommend using ACCP guidelines. Key guideline recommendations for the medical patient are listed in Table 4.

Warfarin versus LMWHs and Fondaparinux. Because of its slow onset of action, variable responses among patients, drug–drug and drug–food interactions, lower efficacy compared with LMWHs, need for frequent monitoring, and complexity of both inhospital and postdischarge supervision, warfarin has largely been abandoned as thromboprophylaxis in Europe. Similarly, the ACCP guidelines concluded that LMWHs, and likely fondaparinux by indirect comparison, are more effective than warfarin in preventing inhospital VTE and should be preferred.[8] Health-system pharmacists should continue to educate themselves on emerging evidence on the use of thromboprophylactic agents. They should also familiarize themselves with the risks, benefits, and duration of use in relation to transitions among levels of care.

Optimal Duration for Thromboprophylaxis

With the average length of stay in U.S. hospitals being approximately 5 days,[109] the recommended duration of prophylaxis in studies and within drug labeling is often not reached. Studies have suggested that the inappropriate duration of therapy is a major cause for failure to receive appropriate thromboprophylaxis among hospitalized patients.[15,33] ACCP guidelines advocate extended thromboprophylaxis of up to 35 days with an LMWH in patients undergoing major orthopedic surgery (especially hip fracture repair and hip replacement) and up to 28 days in patients with active cancer undergoing surgery for their cancer.[8] Recent results from the EXCLAIM study suggest that there is a high-risk subgroup of hospitalized medical patients (namely, women, patients with advanced age, or patients with complete immobility) who may benefit from extended outpatient thromboprophylaxis.[110] Results from two recent trials evaluating the use of rivaroxaban and apixaban in VTE prophylaxis did not demonstrate additional benefits with either drug when used for approximately one month.[111,112] Further studies are needed to determine whether the use of thromboprophylaxis for the duration recommended in the drug labeling is safe and improves outcomes in medical patients. The VTE Discharge Alert Trial is currently assessing if a human alert to physicians within 48 hours of planned patient discharge has any effect on increasing postdischarge prophylaxis or reducing VTE within 90 days of hospital admission in the medical patient. Major bleeding events within 30 days of hospital admission are also being monitored.[113] At a minimum, for the majority of at-risk patients, the optimal duration of prophylaxis is the length of the hospital stay if exposing risk factors are still present while considering the primary diagnosis and predisposing risk factors. Importantly, no studies evaluating the impact of ambulation on VTE have been conducted. A recent study found that despite timely ambulation, medical patients were still at risk of VTE, and this risk was substantially reduced with enoxaparin prophylaxis.[114] Therefore, patient ambulation or mobility should not be used as a reason to discontinue, or restrict, prophylaxis during hospitalization. Currently, ACCP guidelines recommend against extending the duration of thromboprophylaxis beyond the hospital stay or period of patient immobilization in the medical patient.[43]

Safety of Antithrombotic Prophylaxis

One of the major adverse events that can occur with the use of heparin is heparin-induced thrombocytopenia (HIT). HIT is an antibody-mediated adverse effect of heparin that is strongly associated with venous and arterial thrombosis. HIT is diagnosed when any of the following events occurs in association with the presence of HIT antibodies: an otherwise unexplained decrease in platelet count, venous or arterial thrombosis, skin lesions at heparin injection sites, and acute systemic reactions (fever or chills, tachycardia, hypertension, dyspnea, cardiopulmonary arrest) that occur after i.v. heparin bolus administration.[115] Although HIT can occur with a prophylactic dose of both LMWH and UFH, it happens about threefold more frequently with UFH than with LMWH and incurs approximately $41,133 of additional costs per case.[116,117] Because the occurrence of HIT

Table 4.

Existing Guideline Recommendations for Thromboprophylaxis of Hospitalized Medical and Critical Care Patients[a]

Group and Recommendations	Modality and Grade of Recommendation(s)
American College of Chest Physicians (2012)	
Acutely ill hospitalized medical patients at low risk of thrombosis: Do not use pharmacologic prophylaxis or mechanical prophylaxis.	No thromboprophylaxis
Acutely ill hospitalized medical patients at increased risk of thrombosis: Provide anticoagulant thromboprophylaxis with LMWH, low-dose UFH twice or three times daily, or fondaparinux and suggests against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay.	Grade 1B[b]
Acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or are at high risk for major bleeding: Use mechanical thromboprophylaxis using GCSs or IPC.	Grade 2C
Critically ill patients: Use LMWH or low-dose UFH for thromboprophylaxis.	Grade 2C
Critically ill patients who are bleeding or are at high risk for major bleeding: Use mechanical thromboprophylaxis with GCSs and/or IPC at least until the bleeding risk decreases.	Grade 2C
American College of Physicians (2011)	
Recommends assessment of the risk for thromboembolism and bleeding in medical (including stroke) patients before initiation of prophylaxis of VTE	Grade: strong recommendation; moderate-quality evidence
Recommends pharmacologic prophylaxis with heparin or a related drug for VTE in medical (including stroke) patients unless the assessed risk for bleeding outweighs the likely benefits	Grade: strong recommendation; moderate-quality evidence
Recommends against the use of mechanical prophylaxis with GCSs for prevention of VTE	Grade: strong recommendation; moderate-quality evidence
Policy implication: The American College of Physicians does not support the application of performance measures in medical (including stroke) patients that promote universal VTE prophylaxis regardless of risk.	
International Union of Angiology (2006)	
Acutely ill medical patients (patients older than 40 years with acute medical illness and/or reduced mobility with one of the following morbidities: acute heart failure NYHA class III/IV, respiratory disease [respiratory failure with or without ventilation or exacerbation of respiratory disease], active cancer requiring therapy, acute infective disease including severe infection and sepsis, rheumatic disease, ischemic stroke, or acute myocardial infarction) should be considered for prophylaxis. Patients with acute medical illness with reduced mobility and one of the following risk factors—history of VTE, malignant disease, or older than 75 years—should also be considered for prophylaxis.	UFH 5000 units three times daily (grade A), enoxaparin 40 mg once daily (grade A), dalteparin 5000 units once daily (grade A), fondaparinux 2.5 mg once daily (grade B)
National Comprehensive Cancer Network (2011) Cancer patients	LMWH, UFH 5000 units three times daily
American Society of Clinical Oncology (2007) Hospitalized medical patients	LMWH, UFH 5000 units three times daily

[a]LMWH = low-molecular-weight heparin, UFH = unfractionated heparin, GCSs = graduated compression stockings, IPC = intermittent pneumatic compression, NYHA = New York Heart Association, VTE = venous thromboembolism.
[b]Fondaparinux is not approved by the Food and Drug Administration for medical prophylaxis in the United States.

is more frequent with UFH, overall costs are likely reduced by using LMWH over UFH. Taking into consideration that HIT may be a serious, limb-threatening and life-threatening complication, LMWH may be favored over UFH. Only a limited number of case reports of fondaparinux-induced thrombocytopenia have been reported, and this may be an advantage of fondaparinux over LMWH and UFH. The new oral agents will likely also have an advantage over UFH and LMWH with regard to HIT and may be a useful alternative in patients with a history of HIT.

Major and minor bleeding can also occur with the use of prophylactic LMWH, warfarin, fondaparinux, and UFH. Overall, pharmacologic means of VTE prophylaxis carry a slightly higher risk of bleeding than placebo or mechanical means, but major bleeding rates are negligible with prophylactic doses in well-controlled clinical trials.[23–25,118–121] In studies evaluating the safety and efficacy of VTE prophylaxis in medical and surgical patients, the rate of major bleeding was between 0.2% and 2.7% among patients given pharmacologic prophylaxis.

One recent meta-analysis in medical patients demonstrated no difference in major bleeding between pharmacologic prophylaxis and placebo and also showed a reduction in fatal PE with pharmacologic prophylaxis versus placebo.[122] Another meta-analysis concluded that the use of UFH was associated with substantially higher rates of major bleeding than LMWH.[123] A meta-analysis and two primary studies have also demonstrated lower rates of injection-site hematoma with LMWH than UFH.[124,125] Bleeding rates with fondaparinux appear comparable to those with LMWHs for both the medical and surgical patient.[40,116]

Patient groups at high risk for bleeding include those with serious comorbid diseases, especially active malignancy or cerebrovascular, kidney, heart, and liver disease; older patients; those receiving concurrent antithrombotic medications, including antiplatelets and fibrinolytics; patients with thrombocytopenia ($<100,000$ mm^3), a hemoglobin concentration of <13 g/dL (in surgical patients), severe renal insufficiency (creatinine clearance [CLcr] of <30 mL/min), active or recent peptic ulcer disease, recent gastrointestinal or major bleeding, uncontrolled arterial hypertension (systolic blood pressure of >200 mm Hg, diastolic blood pressure of >120 mm Hg, or both), or bacterial endocarditis; and those who have undergone spinal tap or epidural anesthesia within 12 hours.[43–45,126]

A bleeding RAM from the IMPROVE registry was developed and can be accessed at http://omnifik.com/dev/improve/bleeding/.[127] Risk factors for bleeding continue to be discovered and are individualized by patient group. Contraindications to VTE prophylaxis should be agreed on at the institution and pharmacy levels.

The overall avoidance of a substantial number of VTE events and their subsequent morbidity is what makes VTE prophylaxis so persuasive and important. A recent review concluded that mortality rates associated with PE were substantially higher than those associated with major bleeding from the use of anticoagulants, further supporting the focus on the prevention of the initial PE.[128] The initial cost of prophylaxis reduces overall costs by avoiding VTE and its associated morbidity. By and large, there is strong evidence that appropriately dosed thromboprophylaxis has an advantageous and favorable risk:benefit ratio.[8,46]

Recommendations

Most hospitalized patients have multiple risk factors for VTE. Patients at high risk include those in critical care, as well as burn, trauma, surgical, and cancer patients. All hospitalized patients, including patients in critical care or with burns, should be assessed for the risk of VTE using a RAM. Importantly, patients should be reassessed every 24–48 hours, or with pertinent clinical changes, for new or resolved VTE, bleeding risk factors, and contraindications to prophylaxis. According to these risks, patients should be given an LMWH, a UFH, or fondaparinux prophylactically. However, if there is a contraindication to pharmacologic prophylaxis (e.g., active bleeding, high risk of bleeding, allergy [including HIT within 100 days]), with inclusion of such documentation in the patient records, mechanical methods should be used for prophylaxis. Providers should refer to current ACCP guidelines and NCCN/ASCO guidelines for detailed recommendations for VTE prophylaxis for hospitalized patients. Special considerations for trauma, surgical, and cancer patients as well as for obese patients, patients with renal impairment, or pregnant patients are discussed below.

Major Trauma Patients. Trauma patients, including those with acute spinal cord injury, are among those with the highest risk of developing VTE. Recommendations are to administer thromboprophylaxis to all trauma patients.[55] One meta-analysis concluded that UFH alone as thromboprophylaxis in trauma patients was not any more effective than not using thromboprophylaxis.[129] Therefore, according to ACCP guidelines, LMWH is preferred over UFH in trauma patients. One trial demonstrated that UFH combined with mechanical ankle flexion devices was superior to UFH alone in orthopedic trauma patients.[130] Therefore, if used in this patient population, UFH should be combined with mechanical methods and not used alone. For patients undergoing rehabilitation, prophylaxis is recommended to continue with LMWH or warfarin (target International Normalized Ratio [INR] of 2.5 [range, 2–3]) until the risk of VTE subsides, until full ambulation, or for up to three months in trauma patients with spinal cord injury.[8,46]

Patients with Cancer. VTE prevention in this group is particularly important, not only because patients with cancer have a higher risk of VTE but because VTE is often more difficult to diagnose and treat in this population.[8] Patients who are confined to a bed and with an active malignancy should receive prophylaxis with an LMWH, a UFH, or fondaparinux.[8,46] If there is a contraindication to pharmacologic prophylaxis, graduated compression stockings or an IPC device should be used, with strong attention paid to compliance.[8] Although patients with cancer have a particularly increased risk of developing VTE, they continue to have the lowest rates of appropriate VTE prophylaxis.[32–35,131]

VTE prophylaxis should be initiated in cancer patients with solid tumors and additional VTE risk factors, including previous venous thrombosis, immobilization, and the use of hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide.[43] Agents of choice include UFH and LMWH. Additional studies are needed to evaluate anticoagulants in patients with cancer who do not have a traditional indication for thromboprophylaxis, such as those with recent cancer now in remission or undergoing outpatient chemotherapy.[8,46] Agreement on contraindications differs between key organizations and international experts, with some suggesting that pharmacologic prophylaxis be used with platelet counts as low as 5,000 per microliter and others suggesting a low of 50,000.[47] For more information on when to administer prophylaxis to cancer patients, refer to ACCP, NCCN, and ASCO guidelines.

Surgical Patients. An abundance of trials involving surgical patients have demonstrated substantial reductions in VTE with UFH, LMWH, fondaparinux, and warfarin over placebo or equivalence or noninferiority to other effective anticoagulants.[8,44–46] Because the number of surgical studies is so expansive and recommendations vary by patient group, readers are referred to the 2012 ACCP guidelines for specific details. ACCP guidelines include recommendations and background on

- General, vascular, laparoscopic, gynecological, urologic, bariatric, thoracic, and coronary bypass surgery; abdominal–pelvic surgery (including gastrointestinal); major trauma,

- THR, TKR, knee arthroscopy, hip fracture surgery, timing of thromboprophylaxis initiation, screening for DVT before hospital discharge, and duration of thromboprophylaxis for the aforementioned major orthopedic surgeries,
- Isolated lower-extremity injuries distal to the knee, and
- Craniotomy and spinal surgery.

The following key points should be considered when initiating thromboprophylaxis for surgical patients:

1. Aspirin and warfarin, with a target INR of 2.5, may be used for the orthopedic population.
2. Select mechanical methods may be used alone for THR; TKR; hip fracture surgery; gynecologic, urologic, laparoscopic, or coronary artery bypass surgical groups; elective spine surgery; and neurosurgery.[8]
3. LMWH, fondaparinux, and three times daily UFH are typically options for surgical patients with multiple VTE risk factors (i.e., high risk), with LMWH and fondaparinux being preferred over three times daily UFH in many high-risk surgical groups.[8]
4. LMWH, fondaparinux, and twice-daily UFH are options in most moderate-risk surgical groups.[8]
5. The combination of IPC with pharmacologic prophylaxis typically conveys a 60% further risk reduction in VTE events.[8]
6. LMWH is the preferred agent in THR, TKR, and hip fracture surgery if patients do not have an increased risk of bleeding.

Obese Patients. Although more studies are needed, evidence supports the use of weight-based prophylactic dosing of LMWHs in obese patients (i.e., body mass index of >30 kg/m^2). Studies assessing anti-Xa levels at both treatment and prophylactic dosages demonstrated appropriate anti-Xa levels and no accumulation of drug. Appropriate anti-Xa levels have been reported in obese patients receiving enoxaparin, tinzaparin, and dalteparin dosed based on total body weights of up to 144, 165, and 190 kg, respectively.[132–136] One meta-analysis verified that major bleeding rates were not increased in obese patients who received weight-based LMWH when compared with nonobese individuals.[137]

Nadroparin and enoxaparin have been studied in prospective studies of obese patients undergoing bariatric surgery and orthopedic surgery.[138–142] Of note, nadroparin is not available in the United States. The usual recommended prophylactic doses of these agents may be inadequate for VTE prophylaxis in obese patients. For LMWHs, ACCP guidelines recommend using weight-based dosing for obese patients.[8] For enoxaparin, the specific dosing that appeared to be more favorable in bariatric surgery was 40 mg twice daily, though this may still be inadequate in some patients, and higher dosing may be more beneficial.[142] Although dosing suggestions are not yet well-defined in the literature, enoxaparin 0.5 mg/kg every 12–24 hours (e.g., depending on the level of obesity, with every-12-hour administration used for patients with higher body mass indexes) has been used successfully for prophylaxis at some centers.[143–145] Dosage increases of up to 30% have also been suggested.[145]

Patients with Renal Impairment. Several studies have assessed the effects of LMWHs in patients with renal impairment. Tinzaparin and dalteparin offer the most convincing data that these drugs may not accumulate in patients with severe renal impairment in both prophylactic and treatment doses.[147–154] However, one recent study comparing tinzaparin with UFH for the treatment of VTE in elderly patients with renal insufficiency found increased mortality in the tinzaparin group.[155] The trial was stopped early because of these interim results, though the increased mortality was not related to increased bleeding or VTE. There were nonsignificant trends for tinzaparin-treated patients having higher rates of VTE than those receiving UFH[155]; thus, more data are needed. Of note, tinzaparin production was recently discontinued in the United States.[156]

The recent Dalteparin's Influence on Renally Compromised anti-Ten-A (DIRECT) trial was a prospective study of 120 critically ill patients with a CLcr of <30 mL/min, who had at least one trough anti-Xa level measured.[150] The investigators analyzed the safety of prophylactic dosages of dalteparin and found no bioaccumulation of the drug in the patients. Interestingly, 62% of patients had acute renal failure at some point during their prophylactic regimen. These data suggest that in critically ill patients with severe renal insufficiency, VTE prophylaxis with dalteparin is unlikely to contribute to bleeding and is not associated with an excessive anticoagulant effect due to bioaccumulation.[150] Enoxaparin, however, has shown accumulation when used at treatment dosages.[157–161]

Because there is conflicting evidence regarding the accumulation of LMWHs in renally impaired patients, further studies are needed. At this time, ACCP recommends using an alternative agent or dosage-adjusted LMWH in patients who are renally impaired (CLcr of <30 mL/min). Because laboratory results are not immediately available on admission, it is important for pharmacists to review patients' history to determine if their LMWH dose needs to be adjusted or if they should be switched to another agent. Twice-daily UFH 5000 units is an appropriate option in both hemodialysis patients and patients with severe renal impairment in the absence of contraindications. A recent review with recommendations by Nutescu and colleagues[146] addressed LMWH use in both renal impairment and obesity across a wide array of patients.

Pregnant Patients. Pregnancy itself is a risk factor for the development of VTE. VTE in this patient population is complicated, and a thorough clinical history and risk assessment should be sought to determine antepartum and postpartum prophylaxis needs. In general, an LMWH is preferred over a UFH for the prevention and treatment of VTE because of UFH's increased risks of HIT and osteoporosis. At-risk pregnant patients should receive appropriate VTE prophylaxis per ACCP guidelines. For women undergoing cesarean delivery with at least one major or two minor risk factors, LMWH should be used or mechanical prophylaxis for patients with contraindications to LMWH. For women undergoing cesarean delivery with multiple additional risk factors, LMWH should be combined with mechanical methods until discharge. For selected high-risk patients, extended prophylaxis should be considered. Readers are referred to the ACCP guidelines for recommendations regarding the prevention of VTE in pregnant patients.[162]

Emerging Anticoagulant Options

At present, dabigatran, rivaroxaban, and warfarin are the only oral anticoagulants available, though dabigatran and rivaroxaban have only recently gained approval for stroke prevention in nonvalvular atrial fibrillation.[163–166] Dabigatran does not have other indications at this time, and its efficacy is based on the recently published RELY trial, which demonstrated that dabigatran was superior to warfarin with a similar rate of bleeding at a dosage of 150 mg twice daily.[165] Although warfarin has been the only oral anticoagulant available for more than five decades, it has several disadvantages when used for VTE prophylaxis in hospitalized patients, as discussed above. The development of new anticoagulants has focused on finding new oral formulations, specifically targeting single procoagulant complexes critical to the coagulation process, including blocking the initiation of coagulation, preventing the propagation of coagulation, and inhibiting thrombin.[167,168] There are several types of monotargeted oral anticoagulants: direct inhibitors of activated factors IXa and Xa, which are involved in the propagation of coagulation, and direct inhibitors of thrombin activity, which target factor IIa. Rivaroxaban and dabigatran have recently been approved by FDA. The approval of apixaban, however, has been delayed due to FDA's request for additional information.

Rivaroxaban. Rivaroxaban is an oral, reversible, once-daily factor Xa inhibitor that has an oral bioavailability of 80% and a half-life of 7–11 hours; it is 67% renally cleared.[164] Rivaroxaban is a substrate for P-glycoprotein 1 transporter, located in the gut and kidneys, and is also metabolized via cytochrome P-450 isoenzyme 3A4 (CYP3A4), so the use of strong inducers or inhibitors of this isoenzyme should be avoided in patients receiving rivaroxaban. The safety and efficacy of rivaroxaban for VTE prevention after TKR and THR have been evaluated in four Phase III studies (RECORD trials) in Europe and the United States.[169–172] The RECORD 1 and 2 trials were conducted in patients undergoing TKR; the RECORD 3 and 4 trials were conducted in those undergoing THR. Rivaroxaban was found to be superior to enoxaparin for preventing VTE and all-cause mortality with similar bleeding rates. In two of the four RECORD trials, rivaroxaban was superior to enoxaparin in the prevention of symptomatic VTE. The agent is approved for these indications in Europe and Canada and has recently gained FDA approval for the same indications within the United States.[164] In the Phase III MAGELLAN study, the safety and efficacy of extended prophylaxis with oral rivaroxaban (10 mg daily for 31–39 days) were compared to short-term prophylaxis with subcutaneous enoxaparin (40 mg daily for 6–14 days) for the prevention of VTE in medical patients. The results of this study indicate the superiority of rivaroxaban over enoxaparin at day 35 for the composite endpoint of asymptomatic proximal DVT, symptomatic DVT, symptomatic nonfatal PE, and VTE-related death. However, this came at the cost of substantially more major bleeding events.[109] The relative risk of bleeding compared with enoxaparin at 10 and 35 days was 2.3 ($p < 0.001$) and 2.5 ($p < 0.001$), respectively. Because of these safety results, the risk:benefit ratio of rivaroxaban in medical patients is questionable. In the ROCKET-AF study, based on the primary endpoint of stroke or systemic embolism in patients with nonvalvular atrial fibrillation, rivaroxaban was found to be noninferior to warfarin (hazard ratio, 0.88; 95% CI, 0.74–1.03; $p < 0.001$) ($p = 0.12$ for superiority). Rivaroxaban received FDA approval for VTE prevention in TKR, THR, and atrial fibrillation in 2011. However, because of the safety data and higher rates of clinically relevant bleeding, its use in medical patients cannot be recommended at this time.

Apixaban. Apixaban is a new, reversible, direct-acting oral pyrazole-based factor Xa inhibitor that is 25% renally cleared, is 60% bioavailable, and has a half-life of 9–14 hours. The drug is also cleared via the CYP3A4 isoenzyme system; therefore, strong inducers and inhibitors will need to be avoided. Apixaban is currently in advanced stages of testing for the prevention and treatment of thrombotic disorders. It binds to the active site of factor Xa without requiring antithrombin.[167,168]

Currently, there are several multinational Phase III studies of apixaban being conducted for the prevention of thrombotic events, including DVT and PE, in patients undergoing knee or hip replacement surgery. The results for one of these trials (ADVANCE-1) showed that the primary endpoint (symptomatic or asymptomatic DVT, PE, or death from any cause) occurred in 9.0% of apixaban recipients (2.5 mg twice daily), compared with 8.9% of those treated with enoxaparin (30 mg twice daily) in TKR.[173,174] Despite being numerically similar, these figures did not meet the statistical criteria for apixaban noninferiority. The ADVANCE-2 trial was conducted in patients undergoing TKR. The results demonstrated that apixaban (2.5 mg twice daily) was superior to enoxaparin 40 mg subcutaneously once daily for VTE prevention without increased bleeding. The ADVANCE-3 trial was conducted in patients undergoing THR, and its results demonstrated that apixaban was superior to enoxaparin for VTE prevention at 35 days postsurgery with a similar rate of bleeding. In the ADOPT study of apixaban for VTE prevention in medical patients, apixaban showed substantially increased major bleeding at 30 days without demonstrating superiority on the primary composite VTE efficacy endpoint.[168] These results are similar to those of the MAGELLAN trial mentioned above. The agent is also in Phase II clinical testing in patients with metastatic cancer.[174]

Dabigatran. Dabigatran is a potent, competitive, reversible direct thrombin (factor IIa) inhibitor with 80% renal excretion, a 14 to 17-hour half-life, and 6% oral bioavailability.[163] Dabigatran inhibits free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation. It is also a substrate of Pgp1; therefore, strong inducers and inhibitors should be avoided.[167,168] Dabigatran has completed Phase III clinical trials in Europe and the United States to evaluate its potential in thromboembolic disorders. It was approved for marketing by FDA in October 2010 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It has also been approved by the European Medicines Agency for primary prevention of VTE in adult patients who have undergone elective hip or knee replacement and has been subsequently launched in the United Kingdom and Germany.[168]

Three Phase III trials (RE-MODEL, RE-NOVATE, RE-MOBILIZE) have been undertaken to study dabigatran versus enoxaparin in the prevention of major VTE and VTE-related mortality after both knee and hip replacement surgery. The RE-MODEL (TKR) and RE-NOVATE (THR) met noninferiority criteria versus enoxaparin 40 mg daily, but the

RE-MOBILIZE (TKR) failed to meet noninferiority criteria against enoxaparin 30 mg twice daily. Rates of major bleeding were comparable between the treatment groups.[173,174]

Potential Benefits and Limitations of Emerging Agents. The new oral anticoagulants are considered to be more convenient and simpler to use than vitamin K antagonists, because routine measuring of anticoagulant effects and dose adjustment are not required. Their oral route of administration as compared with injectables is favorable and may improve adherence and simplify postdischarge prophylaxis. Ecarin clotting time, thrombin time, activated partial thromboplastin time, and activated clotting time have theoretical potential to be used for measures of anticoagulant effect of dabigatran, whereas factor Xa levels and prothrombin time have the potential to measure the anticoagulant effect of apixaban and rivaroxaban. In addition, direct thrombin inhibitor measurement assays and reversal agents are under development for dabigatran. Most of these agents undergo renal clearance, which could lead to drug accumulation in patients with renal impairment.

Currently, there are no antidotes for rivaroxaban, apixaban, or dabigatran to rapidly reverse drug effects if required. This is also a current limitation shared by fondaparinux. LMWH can be partially reversed by protamine, whereas UFH can be fully reversed with protamine. Because these novel oral anticoagulants have longer half-lives than UFH and LMWH, any adverse effects caused by direct inhibition of thrombin or factor Xa will continue for several hours or days after the cessation of therapy.

Cost-Effectiveness of Antithrombotic Prophylaxis

For the initial hospital admission, the costs of DVT and PE are $9,805 and $14,146, respectively, and readmission costs for the same events are $11,862 (DVT cost significantly higher, $p = 0.006$) and $14,722, respectively.[42] With the cost of prophylaxis for approximately 10 days being $20–$250 for most pharmacologic agents, cost efficacy for pharmacologic prophylaxis is well established. A median of 10 days is a common duration of therapy for prophylaxis used in many medical and surgical trials not requiring an extended duration of therapy. A minimum duration of 10 days is also recommended for THR, TKR, and hip fracture surgery patients. Length of hospitalization and hospital costs have also been found to be substantially increased for patients who develop VTE.[175,176] One retrospective analysis demonstrated that total costs were not different for patients who were given prophylaxis with LMWH versus UFH, though VTE rates were substantially lower with LMWH versus UFH.[177] Two other studies found lower total costs of LMWH versus UFH[178,179] and cost-effectiveness of primary prophylaxis to prevent VTE over no prophylaxis.[111] With the introduction of generic enoxaparin and future agents—including a generic fondaparinux, dabigatran, apixaban, and rivaroxaban—the cost of VTE prophylaxis will likely continue to decrease.

Monitoring Antithrombotic Prophylaxis

Although the incidence of HIT with LMWH and UFH varies by patient group, HIT occurs much more frequently (i.e., threefold) with the use of UFH compared with LMWH.

Postoperative orthopedic, cardiac, and vascular surgery patients receiving UFH for one to two weeks for thromboprophylaxis have the highest risk of HIT, ranging from 1% to 5%.[115] In this patient group, platelet count should be monitored at least every other day between postoperative days 4 and 14 or until UFH is stopped (if before day 14), whichever occurs first.[115] The risk of HIT is lower (0.1–1%) among postoperative patients receiving an LMWH or intravascular catheter UFH flushes and medical or obstetric patients receiving LMWH after previously receiving UFH. For these patients, platelet monitoring should occur at least every two or three days from day 4 to 14, or until the UFH or LMWH is stopped (if before day 14), whichever comes first.[115] When the estimated risk of HIT is less than 0.1%, the risk is described as "rare." Patients in this group include medical and obstetric patients receiving only LMWH or medical patients receiving only intravascular catheter UFH flushes, and platelet monitoring is not recommended.

Because LMWH and fondaparinux are cleared renally, pharmacists play an integral role in monitoring the safety and efficacy of therapy. They should pay close attention to patients' renal function and make appropriate dosage changes or modify prophylaxis to other appropriate regimens in collaborative environments. This may be accomplished by measuring anti-Xa levels.

Summary

Despite decades of evidence showing that pharmacologic and mechanical means can help prevent VTE in hospitalized at-risk patients, current national and international prevention strategies remain suboptimal. National organization positions are shifting to include omission of appropriate care as an adverse event or adverse drug event. Therefore, omission of VTE prophylaxis in a patient who develops a VTE is considered an adverse drug event if pharmacologic prophylaxis was indicated or as an adverse event if mechanical prophylaxis was indicated. To date, no adverse-drug-event studies are including "omission" of VTE prophylaxis as an adverse drug event. Inclusion of this adverse drug event will substantially increase the financial implications of adverse drug events nationally.

Future studies are needed in VTE prevention, including elicitation of the optimal duration of thromboprophylaxis (especially after hospital discharge because of the short lengths of stay in U.S. hospitals), the optimal use of currently approved agents for prophylaxis, the impact of preventable VTE as an adverse event or adverse drug event, and validation of individual scoring methods, especially in hospitalized settings. Hospital pharmacy leadership and proactive engagement are driving forces to ensure appropriate prophylactic management of VTE in hospitalized patients.

Recent data revealed that inhospital, pharmacy-driven VTE prevention programs can increase the use of appropriate thromboprophylaxis and reduce VTE events. VTE prophylaxis programs and anticoagulation management, especially in hospitalized settings, are opportunities that pharmacists can take advantage of in their respective health care settings to reduce unnecessary morbidity and mortality from this disease. Because of their expertise in pharmacotherapy, pharmacists are poised to take a leadership role in VTE prevention programs to positively affect patient care within hospitals and beyond.

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