Improving anticoagulant use for prevention of venous thromboembolism

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Articles based on the proceedings of a symposium held December 8, 2009, during the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada. This activity was supported by an educational grant from Ortho-McNeil, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., administered by Ortho-McNeil Janssen Scientific Affairs, LLC.

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See page S31 or http://ce.ashp.org to locate the continuing-education learning objectives, self-assessment questions, and instructions covering the articles in this supplement.
Symposium Introduction

Improving anticoagulant use for prevention of venous thromboembolism

Introduction

Stuart T. Haines

Venous thromboembolism (VTE) is a common and costly cause of morbidity and mortality in the United States. Each year an estimated 600,000 Americans experience symptomatic VTE. Nearly a third of these patients will experience recurrent VTE events over the next 10 years, and as many as 100,000 will die from pulmonary embolism (PE). The health care costs of VTE amount to nearly $500 million annually in the United States.

VTE is preventable, yet the problem persists despite national quality improvement initiatives. Reducing the frequency of VTE is a major concern for health-system pharmacists and administrators, particularly because of mandatory practice and outcomes reporting and pay-for-performance requirements by accreditation and governmental bodies.

Anticoagulants play an important role in reducing the frequency of VTE. Currently available agents have shortcomings that make their use problematic, especially in certain patient populations and clinical scenarios. Several new anticoagulants under development offer advantages over traditional agents, including the potential to improve patient outcomes. Health-system pharmacists have a key role in efforts to improve anticoagulant use to prevent VTE, particularly in evaluating the place of new anticoagulants in VTE prevention.

The first article in this supplement describes risk factors for VTE, quality improvement efforts aimed at VTE prevention, and strategies that health-system pharmacists can use to improve anticoagulant use and outcomes in patients at risk for VTE. In the second article, the difficulties and issues associated with VTE risk assessment and the use of drug therapies for VTE prophylaxis are discussed. The third article provides an overview of the shortcomings of currently available anticoagulants and the characteristics of some of the new agents demonstrated in Phase III clinical trials. The mechanisms of action, pharmacokinetics, administration, efficacy, safety, and potential for drug interactions of emerging anticoagulants for prevention of VTE are described in detail. Finally, the fourth article discusses several clinical and management challenges related to the use of anticoagulants for VTE prevention in health systems.

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SYMPOSIUM Improving the quality of care

Improving the quality of care for patients at risk for venous thromboembolism

STUART T. HAINES

Purpose. To describe risk factors for venous thromboembolism (VTE), quality improvement efforts for VTE prevention, and strategies health-system pharmacists can use to improve anticoagulant use and outcomes in patients at risk for VTE.

Summary. Risk factors for VTE involve the presence of one or more components of Virchow’s triad (endothelial injury, circulatory stasis, and hypercoagulable states) and are exceedingly common in hospitalized patients. Several effective methods for VTE prophylaxis are readily available but remain underused. Quality improvement initiatives to improve VTE prophylaxis rates include evidence-based clinical practice guidelines, mandatory practice and outcomes reporting, and pay-for-performance requirements. The development and implementation of VTE risk assessment tools and treatment algorithms, protocols, policies, and procedures are among the strategies that health-system pharmacists can use to improve anticoagulant use and quality of care in patients at risk for VTE.

Index terms: Anticoagulants; Hospitals; Patient care; Pharmacists, hospital; Protocols; Quality assurance; Risk management; Venous thromboembolism

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Rudolf Virchow, a 19th-century German physician and physiologist, described the three main types of abnormalities that can result in thrombus (clot) formation in blood vessels: endothelial injury, circulatory stasis, and hypercoagulable states. These three abnormalities—known as Virchow’s triad—are the fundamental causes of venous thromboembolism (VTE). Virchow understood that injury to the vascular endothelium (i.e., lining of the inner wall of blood vessels) through trauma, surgery, or insertion of a catheter provokes a cascade of events, including fibrin formation and platelet adhesion, and results in clot formation. He also recognized physicians and pharmacists, and the American Society of Health-System Pharmacists for his participation in the symposium and for his work on this article. This article was developed with the assistance of a medical writer working with ASHP Advantage. The medical writer, Susan R. Dombrowski, M.S., reports that she has no relevant financial relationship with Procter & Gamble. Dr. Haines received an honorarium from the American Society of Health-System Pharmacists for his participation in the symposium and for his work on this article. This article was developed with the assistance of a medical writer working with ASHP Advantage. The medical writer, Susan R. Dombrowski, M.S., reports that she has no relevant financial relationship with a commercial interest, as defined by the Accreditation Council for Pharmacy Education. The author approved the final article and all its content.

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References


that clots are more likely to form in slow-moving blood than in blood that flows swiftly. The forces (i.e., pressures) that propel blood and the rate of blood flow are much lower in the veins than in the arteries, so spontaneous clot formation is more likely in the veins than in the arteries. A near cessation in blood flow (i.e., stasis) alone can provoke clot formation. Circulatory stasis and clots can occur during prolonged periods of immobility (e.g., in elderly patients or air travelers).

Virchow also was aware that some people are more or less prone to clot formation than others because of hereditary deficiencies or genetic mutations (e.g., people with hemophilia have a reduced tendency to clot because of a deficiency of clotting factor VIII or IX). Clot formation is associated with numerous hypercoagulable states (i.e., thrombophilias) characterized by excessive amounts of procoagulant substances in the circulation or deficiencies of endogenous anticoagulants caused by heredity, genetic mutations, acquired diseases, or malignancy.

Virchow understood the role that the three phenomena—vessel injury, blood stasis, and circulating factors—play in the development and propagation of clots. He reached this understanding without the benefit of electron microscopes, mass spectrometry, or enzyme-linked immunosorbent assay. Today’s clinicians can still use Virchow’s triad to identify patients at risk.

**Identifying patients at risk**

Most hospitalized patients are at risk for VTE, but VTE prophylaxis is underutilized. Table 1 lists the major risk factors for VTE, and these risk factors reflect the presence of one or more components of Virchow’s triad. For example, patients undergoing major surgery experience endothelial injury and are immobilized during and after the procedure. Patients undergoing orthopedic procedures involving a hip or knee are often inactive for several days during a postoperative recovery period. Major trauma from a motor vehicle accident or gunshot results in endothelial injury; surgical repair often is required, with additional endothelial injury and immobilization during the procedure and recovery period.

Patients with malignancy, a common cause of hospitalization, are in a hypercoagulable state. Some malignancies (e.g., brain tumors; adenocarcinomas of the lung, ovary, pancreas, colon, stomach, prostate, and kidney; and hematologic malignancies) are associated with a greater risk for VTE than are others. Moreover, many cancer patients require surgery, have indwelling catheters in place, and are frail and immobilized. The risk for VTE is particularly high in patients who have metastatic disease and are receiving chemotherapy.

Many patients with major medical illness (e.g., congestive heart failure, respiratory failure, myocardial infarction, sepsis) are hospitalized. Venous stasis may develop during their hospitalization.

Increasing age is an independent risk factor for VTE. Hospitalized medical and surgical patients typically are more than 40 years of age, and advanced age adds to the risk for VTE associated with major medical illness and surgery.

A history of deep vein thrombosis (DVT) or pulmonary embolism (PE) often reflects the presence of a hypercoagulable state that places patients at high risk for recurrence. DVT in the lower legs can damage the venous valves and slow the rate of return blood flow to the heart or can result in retrograde flow in the affected vein. Partial venous obstruction from the initial clot may persist, predisposing the patient to recurrent thrombus formation.

Various contributing risk factors for VTE (Table 1) may be present in hospitalized patients. Inherited or acquired hypercoagulable states are among the risk factors that may be present in hospitalized patients.

### Table 1. Risk Factors for VTE

| Major Risk Factors | | | | | |
|--------------------|------------------|
| Major surgery (especially involving the hip, knee, or abdomen) | Major trauma | Malignancy (especially metastatic disease) | Major medical illness (e.g., CHF, MI, sepsis) | Prolonged immobility (≥ 3 days) | Previous DVT/PE | Increasing age (> 40 yr) |

| Contributing Risk Factors | | | | | | | |
|---------------------------|------------------|------------------|------------------|------------------|------------------|
| Thrombophilia/hypercoagulable states | Antithrombin III deficiency | Protein C or S deficiency | Activated protein C resistance/Factor V Leiden | Prothrombin (20210) gene mutation | Antiphospholipid antibodies | Use of estrogens/raloxifene/tamoxifen | Pregnancy/early post-partum period | Obesity |

CHF = congestive heart failure; DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism; VTE = venous thromboembolism

*This list is not inclusive.*
The most common, factor V Leiden, is a genetic abnormality in coagulation factor V that leads to activated protein C resistance (i.e., failure of the natural anticoagulant protein C to regulate clotting activity of factor V). An acquired hypercoagulable state commonly associated with autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis, Crohn’s disease) is the presence of antiphospholipid antibodies.

Medications with estrogenic activity, including estrogen-containing oral contraceptive tablets and skin patches, estrogen-replacement therapy, and vaginal contraceptive rings that contain estrogen, as well as estrogen agonist–antagonists (i.e., selective estrogen receptor modulators), can provoke clot formation. The mechanism is not entirely understood, but estrogens are believed to induce a hypercoagulable state in a dose-dependent manner. Pregnancy and the early postpartum period also are associated with an increased risk for VTE, presumably because of the high levels of estrogen present at those times.

Obesity increases the risk for VTE, possibly from circulatory stasis caused by pressure from excessive body weight on the leg veins and reduced venous return from the lower extremities. The effect of obesity also could be indirect through diminished physical activity and an increased risk for medical illnesses that predispose patients to VTE (e.g., heart failure, osteoarthritis requiring joint replacement surgery).

Quality of care

Emphasis on the quality of patient care has increased over the years, and the use of practice guidelines and quality measures has moved from voluntary to mandatory. Numerous clinical studies over the past several decades have evaluated the efficacy of various nonpharmacologic and pharmacologic interventions for preventing VTE. In the mid to late 1980s, various organizations used the findings of these studies to develop evidence-based clinical practice guidelines for prophylactic therapy in patients at risk for VTE. As clinicians’ acceptance of these guidelines increased, consensus standards of practice for providing patient care were developed. Organizations devoted to quality improvement began promulgating the use of quality measures to ensure that standards of practice were met and to assess hospital and physician performance and patient outcomes. Over the past four or five years, it has become mandatory to report these quality measures for comparison among practitioners and facilities and identification of those with exemplary performance. Recently, pay-for-performance requirements have been established, with quality goals and financial incentives and rewards for meeting those goals.

Perhaps the best known evidence-based clinical practice guidelines for VTE prevention are those published by the American College of Chest Physicians (ACCP) as part of a set of guidelines regarding the use of antithrombotic and thrombolytic therapy. These guidelines are updated periodically and released as a supplement to the periodical Chest; the most recent (8th) edition was published in June 2008. The 2008 ACCP guideline for VTE prevention is very comprehensive—72 pages long, with 89 recommendations and 728 references. The ACCP guidelines are authoritative and provide a basis for many of the guidelines and quality improvement initiatives of other organizations.

In August 2008, the Agency for Healthcare Research and Quality (AHRQ), a governmental organization, released Preventing Hospital-Acquired Venous Thromboembolism: A Guide for Effective Quality Improvement. This publication relies heavily on the ACCP guidelines, but it also addresses systems of care that should be implemented in hospitals.

Other evidence-based clinical practice guidelines focus on specific patient populations at risk for VTE. For example, guidelines for VTE prevention in patients with cancer are available from the American Society of Clinical Oncology, and guidelines for women during pregnancy or the early postpartum period are available from the American College of Obstetricians and Gynecologists.

The American Academy of Orthopaedic Surgeons (AAOS) Clinical Guideline on Pulmonary Embolism in Patients Undergoing Total Hip Or Knee Arthroplasty is available on the organization’s website, but it has not been published in a peer-reviewed journal. The AAOS document is controversial; it contains recommendations for the use of aspirin to prevent PE in orthopedic surgery that are not consistent with the ACCP guidelines. The ACCP guidelines recommend against the use of aspirin alone for VTE prevention in these patients.

Clinical practice guidelines require the interpretation of evidence. The recommendations and conclusions drawn from the evidence may differ depending on the experience and values of the individuals writing the guidelines. Discrepancies among guidelines from different sources often reflect conflicting opinions among experts.

The clinical studies that are the source of evidence-based guidelines often have stringent patient inclusion and exclusion criteria. Extrapolation of the results of clinical studies to patient populations that did not meet the inclusion criteria is inappropriate, but clinicians often must make well-reasoned inferences when data regarding the best course of action are lacking.

The processes used to develop and publish evidence-based guidelines are time-consuming, often requiring years. By the time guidelines are published, they may not reflect current data. Nevertheless, evidence-based guidelines for VTE prophylaxis are
valuable tools for ensuring quality care.

AHRQ has identified and ranked 10 safety practices on the basis of the strength of evidence. Appropriate VTE prophylaxis in patients at risk is ranked first on this list of the safety practices that can have the greatest impact on patient care.

National quality improvement initiatives have been developed by various organizations to drive efforts to improve the care of patients at risk for VTE. The Joint Commission and National Quality Forum outlined core performance measures that hospitals are required to report, which facilitates quality comparisons among institutions. Several of the core performance measures pertain to VTE (Table 2). The incidence of VTE during or within 30 days after a hospital stay that could have been avoided by using prophylaxis is among the data reported by hospitals.

The Surgical Care Improvement Project (SCIP) is a national initiative developed by the Centers for Medicare and Medicaid Services (CMS), Centers for Disease Control and Prevention, and various organizations, with a goal of reducing postoperative complications by 25% before 2010. The initiative represents the efforts of a coalition of major public and private health groups, including the American Medical Association, American College of Surgeons, American Hospital Association, Veterans Health Administration, and Premier, Inc. Participation in SCIP involves collecting and submitting quality data, sharing best practices and implementation strategies, and making system changes based on quality improvement data. Two SCIP process measures have been established for ordering and administering VTE prophylaxis, and two proposed SCIP outcome measures include reporting the incidence of DVT and PE during hospitalization or within 30 days after surgery (Table 3).

In October 2008, CMS discontinued payment for certain costly, avoidable secondary diagnoses that result from hospitalization and cause serious injury or death. CMS considers VTE after total hip or knee replacement surgery one of these avoidable “never events.” Establishing these outcomes as “never events” without reimbursement is an application of pay-for-performance requirements.

Anticoagulant medications play a central role in preventing VTE, but the drugs are a common cause of adverse events because of their narrow therapeutic index, complex dosing, need for laboratory monitoring, and inappropriate medication use behaviors by patients (e.g., sporadic adherence, failure to keep follow-up appointments, dietary indiscretions). Anticoagulants present a patient management challenge in hospitals, and anticoagulant therapy practices are poorly standardized. Reducing the likelihood of patient harm from the use of these drugs is a Joint Commission National Patient Safety Goal (NPSG.03.05.01). This NPSG was phased in gradually for full implementation by January 1, 2009, but many hospitals had difficulty meeting that deadline. Therefore, the Joint Commission has clarified and simplified its requirements for the NPSG. Evaluating anticoagulation safety practices is a Joint Commission requirement that

### Table 2. Joint Commission and National Quality Forum Core Performance Measures Pertaining to VTE Prophylaxis

<table>
<thead>
<tr>
<th>VTE Core Performance Measures</th>
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<tr>
<td>Risk assessment and prophylaxis</td>
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<tr>
<td>1. Documentation of VTE prophylaxis given or why no prophylaxis was given within 24 hours of hospital admission</td>
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</tr>
<tr>
<td>2. Documentation of VTE prophylaxis given or why no prophylaxis was given within 24 hours of admission or transfer to ICU</td>
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<tr>
<td>VTE outcomes</td>
<td></td>
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<tr>
<td>6. Incidence of potentially preventable hospital-acquired VTE</td>
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<table>
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<tr>
<th>Stroke Core Performance Measures</th>
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<tbody>
<tr>
<td>Prophylaxis</td>
<td></td>
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<tr>
<td>1. Documentation of VTE prophylaxis within 24 hours of hospital admission</td>
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</tbody>
</table>

*ICU = intensive care unit; VTE = venous thromboembolism.

### Table 3. SCIP Process and Outcome Measures for VTE

<table>
<thead>
<tr>
<th>Process Measures</th>
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<tbody>
<tr>
<td>SCIP VTE-1. Ordered appropriate VTE prophylaxis any time from hospital arrival to 24 hours after anesthesia end time</td>
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</tr>
<tr>
<td>SCIP VTE-2. Received appropriate VTE prophylaxis within 24 hours prior to anesthesia start time to 24 hours after anesthesia end time</td>
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<table>
<thead>
<tr>
<th>Outcome Measures (proposed)</th>
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<tbody>
<tr>
<td>SCIP VTE-3. Intra- or post-operative PE diagnosed during index hospitalization and within 30 days of surgery</td>
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<tr>
<td>SCIP VTE-4. Intra- or post-operative DVT diagnosed during index hospitalization and within 30 days of surgery</td>
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</table>

*DVT = deep vein thrombosis; PE = pulmonary embolism; SCIP = Surgical Care Improvement Project; VTE = venous thromboembolism.
remains a top priority because of its direct impact on patient outcomes. Other requirements are important (e.g., the use of oral unit dose products, prefilled syringes, and premixed infusion bags; obtaining a baseline international normalized ratio prior to initiating warfarin therapy; educating prescribers, staff, patients, and family members), but continual efforts aimed at evaluating and implementing institutionwide anticoagulation safety practices will likely have the greatest impact on patient outcomes.

Closing the gap

The culture of medicine has undergone a gradual evolution over the past several decades.21 In the mid-20th century, health care typically was provided by individuals in solo practices who were autonomous and made decisions on the basis of their knowledge and experience. These individuals carried considerable responsibility and were expected to be infallible, but continuous learning was required to stay abreast of new developments in medicine.

Modern 21st-century medical care is characterized by group practices in which teamwork with input from members of various health care professions is used for problem solving and continuous quality improvement. The burden of decision-making is shared, because it is understood that no one is infallible. Modern medicine is a dynamic field, with rapid changes brought about by the introduction of new information and technologies.

An appreciation of the limitations of 20th-century medicine and the need for alternative approaches to improve the quality of care and patient outcomes in the 21st century provides impetus for identifying strategies for changing the health care culture. These strategies may include obtaining support from institutional management and establishing interprofessional teams. This approach reduces the isolation that all too often inhibits potentially valuable input for solving problems and improving clinical practices. Health-system pharmacists in collaboration with other members of the health care team can play an important role in creating cultural changes and improving VTE prophylaxis practices. Developing hospitalwide or unit-specific treatment algorithms or protocols, policies, and procedures for anticoagulant use is an important undertaking. Topics that may be addressed include anticoagulant selection (i.e., indications for use), dosing, duration of therapy, laboratory and clinical monitoring, adverse event management, transition care (e.g., at the time of transfer from an intensive care unit to a medical floor), and hospital discharge planning. Standardized order sets for anticoagulants should be developed.

In order to achieve measurable and meaningful improvements in quality, multiple strategies will be needed, including creating useful tools, educating practitioners, and providing performance feedback. Several studies have shown that VTE prophylaxis rates improved at institutions that developed and consistently used VTE risk assessment tools and admission order sets. These tools can be paper-based or automated through the use of informatics (e.g., electronic risk scoring systems with alert capabilities to identify high-risk patients, and computerized physician order entry programs with standardized orders and links to treatment guidelines, algorithms, and protocols).22-25

The implementation of VTE risk assessment tools and treatment algorithms, protocols, policies, and procedures requires a comprehensive educational program for health care practitioners, patients, and family members. Health care practitioners should be informed about the rationale for and the logistics of using any new tool or procedure. Inservice education programs and electronic or print newsletters are possible methods for educating staff.

Quality metrics should be developed and data collected in order to assess institutional performance as well as provide ongoing feedback to practitioners and teams. This feedback can be used to identify weaknesses and opportunities for quality improvement.

Conclusion

Historically, implementing changes to improve the quality of care has been a slow process. Quality improvement initiatives, mandated practice and outcomes reporting, and pay-for-performance requirements for VTE prophylaxis demand the attention of health-system pharmacists. The challenges associated with fulfilling these requirements represent an opportunity for health-system pharmacists to collaborate with other members of the health care team to improve the use of anticoagulants and the quality of care in patients at risk for VTE.

References

7. Francis CW. Clinical practice. Prophylaxis for thromboembolism in hospital-
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Issues in assessing and reducing the risk for venous thromboembolism

William E. Dager

**Purpose.** To describe issues and challenges associated with venous thromboembolism (VTE) risk assessment and the use of drug therapies for VTE prophylaxis.

**Summary.** Patients at risk for VTE are a heterogeneous group. Systems for scoring VTE risk have been developed to identify patients who warrant prophylaxis, but most risk-scoring systems are complex and have not been validated. The optimal drug therapies and dosing strategies for reducing VTE risk are not well defined for many clinical situations, despite the availability of evidence-based guidelines from authoritative sources. Patient characteristics can influence the agent selected, dosing, timing of initiation, and duration of drug therapy. Individualized approaches to prophylaxis in patients undergoing major orthopedic surgery should take into account the presence of severe renal impairment, critical illness, morbid obesity, epidural catheters, and history of heparin-induced thrombocytopenia. To provide safe, effective VTE prophylaxis, clinicians, including health-system pharmacists, should collaborate in developing management plans tailored to patients' needs.

**Conclusion.** Preventing VTE is a challenge that can be addressed by gaining an understanding of the issues involved in patient assessment and prophylactic drug therapy and using a team approach to optimize patient outcomes.

**Index terms:** Anticoagulants; Dosage; Drugs; Heparin; Hospitals; Pharmacists; hospital; Protocols; Risk management; Team; Thrombocytopenia; Toxicity; Venous thromboembolism

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or life-threatening events will differ between trials, making it difficult to cross compare trial observations for a particular agent or agents. The American College of Chest Physicians (ACCP) updated its evidence-based clinical practice guidelines for VTE prevention in 2008. Recommendations for VTE prophylaxis are provided in these guidelines for patients undergoing various types of surgery, including vascular, gynecologic, urologic, laparoscopic, bariatric, thoracic, coronary artery bypass, neurosurgery, general, and orthopedic surgery. General surgery patients are classified on the basis of whether they are at low, moderate, or high risk for VTE or have multiple risk factors for VTE or a high risk for bleeding. Bleeding is a particularly important concern after surgery, since pharmacologic interventions to prevent VTE increase the risk for oozing or bleeding at the surgical site.

Orthopedic surgeries specifically addressed by the ACCP guidelines include procedures for total hip and knee replacement, knee arthroscopy, hip fracture, and spinal cord injury. Patients undergoing total hip or knee replacement or hip fracture surgery are well studied, because the large number of Americans who undergo these procedures every year have a high risk for VTE and associated health care costs. Patients with trauma, burns, or medical illness (acute medical illness, cancer, critical care) and long-distance travelers also are within the scope of the ACCP guidelines. The types of interventions outlined in the ACCP guidelines include graduated compression stockings (GCS), intermittent pneumatic compression (IPC), unfractionated heparin (UFH), low molecular weight heparin (LMWH), the indirect factor Xa inhibitor fondaparinux, and vitamin K antagonists (e.g., warfarin).

Determining which patients require VTE prophylaxis involves a risk factor assessment (Table 1), for which a risk-scoring system may be used. Such systems assign points to each VTE risk factor (usually weighted on the basis of the contribution of the factor to VTE risk), and prophylaxis is indicated for a patient if the sum of the points for all of his or her risk factors exceeds a threshold. The threshold reflects the level beyond which the risk is unacceptably high without pharmacologic prophylaxis. Most of these risk-scoring systems are complex to use, have not been validated, and do not take into consideration bleeding risk, although a model for predicting cancer chemotherapy-related VTE recently was validated. The opt-out approach involves the automatic ordering of VTE prophylaxis unless a condition exists suggesting that prophylaxis is unnecessary or potentially harmful (Table 2).

Requirements for VTE prophylaxis can change during the course of hospitalization and after discharge. Therefore, the need for prophylaxis should be reassessed periodically.

**Initiating prophylaxis**

The initiation of VTE prophylaxis is a challenge for clinicians, especially when prophylaxis is needed for surgical patients. The Surgical Care Improvement Project (SCIP) is a national quality improvement initiative developed by the Centers for Medicare and Medicaid Services.

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**Table 1.**

| Risk Factors for VTE Commonly Used in Risk Scoring Systems 
  |
|---------------------------------------------------------------|
| **Advanced age** |
| **History of VTE** |
| **Malignancy** |
| **Congestive heart failure** |
| **Respiratory disease/chronic obstructive pulmonary disease** |
| **Obesity (BMI > 30 kg/m²)** |
| **Prolonged immobility/length of stay ≥ 3 days** |
| **Surgery/trauma** |
| **Stroke** |
| **Acute medical illness** |
| **Inflammatory bowel disease (Crohn’s disease/ulcerative colitis)** |
| **Hypercoagulable states** |

BMI = body mass index; VTE = venous thromboembolism

**Table 2.**

<table>
<thead>
<tr>
<th>Criteria for Opting Out of VTE Prophylaxis at the University of California Davis Medical Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imminent invasive procedure</strong></td>
</tr>
<tr>
<td><strong>Use of warfarin with INR &gt; 1.4 or on therapeutic anticoagulation</strong></td>
</tr>
<tr>
<td><strong>Recent intraocular or intracranial surgery</strong></td>
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<tr>
<td><strong>Thrombocytopenia</strong></td>
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<tr>
<td><strong>Spinal tap or epidural anesthesia anticipated within 12 hr</strong></td>
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<tr>
<td><strong>Active bleeding</strong></td>
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<tr>
<td><strong>Active or chronic severe liver disease</strong></td>
</tr>
<tr>
<td><strong>Receiving comfort care</strong></td>
</tr>
<tr>
<td><strong>Healthy, fully ambulatory, and &lt; 40 years old</strong></td>
</tr>
<tr>
<td><strong>History of HIT/hypersensitivity to UFH or LMWH</strong></td>
</tr>
</tbody>
</table>

HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism
The need for and risks associated with VTE prophylaxis in orthopedic surgery patients (i.e., the risks for bleeding and thrombosis) change over time and depend on the type of orthopedic surgery. The risk for DVT and bleeding is initially higher after knee replacement surgery than after hip replacement surgery. However, the risk for pulmonary embolism (PE) is higher after hip surgery than knee surgery, possibly because of the proximity of the hip to the lungs.

### Duration of prophylaxis

The duration of VTE prophylaxis needed may depend on the period of VTE risk benefiting from prevention. This can be influenced by patient characteristics (e.g., prolonged immobility) and differs among medical patients and surgical patients and different types of surgeries. For example, older, obese patients may require additional prophylaxis after surgery. In a retrospective study of orthopedic patients with VTE despite prophylaxis, the median time to VTE diagnosis was significantly longer after total hip replacement surgery (17 days) than after total knee replacement surgery (7 days, p < 0.001). A longer duration of VTE prophylaxis (six weeks) is now frequently used for patients undergoing total hip replacement surgery. "Prophylaxis in patients undergoing total knee replacement surgery (30 days).

Knee and hip replacement surgeries are invasive, traumatic procedures. All three components of Virchow’s triad (endothelial injury, circulatory stasis, and a hypercoagulable state) are present and promote thrombus formation in patients undergoing these surgeries. The amount of surgical blood loss has diminished with newer surgical techniques, and this may reduce any delay in starting prophylaxis and the risk for VTE.

Regardless, a high risk for VTE is associated with lower-extremity orthopedic procedures unless prophylaxis is provided. In the absence of VTE prophylaxis after knee replacement surgery, the risk for proximal DVT is 5–22% and PE is 1.5–10%. After untreated hip replacement surgery, the risk for proximal DVT is 18–36% and the risk for PE is 0.9–28%.

Fatal PE poses the greatest concern, regardless of the reason for hospitalization. The incidence in orthopedic surgery patients appears to be low when prophylaxis is used (0.1%), although the true incidence of fatal PE is unknown because autopsies in cases of sudden death often are not performed. Asymptomatic VTE confirmed by venography is much more common than fatal PE, even when prophylaxis is used. Asymptomatic VTE is a concern because of the potential for long-term consequences (e.g., postthrombotic syndrome characterized by persistent edema, pain, purpura, dermatitis, pruritus, cellulitis, and ulceration).

### Warfarin

Determining the appropriate target range for INR during prophylactic warfarin therapy is a dilemma for clinicians. The target range recommended by ACCP for VTE treatment as well as prophylaxis in most situations is 2.0 to 3.0. This goal also is recommended by ACCP during warfarin therapy in patients with atrial fibrillation to decrease the risk of cardioembolic stroke. The American Academy of Orthopaedic Surgeons (AAOS) recommends a goal INR of 2.0 or less for prevention of PE in patients undergoing total hip or knee replacement. AAOS recommends warfarin therapy for two to six weeks starting the night before, or after, hip or knee replacement surgery. However, the AAOS recommended range is not as well supported by evidence as are the ACCP guidelines. The goal INR range used in most published studies of patients undergoing hip
or knee replacement is 2.0 to 3.0, although lower ranges (e.g., 1.8 to 2.5, 1.5 to 3.0) have been studied. However, the target range of 1.5 to 2.0 has not been adequately studied. Limited data are available on the goal INR range in patients undergoing hip fracture surgery.

An INR greater than 1.8 with warfarin therapy might reflect sufficient anticoagulation to prevent or treat established subclinical thrombosis in patients for whom bleeding concerns are present. A model for warfarin dosing suggests that a target INR range of 1.7 to 3.3 might be acceptable for patients at risk for VTE, although this model requires validation. However, according to ACCP, INR values less than the recommended range (2.0 to 3.0) may not provide adequate protection against VTE, and such values do not necessarily reduce the risk of bleeding.

Because of concern about spinal hematoma formation in patients with epidural catheters, warfarin initiation should be delayed for at least two hours after removal of the epidural catheter. The first INR measurement should not be taken for at least 12 hours after warfarin initiation because of the lag time before any effect on the INR in more sensitive patients may occur. When the first dose is given the night before or after surgery, the goal INR range usually is not reached until the third postoperative day or later.

Several bedside factors should be taken into consideration in providing warfarin therapy for VTE prevention. In the early postoperative period, fluid may be collected from drains implanted at the surgical site. The appearance of substantial amounts of blood in the drainage container may be a signal of transient sensitivity to warfarin or may suggest excessive bleeding and the need to watch the INR response and warfarin dose accordingly.

For various reasons (e.g., interruption of the medication administration process by a diagnostic procedure), hospitalized patients do not always receive their medications at the proper times, although medication administration and dispensing cabinet records might suggest otherwise. In evaluating the absence of an INR response and adjustment of the warfarin dose, the possibility, albeit uncommon, that a patient did not receive or take his or her dose of warfarin should be considered.

Patient education can play a critical role in the success of warfarin therapy after hospital discharge. The proper timing of this education for surgical patients is important because they typically are in pain and may be unable to retain information and instructions provided during the early postoperative period. However, waiting until hospital discharge to provide patient education is inadvisable because of the high likelihood that the patient will be overwhelmed with information about other aspects of home care. In planning patient education about warfarin and other drug therapies that will be used at home, coordination with other members of the health care team, particularly nurses, is wise.

Aspirin

There is a lack of consensus among orthopedic surgeons, chest physicians, and other practitioners on the use of aspirin for VTE prophylaxis. AAOS considers aspirin alone an option for PE prophylaxis in patients undergoing total hip or knee replacement, especially patients at high risk for bleeding. The dosage recommended by AAOS is 325 mg twice daily for six weeks starting the day of surgery, although 81 mg/day may be used if gastrointestinal symptoms develop. By contrast, ACCP recommends against the use of aspirin alone as thromboprophylaxis for any patient group. This grade 1A recommendation is a strong one based on randomized trials with consistent results.

In the Pulmonary Embolism Prevention (PEP) trial, a large, randomized, placebo-controlled study of patients undergoing hip or knee replacement or hip fracture surgery, aspirin 160 mg/day for 35 days starting preoperatively significantly reduced the incidence of VTE by 36%, from 2.5% with placebo to 1.6% with aspirin (p = 0.0003). Both treatment groups received the study drug in combination with whatever prophylaxis was considered necessary. Interpretation of the PEP study results is complicated by the extensive use of post-hoc analysis. Surprisingly, a higher incidence of acute myocardial infarction was observed in the aspirin group than in the placebo group. Additional data are needed to resolve the controversy surrounding the use of aspirin alone for VTE prophylaxis in orthopedic surgery patients.

LMWH

The use of LMWH products for VTE prophylaxis is not always straightforward, especially for patients with certain unique needs. The LMWH usually is initiated 12–24 hours after hip or knee replacement surgery, which is consistent with recommendations from both ACCP and AAOS. Subsequent dosing should be provided in accordance with the manufacturer’s prescribing information; the dosing interval usually is every 12–24 hours, although an interval of 24 hours may be preferred for long-term prophylaxis.

The effects of enoxaparin are increased in patients with severe renal impairment (i.e., creatinine clearance <30 mL/min, which includes chronic kidney disease [CKD] stage 4 or 5), and the risk of bleeding complications may be increased. Most of the data driving this recommendation came from patients with CKD stage 3 or 4, not dialysis-dependent CKD. Therefore, dosage reduction (e.g., decreasing the enoxaparin dose by 50% or increasing the dosing interval from 12 hours to 24 hours) is
recommended when the creatinine clearance (CrCl) is between 20 and 30 mL/min. Patients on hemodialysis and those with CKD stage 5 were excluded from clinical trials; therefore, dosing in this population remains unclear. Tinzaparin and dalteparin appear safe to use without dosage adjustment or anti-factor Xa monitoring in patients with CrCl that exceeds 20 mL/min.30,31

Although four to six weeks of VTE prophylaxis appears warranted after total hip and knee replacement surgery, the ACCP guidelines recommend VTE prophylaxis with LMWH for at least 10 days and extended prophylaxis for up to 35 days for patients undergoing hip or knee replacement surgery or hip fracture surgery.3,4 The recommended duration of LMWH in the AAOS guidelines is 7–12 days.4 As part of the preoperative evaluation, selection of the pharmacologic agent to be used after discharge should take into consideration the costs and available options on the patient’s insurance plan so that authorization can be obtained, if needed.

Dosing of LMWH products in patients with obesity has been studied because of concerns about a potentially increased risk for VTE due to inadequate prophylaxis when fixed doses of LMWH are used in this patient population. In a retrospective, multicenter study, 817 orthopedic surgery patients received fixed subcutaneous (s.c.) doses of enoxaparin 40 mg/day starting 12 hours before surgery.32 The incidence of VTE detected with bilateral venography during postoperative days 7–10 was 18.7%. There was no relationship between body weight or body surface area and thrombosis, but there was a strong relationship between body mass index (BMI) and thrombosis (p = 0.0002). The incidence of VTE was 31.8% in patients with a BMI exceeding 32 kg/m² (i.e., obese patients) and 16.7% in patients with a BMI less than 32 kg/m² (p < 0.001).

There was no relationship between bleeding and BMI. Two s.c. enoxaparin dosing regimens were compared in a nonrandomized study of 481 patients undergoing bariatric surgery for morbid obesity.33 The first 92 patients enrolled received 30 mg every 12 hours, and the subsequent 389 patients received 40 mg every 12 hours. Early ambulation, GCS, and IPC were used in both groups. The two groups had a similar BMI (51.7 kg/m² for the first group and 50.3 kg/m² for the second group). The incidence of postoperative DVT complications was significantly lower (0.6%) in the second group (the group receiving the larger enoxaparin dosage) than in the first group (5.4%, p < 0.01). One patient in each group required treatment for hemorrhage (i.e., the larger enoxaparin dose was not associated with an increased risk for bleeding). However, duration is another consideration. In a single practitioner’s report of experience with 308 consecutive bariatric surgery patients, the incidence of thromboembolism was significantly higher in patients who received 3 days (4.5%) of prophylaxis than in those who received 10 days (0%) of prophylaxis. The patients’ median BMI was 47 kg/m², and the enoxaparin dose was 30 mg twice daily for the duration of hospitalization (approximately two to three days) and 40 mg once daily after discharge.34

A subgroup analysis of the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients (PREVENT) trial, which compared dalteparin 5000 units/day with placebo, demonstrated no difference in outcomes between obese (BMI 34 ± 5 kg/m², n = 1118) and non-obese (BMI 25 ± 4 kg/m², n = 2563) subjects.35 Additional information is needed to determine the possible benefit of dalteparin doses greater than 5000 units/day in morbidly obese patients. In a small analysis of VTE prophylaxis with 40 mg of enoxaparin after total hip arthroplasty or total hip replacement, injection into the thigh in patients with a BMI over 25 kg/m² was associated with a loss of anti-Xa activity, compared with other sites.36

Analysis of the results of these and other studies has led some clinicians to recommend increasing the dosages of LMWH used for VTE prophylaxis in patients with morbid obesity (i.e., a BMI of 40 kg/m² or higher) by 30% over dosages used for nonobese patients.37 Clinical practice guidelines have yet to include such a recommendation.

The efficacy of LMWH for VTE prophylaxis may be diminished in critically ill patients in the intensive care unit (ICU) because of antithrombin deficiency, fluid overload, edema, or other factors.37-39 In 89 ICU patients, therapeutic anti-factor Xa levels (0.1–0.3 IU/mL) were achieved 4 hours, 12 hours, and 24 hours after a 40-mg s.c. dose of enoxaparin in 56.5%, 39.3%, and 12.6% of the patients, respectively.38

The pharmacokinetics and pharmacodynamics of enoxaparin 30 mg s.c. every 12 hours were compared in two cohorts of critically ill patients suffering from multiple trauma with or without a 10-kg or greater increase in body weight due to peripheral edema.37 The area under the curve (AUC) for plasma anti-factor Xa activity over the 12-hour period after a dose was highly variable in both groups. The 12-hour AUC, peak plasma anti-factor Xa activity, and antithrombin activity were significantly lower in the patients with edema than in those without edema (p < 0.05). Another study compared a group of 16 ICU patients with a group of 13 noncritically ill medical patients.39 The AUC for anti-factor Xa activity over the 12-hour period after a 40-mg s.c. dose of enoxaparin was significantly lower in the ICU.
patients than in the noncritically ill medical patients \( (p = 0.008) \).

**Fondaparinux**

The use of fondaparinux for VTE prophylaxis can be problematic in certain settings secondary to its extended duration of activity and potential for a higher level of anticoagulant effect. ACCP recommends (grade 1A) fondaparinux 2.5 mg s.c. once daily starting six to eight hours after or the next day after hip fracture surgery and other major orthopedic surgeries.\(^5\) The dosing used for VTE prophylaxis may have a therapeutic effect on subclinical thrombosis that develops during surgery. In a meta-analysis of four studies comparing the efficacy of fondaparinux 2.5 mg s.c. once daily with s.c. enoxaparin 30 mg twice daily or 40 mg once daily for preventing VTE in patients undergoing major hip or knee surgery, the incidence of VTE confirmed by venography (i.e., asymptomatic VTE) was significantly lower with fondaparinux (6.8%) than with enoxaparin (13.7%, \( p < 0.001 \)).\(^8\) In Phase II fondaparinux dose-finding clinical trials, no significant differences in outcomes were observed with daily doses ranging from 2.5 mg to 12 mg in patients with acute coronary syndrome or 5 mg to 10 mg in patients with established VTE.\(^6,10\) Results in the OASIS 5 trial showed no difference between 2.5 mg of fondaparinux and 1 mg/kg twice-daily warfarin.\(^11\) In obese and nonobese patients receiving fondaparinux for the treatment of VTE (i.e., to prevent VTE recurrence), which involves fixed 10-mg doses for patients weighing more than 100 kg, the incidence of bleeding decreased as weight increased.\(^12\) However the efficacy of the drug in preventing VTE recurrence was not diminished by an increase in weight. These observations support the theory that prophylactic dosing of fondaparinux for prevention of VTE has a potential therapeutic antithrombotic effect.

In August 2009, the Food and Drug Administration (FDA) issued a warning not to administer the initial fondaparinux dose earlier than six to eight hours after surgery because of the risk of bleeding.\(^44,45\) Spinal hematoma formation is a concern during the insertion of epidural catheters in patients receiving fondaparinux (or other anticoagulants), so the drug should be discontinued sufficiently in advance of the placement of an epidural catheter.\(^3\) The anticoagulant effect of fondaparinux can persist for two to four days after the drug is discontinued.\(^46\)

**Heparin-induced thrombocytopenia**

Heparin-induced thrombocytopenia (HIT) is a rare immune-mediated adverse effect associated with LMWH and UFH therapy that clinicians need to be aware of because it increases the risk for thrombosis.\(^47\) The risk for HIT depends on the duration of heparin exposure and the dosage used. The condition typically develops if heparin therapy is continued for a week or longer. It may also develop later if the patient is re-exposed to heparin within 100 days, especially within one month. Whether VTE in a patient discharged from the hospital receiving heparin for VTE prevention represents HIT or failure of prophylaxis (e.g., nonadherence) can be difficult to ascertain. In delayed-onset HIT, thrombocytopenia may occur up to 40 days after heparin therapy is discontinued. Given the potential for VTE to occur after discharge, the platelet count should be checked in any patient with VTE after recent surgery. If more than 100 days has elapsed since heparin therapy was administered, the risk for VTE is similar between heparin-naïve patients and those with a history of HIT.

The development of HIT requires discontinuation of heparin. Fondaparinux is one option that has been used to treat HIT, although rare cases of HIT-type reactions and thrombosis have been reported in patients receiving fondaparinux.\(^48\) The direct thrombin inhibitors typically are the initial anticoagulants used in the setting of HIT. One treatment option that is currently available for prophylaxis in patients with a recent history of HIT might be lepirudin administered subcutaneously.\(^49,50\) Emerging anticoagulants that may prove useful in patients with HIT include the oral direct factor Xa inhibitor rivaroxaban and desirudin, a direct thrombin inhibitor given by s.c. injection.\(^49,50\) The cost of using these agents is currently unknown until available.

The reported risk for HIT is highest among patients undergoing orthopedic, cardiac, and vascular surgery who receive UFH for one to two weeks.\(^51\) When examining a consecutive series of 146 patients with sufficient suspicion of HIT for initiating a direct thrombin inhibitor at UC Davis Medical Center, HIT was not found in any orthopedic patients.\(^51\) During this period, none of the more than 900 orthopedic surgery patients who received a short course of UFH while transitioning to warfarin developed HIT.\(^52\) The lack of HIT with the use of heparin in this population was attributed to the short-term use of UFH and transition to warfarin for a minimum of one month for prophylaxis.

**Surveillance ultrasound**

The use of ultrasound screening for DVT after orthopedic surgery has been suggested as a way of identifying patients for treatment. The clinical usefulness of such screening was evaluated in a study of 346 patients undergoing hip or knee replacement surgery followed by 10 days of LMWH therapy.\(^52\) Patients were randomly assigned to receive prolonged prophylaxis with LMWH for an additional three weeks or postoperative ultrasound screening for proximal and distal thrombosis. Therapeutic anticoagulation was provided to pa-
patients in whom thrombosis was detected by screening, but patients with negative screening results did not receive additional LMWH therapy after day 10. The incidence of symptomatic VTE 35 days after hip or knee replacement surgery was 4.3% with prolonged prophylaxis and 2.3% with screening, a difference that was not significant ($p = 0.37$). Screening did not reduce the rate of symptomatic VTE over the subsequent three-month follow-up period.

Guidelines from ACCP recommend against the routine use of ultrasound screening for DVT before hospital discharge of asymptomatic patients after major orthopedic surgery (grade 1A) because ultrasound screening is unreliable. Moreover, positive ultrasound test results could affect institutional performance reports on Joint Commission and National Quality Forum core performance measures and SCIP outcome measures. Further, they could reduce reimbursement from CMS (the agency considers VTE after total hip or knee replacement surgery an avoidable “never event”).

**Team approach**

In providing VTE prophylaxis, the risk for thrombosis must be weighed against the risk for bleeding from prophylactic interventions. The risk for thrombosis usually is a concern for internists, whose primary goal is ensuring that adequate prophylaxis is given for the proper duration on the basis of risk factor assessment. The risk for bleeding usually is a concern for surgeons primarily in the early postoperative period, and the timing of pharmacotherapy to avoid bleeding during this period is a challenge.

Health-system pharmacists should collaborate with other members of the health care team in preventing VTE, especially for patients with unique needs (e.g., patients with severe renal impairment, morbid obesity, epidural catheters, or HIT and critically ill patients). Managing laboratory values alone has limitations and is insufficient; input is needed from clinicians who can make patient assessments at the bedside.

**Conclusion**

Clinicians face a variety of challenges in identifying patients at risk for VTE and devising prophylactic strategies. Patients at risk for VTE are a heterogenous group with diverse characteristics and needs, and many questions remain about the optimal pharmacotherapeutic approach to meet their needs. Health-system pharmacists can improve outcomes in patients at risk for VTE by gaining an understanding of the issues involved in patient assessment and prophylactic drug therapy and by using evidence-based clinical practice guidelines and their clinical expertise to advise other members of the care team about the proper use of drug therapies for VTE prophylaxis.

**References**

20. Fuster V, Ryden LE, Cannom DS et al. ACC/AHA/ESC 2006 guidelines for the


Emerging anticoagulants for venous thromboembolism prevention

TOBY C. TRUJILLO

Purpose. To discuss the advantages and disadvantages of currently available anticoagulants, describe the characteristics of the ideal anticoagulant, and compare and contrast the mechanisms of action, pharmacokinetics, administration, efficacy, safety, and potential for drug interactions of currently available and emerging anticoagulants for prevention of venous thromboembolism (VTE).

Summary. Despite the proven efficacy of currently available agents for VTE prevention, several shortcomings exist that may prevent their use under various circumstances. These include administration by injection, narrow therapeutic index, unpredictable pharmacokinetics and pharmacodynamics, need for laboratory monitoring, risk for bleeding, and drug interactions. The ideal anticoagulant would overcome many of these issues; in particular, it would be available as an oral formulation. Dabigatran, an oral direct thrombin (factor IIa) inhibitor, and apixaban and rivaroxaban, oral direct factor Xa inhibitors, represent new agents for anticoagulation that may address many of these issues. While not available as an oral agent, desirudin is an additional option and offers increased flexibility when a non-heparin-based injectable anticoagulant is desired. Current literature indicates that these agents generally do not require laboratory monitoring and are safe and effective for VTE prevention in clinical studies of patients undergoing major orthopedic surgery.

Conclusion. The development of new anticoagulants that may overcome limitations of existing agents represents an opportunity to further improve outcomes in patients at risk for VTE in orthopedic surgery.

Index terms: Anticoagulants; Apixaban; Dabigatran; Desirudin; Dosage; Drug administration; Drug interactions; Hemorrhage; Mechanism of action; Pharmacokinetics; Rivaroxaban; Surgery; Toxicity; Venous thromboembolism

Venous thromboembolism (VTE), especially as a hospital-acquired condition, should be of concern to all health care practitioners. VTE incurs significant morbidity and mortality for individual patients, as well as significant overall costs to the health care system. In addition, pulmonary embolism (PE) is the number one preventable cause of death for hospitalized patients. As we consider how to meet quality measures for the prevention and treatment of VTE, we need to be cognizant of advances in VTE prevention strategies that may help overcome shortcomings of the currently available pharmacologic and mechanical options for prophylaxis.

It is of course appropriate for pharmacists to focus on advances in anticoagulant therapy, but it is also important to be aware of changes in medical practice that may affect the overall risk of VTE. For example, operative techniques for orthopedic procedures have changed substantially, and the changes most likely affect overall VTE risk. Another example is the lower overall risk of VTE with epidural anesthesia versus general anesthesia.1 These factors typically enter into the operating physician’s choice of VTE prevention strategy. Much has been made in the literature of differences be-
Evolution of anticoagulants

Many advances have been made in anticoagulant therapy since the 1930s and 1940s when unfractionated heparin (UFH) and the vitamin K antagonist warfarin were the primary options for treating patients. Most of these advances have resulted from efforts to overcome the shortcomings of UFH and warfarin and focus on more specific targets in the coagulation cascade to improve safety, efficacy, and convenience. The shortcomings of these older agents include a narrow therapeutic index, unpredictable pharmacokinetics and pharmacodynamics (i.e., dose-response relationship), need for laboratory monitoring, and risk for bleeding. Warfarin, which is administered orally, provides some advantages over injectable anticoagulants. However, warfarin exhibits complex pharmacokinetics and pharmacodynamics and interacts with many medications and foods. These issues, along with patient nonadherence, make the drug less than ideal in many circumstances.

Desirudin, an injectable DTI, has been approved for VTE prevention in orthopedic surgery since 2003. Compared with other DTIs, desirudin will likely be available in a dosage form that is more amenable with VTE prevention. New oral agents have the potential to be used in a variety of settings and may eventually take the place of warfarin in prophylactic and therapeutic regimens for many patients.

Despite advances over the years, most currently available anticoagulants affect multiple components of the coagulation cascade (Figure 1). UFH, LMWHs, and fondaparinux all inhibit coagulation proteins by binding to antithrombin and accelerating its ability to inactivate clotting factors. The clotting factors affected include factor Xa and factor IIa (thrombin), although the extent of inhibition of each varies depending on the agent being used. Warfarin and other vitamin K antagonists also affect multiple coagulation proteins and disrupt the production of functional vitamin K-dependent clotting factors II, VII, IX, and X as well as the anticoagulant proteins C and S. Argatroban, lepirudin, and bivalirudin are DTIs that do not bind antithrombin. The development of
new agents has led to the identification of compounds that directly target and inhibit specific coagulation proteins.

The currently available anticoagulants have many limitations. The need for s.c. administration of LMWH and fondaparinux and i.v. administration of DTIs is a disadvantage for patients requiring extended VTE prophylaxis in the outpatient setting (e.g., patients recovering from hip replacement surgery). The need for enoxaparin dosing adjustment in patients with severe renal impairment (creatinine clearance <30 mL/min), the lack of data for dosing dalteparin in patients with severe renal impairment, and the risk of heparin-induced thrombocytopenia can limit the use of LMWH. Fondaparinux is contraindicated in patients with severe renal impairment. The available DTIs should be used cautiously in patients with organ dysfunction (renal impairment for lepirudin and bivalirudin, and hepatic impairment for argatroban), and data on their use in VTE prevention are limited.

Emerging anticoagulants

A large number of oral and injectable anticoagulants that target factor Xa, factor IIa, or other components of the coagulation cascade are in development and have potential applications in VTE prevention, treatment, or both (Figure 2). Desirudin is an injectable DTI typically administered via the s.c. route. The drug was approved by the Food and Drug Administration (FDA) in 2003 for prevention of VTE in major orthopedic procedures and became commercially available in 2010. Desirudin provides an option when an injectable DTI is preferable for the prevention and possibly treatment of thromboembolic diseases.

Altering the molecular structure of warfarin to address some of its shortcomings has been investigated. A new oral vitamin K antagonist, tecarfarin, is currently in development. Tecarfarin is not metabolized by cytochrome P-450 enzymes, so its use circumvents many of the concerns about drug interactions associated with warfarin. A recent study demonstrated that a higher level of international normalized ratio (INR) control may be achievable with tecarfarin than with warfarin in patients with atrial fibrillation.

The agents that have received the most attention recently and are the most likely to come to market in the near future include the oral direct thrombin (factor IIa) inhibitor dabigatran and two oral direct factor Xa inhibitors, apixaban and rivaroxaban (Table 1). Dabigatran and rivaroxaban have been available in Europe and Canada since 2008 for use in the prevention of deep vein thrombosis (DVT) and PE in major orthopedic procedures. Rivaroxaban is the only agent among the three for which a new drug application has been submitted to FDA. An application for dabigatran was not submitted to FDA in 2009 as had been expected. An FDA advisory committee recommended approval of rivaroxaban in March 2009. However, in May 2009 additional information was requested by FDA, although no new clinical or nonclinical studies were requested.

Pharmacokinetic and pharmacodynamic characteristics of emerging anticoagulants are listed in Table 1. Desirudin has a short half-life of only 2 hours, similar to other commercially available DTIs. Although desirudin is eliminated primarily by the kidney, its short half-life and ability to be monitored by activated partial thromboplastin time (aPTT) make it a potential option for patients who have various levels of renal insufficiency. The current labeling provides specific dosing recommendations for various levels of renal function. In addition, routine aPTT monitoring would allow patients who are accumulating unsafe drug levels to be identified and dosing to be adjusted.
This agent would be an option for patients requiring non-heparin anticoagulant therapies, as an alternative to the synthetic pentasaccharide fondaparinux.

The times to peak plasma concentration and half-lives of the three emerging oral anticoagulants dabigatran, rivaroxaban, and apixaban are similar. Their half-lives facilitate administration once or twice daily. The bioavailability of dabigatran is low, requiring the administration of large doses to achieve therapeutic concentrations. In addition, dabigatran is administered as a prodrug, dabigatran etexilate, that requires an acidic environment for absorption. Therefore, clinically relevant interactions with proton pump inhibitors and other acid-suppressing therapies are likely for dabigatran. However, the risk for drug interactions with dabigatran is low compared with the other emerging agents because cytochrome P-450 enzymes are not involved in metabolism of the drug. Since dabigatran is eliminated primarily by the kidneys, dosage reduction may be required for patients with renal impairment. Drug accumulation is a concern because of the potential for bleeding, and further research is needed to fully characterize how the drug may be used safely in patients with various levels of renal impairment.

In contrast to dabigatran, the bioavailability of apixaban and rivaroxaban is greater than 50% and 80%, respectively. Renal elimination is higher for rivaroxaban (66%) than for apixaban (25%), but the 66% for rivaroxaban includes an inactive metabolite. Approximately 30% of the parent drug is cleared by the kidneys in patients taking rivaroxaban. Nevertheless, renal impairment may be a consideration in the dosing of rivaroxaban. Apixaban is less likely than rivaroxaban to accumulate in patients with renal impairment. Although use in patients with renal impairment may be of less concern with apixaban and rivaroxaban, both agents are metabolized by cytochrome P-450 3A4. These drugs can interact with potent inhibitors of both CYP3A4 and P-glycoprotein, and their use will likely require a level of vigilance for potential drug interactions similar to that for warfarin.

**Dabigatran efficacy and safety.** The efficacy and safety of dabigatran for VTE prevention was explored in three key clinical trials involving patients undergoing major orthopedic surgery. Dabigatran was compared with s.c. enoxaparin in three randomized double-blind studies, two of which looked at VTE prevention in patients undergoing total knee replacement surgery (known as RE-MOBILIZE and RE-MODEL), while the third study, known as RE-NOVATE, was conducted in patients undergoing total hip replacement surgery (Table 2). The same primary efficacy outcome (total VTE events and all-cause mortality) was used in all three studies, but the bleeding definitions used in the safety analysis varied somewhat. The same two dabigatran dosages (150 mg or 220 mg twice daily) were used in all three studies, although a half dose was used as the initial dose in RE-NOVATE. The timing of the first dose was 1-4 hours after surgery in two studies (RE-MODEL and RE-NOVATE) and 6-12 hours after surgery in the other study. The duration of therapy was shorter in the RE-MODEL and RE-MOBILIZE studies of knee replacement patients than in RE-NOVATE (i.e., hip replacement patients), but this difference is appropriate given the current guideline-based recommendations for duration of VTE prophylaxis in these two patient populations.

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**Table 1. Characteristics of Emerging Anticoagulants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran Eteixlate*</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
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<td>Factor Xa inhibition</td>
<td>Factor Xa inhibition</td>
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<td>Proton pump inhibitors</td>
<td>Potent inhibitors of both CYP3A4 and P-glycoprotein</td>
<td>Potent inhibitors of both CYP3A4 and P-glycoprotein</td>
<td>Pharmacodynamic with other agents that affect platelet function or coagulation</td>
</tr>
</tbody>
</table>

*Dabigatran is administered as a prodrug, dabigatran etexilate. 
*Renal elimination of rivaroxaban and its inactive metabolite is 66%. Approximately 30% of the parent drug is cleared by the kidneys.
The enoxaparin dosing regimen commonly used in North America (30 mg twice daily) was used in RE-MOBILIZE, but the less intense regimen preferred in Europe (40 mg once daily) was used in the other two studies. These differences in dosing are important to consider because they may have affected the study results and may have different implications for clinical practice in different regions of the world.

In RE-NOVATE (i.e., total hip replacement surgery patients receiving the European enoxaparin dosing regimen), the primary efficacy outcome (i.e., composite of total VTE events and all cause mortality) had occurred after 28–35 days in 53 (6.0%) of 880 patients in the dabigatran 220 mg/day group, 75 (8.6%) of 874 patients in the dabigatran 150 mg/day group, and 60 (6.7%) of 897 patients in the enoxaparin group. Both dabigatran doses were judged non-inferior to enoxaparin.26 There were no significant differences in the incidence of major bleeding between enoxaparin (1.6%) and either dose of dabigatran (2.0%, p = 0.44 for 220 mg/day; 1.3% p = 0.60 for 150 mg/day). Similarly, the rates of clinically relevant non-major and minor bleeding did not differ between enoxaparin and either dose of dabigatran.

Despite these positive results in evaluating the potential benefit of dabigatran in VTE prevention, it is most instructive to look at the two studies involving knee replacement patients (Table 2). In RE-MODEL, both the 150 mg and 220 mg once daily dose of dabigatran met the non-inferiority criteria with enoxaparin 40 mg once daily. In RE-MOBILIZE (i.e., total knee replacement surgery patients receiving the North American enoxaparin dosing regimen), dabigatran was judged inferior to enoxaparin (i.e., non-inferiority criteria were not met).24 The incidence of the primary outcome after 12–15 days of treatment was 31% with dabigatran 220 mg/day (p = 0.02 versus enoxaparin), 34% with dabigatran 110 mg/day (p < 0.001 versus enoxaparin), and 25% with enoxaparin. Potential explanations for the lack of positive findings for dabigatran include the use of a more intense enoxaparin dosing regimen compared with that used in RE-NOVATE as well as a lower initial dose of dabigatran. The rates of major bleeding and clinically relevant non-major bleeding were similar with both dabigatran doses and enoxaparin (rates of minor bleeding were not reported). Thus, on the basis of the current results, dabigatran appears to be a potentially useful option for VTE prevention but may be less effective than more aggressive regimens of the LMWH enoxaparin.

Despite the varied results in VTE prevention, the dabigatran clinical trial program is a promising one and includes other studies of the drug for use in VTE treatment, for thrombosis prevention in patients with atrial fibrillation, and in conjunction with antiplatelet therapy for the treatment acute coronary syndrome (ACS).27,28 In patients with atrial fibrillation, dabigatran 150 mg twice daily was associated with lower rates of stroke and systemic embolism and similar rates of major hemorrhage compared with warfarin.29 In addition, in patients with acute VTE, dabigatran 150 mg twice daily was as effective as warfarin in preventing VTE recurrence, with a similar incidence of bleeding.27

Apixaban efficacy and safety.

The efficacy and safety of apixaban 2.5 mg twice daily and enoxaparin for VTE prevention in patients undergoing major orthopedic surgery were compared in three randomized, double-blind studies known as...
ADVANCE-1, 2, and 3,28,30 Results have been reported only for ADVANCE-1 and ADVANCE-2. Similar to dabigatran, the apixaban clinical trial program also includes studies of use of the drug for VTE treatment, stroke prevention in patients with atrial fibrillation, and treatment of ACS in conjunction with antiplatelet therapy.

ADVANCE-1 involved 3195 patients undergoing total knee replacement and compared apixaban with enoxaparin 30 mg s.c. twice daily beginning 12–24 hours after surgery and continued for 10–14 days.29 The primary efficacy outcome was total VTE events, and the criteria for non-inferiority included an upper limit of the 95% confidence interval of 1.25. After 10–14 days of treatment, the primary efficacy outcome occurred in 9.0% of apixaban-treated patients and 8.8% of enoxaparin-treated patients (p = 0.06, relative risk, 1.02; 95% confidence interval, 0.78 to 1.32). Since the upper boundary of the 95% confidence interval exceeded 1.25, apixaban did not meet the criteria for non-inferiority to enoxaparin. Although the trial did enroll a sufficient number of patients based on the prespecified power analysis, the overall event rate was much lower than anticipated and likely influenced the statistical analysis. The incidence of major bleeding and clinically relevant non-major bleeding was significantly lower with apixaban (2.9%) than with enoxaparin (4.3%, p = 0.03).

ADVANCE-2 involved 3057 patients undergoing total knee replacement, and the comparison was made between apixaban and enoxaparin 40 mg s.c. once daily beginning 12 hours before surgery.30 After 12 days, the incidence of total VTE events was significantly lower with apixaban (15.1%) than enoxaparin (24.4%, p < 0.001). There was no significant difference between apixaban and enoxaparin in the incidence of major bleeding and clinically relevant non-major bleeding (3.5% versus 4.8%, respectively, p = 0.09).

As with dabigatran, the results of apixaban clinical trials in patients undergoing major orthopedic surgery depended on the enoxaparin dosing regimen used. Although underlying issues with statistical power and methodology were likely in play, the results were less favorable with the more aggressive regimen of enoxaparin 30 mg twice daily than with the 40 mg once-daily regimen. Additional studies comparing the efficacy of apixaban with the North American enoxaparin regimen are needed.

**Rivaroxaban efficacy and safety.** The efficacy and safety of rivaroxaban for preventing VTE in patients undergoing major orthopedic surgery have been evaluated in four randomized, double-blind clinical trials.31-34 The rivaroxaban clinical trial program also includes studies of the drug for VTE treatment, VTE prevention in medicated ill patients, thrombosis prevention in patients with atrial fibrillation, and treatment of ACS in conjunction with antiplatelet therapy. Results of the Einstein-Extension Study of extended rivaroxaban therapy for 6–12 months in patients with established VTE were recently reported.35 The drug was effective for preventing VTE recurrence, with a low risk for major bleeding.

Two of the rivaroxaban studies in patients undergoing major orthopedic surgery involved total hip replacement surgery, and the other two studies involved knee replacement surgery (Table 3).31-34 The same rivaroxaban dosage (10 mg once daily) and primary endpoint (total VTE or death) were used in all four studies, but the duration of therapy and enoxaparin dosing varied. In the studies of total hip replacement (known as RECORD 1 and RECORD 2), the European enoxaparin dosing regimen was used, but a longer and more appropriate duration of enoxaparin therapy was used in RECORD 1 (35 days) than in RECORD 2 (14 days).31,32 Rivaroxaban was judged superior to enoxaparin in RECORD 1 because the incidence of the primary outcome after 35 days of treatment was significantly lower in the rivaroxaban group (1.1%) than in the enoxaparin group (3.7%, p < 0.001).31 There was no significant difference between rivaroxaban and enoxaparin in the incidence of major bleeding (0.3% versus 0.1%, respectively, p = 0.18). The results of RECORD 2 are consistent with these findings.

Rivaroxaban was judged superior to enoxaparin in the two clinical studies of patients undergoing knee replacement surgery.31,34 The results of RECORD 4 provide greater insight for American clinicians than the results of RECORD 3 because the North American enoxaparin dosing regimen was used in RECORD 4 and the European enoxaparin regimen was used in RECORD 3. In RECORD 4, the primary efficacy outcome occurred in significantly fewer rivaroxaban-treated patients (6.9%) than enoxaparin-treated patients (10.1%, p = 0.0118) after 14 days of treatment.34 There was no significant difference between rivaroxaban and enoxaparin in the incidence of major bleeding (0.7% versus 0.3%, respectively, p = 0.1096). Similarly, no significant difference between treatments in major bleeding rates was observed in RECORD 3 (p = 0.93).

**Desirudin efficacy and safety.** The efficacy and safety of desirudin for preventing VTE in patients undergoing hip replacement surgery has been established for over a decade. Two randomized, multicenter, placebo-controlled trials compared desirudin at a dose of 15 mg s.c. twice daily with either UFH 5000 units three times daily36 or enoxaparin 40 mg s.c. once daily.37 In the latter, desirudin was given 30 minutes prior to surgery after the induction
of regional anesthesia if used, while enoxaparin was initiated the evening before surgery. Both regimens were continued for 8–12 days (mean, 9.7 days). The primary endpoint of major thromboembolic events included proximal DVT, fatal or non-fatal PE, or unexplained death. Of the 2079 total patients enrolled, 1587 were included in the final analysis, which showed desirudin to be superior to enoxaparin at preventing the primary endpoint (4.5% versus 7.5%, \( p = 0.01 \)). There were no differences between the two groups with respect to rates of blood loss, serious bleeding, wound hematoma, or infection.

### The ideal anticoagulant

Given the recent focus on new anticoagulant agents for VTE prevention and for other patient populations, it is useful to consider what characteristics an ideal anticoagulant might have and then to evaluate these new options against the ideal agent. The ideal anticoagulant for VTE prevention would have a wide therapeutic index and predictable pharmacokinetics (i.e., little variability among patients and within an individual) and pharmacodynamics (i.e., dose-response relationship), with no need for laboratory monitoring. The drug should be available for both i.v. and oral administration and have a rapid onset of action, even after oral administration. The ideal agent would be able to be initiated in the hospital and continued on an outpatient basis to circumvent the bridge therapy that is sometimes needed in the transition from injectable anticoagulants to warfarin for VTE prevention. Action that is rapidly reversible with or without an antidote is desired. The ideal anticoagulant would be safe, even when used on a long-term basis. It should not have clinically important adverse effects or interact with common foods or other drugs. An agent that does not accumulate or require dosage adjustment in patients with renal or hepatic impairment is preferred. A reasonable cost also is desired.

While desirudin does not fit many of these criteria, it does represent an important addition to the available options for VTE prevention. It offers an additional option for patients in need of a non-heparin based regimen. Its short half-life and monitoring by aPTT make it an attractive option for acutely ill patients. According to the current prescribing information, with desirudin the aPTT should not exceed two times the control value. Dosing recommendations for patients with various levels of renal insufficiency are available. In patients with a creatinine clearance of 30–60 mL/min, the recommended dose is 5 mg s.c. every 12 hours. In patients with a creatinine clearance of <30 mL/min, the recommended dose is 1.7 mg s.c. every 12 hours. In each instance, the aPTT can be used to monitor for drug accumulation and excessive anticoagulant effect. Issues that require further investigation include use of the agent in knee replacement patients, its appropriate use during epidural anesthesia, and the optimal duration of therapy. In the clinical trials discussed here, desirudin was given for an average of 10 days. However, current guidelines recommend 28–35 days of therapy as the standard of care in hip replacement patients. Additional studies are needed to characterize the feasibility

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### Table 3.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RECORD 1</th>
<th>RECORD 2</th>
<th>RECORD 3</th>
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<tr>
<td>No. patients</td>
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<td>2509</td>
<td>2531</td>
<td>3148</td>
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<td>Type of surgery</td>
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<td>Total knee replacement</td>
<td>Total knee replacement</td>
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<td>Timing of initial rivaroxaban dose</td>
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<td>6–8 hr after surgery</td>
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</tr>
<tr>
<td>Duration of rivaroxaban therapy (days)</td>
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<td>35</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Enoxaparin dosage</td>
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<td>40 mg once daily</td>
<td>30 mg twice daily</td>
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<tr>
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<td>12 hr before surgery</td>
<td>12–24 hr after surgery</td>
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<td>Duration of enoxaparin therapy (days)</td>
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<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Total VTE or death</td>
<td>Total VTE or death</td>
<td>Total VTE or death</td>
<td>Total VTE or death</td>
</tr>
<tr>
<td>Non-inferiority margin (%)</td>
<td>3.5</td>
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<td>1.5</td>
<td>4</td>
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</tbody>
</table>

*aAll rivaroxaban doses were administered orally. All enoxaparin doses were administered subcutaneously.

bN/A = not applicable; NR = not reported; VTE = venous thromboembolism.
and cost-effectiveness of desirudin for the recommended duration of therapy. The emerging oral anticoagulants dabigatran, apixaban, and rivaroxaban have many but not all of the characteristics of the ideal anticoagulant. They offer the option of oral administration and elicit a consistent dose response, in contrast to warfarin. They appear safe and effective for VTE prevention in patients undergoing major orthopedic surgery, although data from additional comparative studies using the twice-daily enoxaparin regimen for a sufficient duration are needed, especially for apixaban and dabigatran. Laboratory monitoring is likely not required during therapy with these drugs, provided that they are used in a manner consistent with available clinical trials. However, many patients will likely fall outside the strict inclusion and exclusion criteria of clinical trials, and the potential to monitor anticoagulant response will be of high value. Both dabigatran and rivaroxaban can be assessed with common tests such as the aPTT and the prothrombin time/INR. However, the correlation between prolongation of these coagulation assay results and the efficacy and safety of these agents is as yet unclear, and more work will be required before these agents can be monitored with existing coagulation tests. Drug interactions mediated by cytochrome P-450 enzymes are not an issue with dabigatran, but renal impairment is of concern. Patients with significant renal insufficiency were excluded from clinical studies, and the drug will likely need to be avoided in this patient population. In addition, although baseline renal function may be sufficient to warrant use of dabigatran in a given patient, rapid changes and fluctuations in renal function for any reason will place the patient at risk for drug accumulation and toxicity. Drug interactions are among the major challenges with warfarin administration. Although the potential for drug interactions is of less concern with apixaban and rivaroxaban, it is by no means nonexistent. Both agents are metabolized through cytochrome P450 3A4, and routine monitoring for potential drug interactions will be needed to ensure that these agents are used safely and effectively.

The actions of dabigatran, apixaban, and rivaroxaban are not readily reversible. The drugs are not likely to be removed by dialysis, their half-lives are not short, and no antidotes are available; therefore, these drugs are not likely to be options in patients in whom reversibility is paramount. The management of bleeding in patients receiving these drugs may be a problem and requires further investigation.

The costs of dabigatran, apixaban, desirudin, and rivaroxaban remain to be determined. However, any analysis of cost should include the potential cost savings associated with avoiding the need for laboratory monitoring and reducing readmissions for post-operative VTE. These considerations, as well as any changes in costs associated with adverse effects, should be taken into consideration along with drug acquisition cost in evaluating the cost of using these drugs for VTE prevention.

Conclusion

Several new options for the pharmacologic prevention of VTE in major orthopedic surgery have recently become available or soon will be available. The new anticoagulants have many of the characteristics of the ideal anticoagulant, although significant safety and efficacy considerations will need to be addressed for each agent. These agents have the potential to overcome many of the shortcomings of currently available anticoagulants and to improve outcomes in patients at risk for VTE.

References

18. Gross PL, Weitz JI. New anticoagulants for treatment of venous thromboemb-
SYMPOSIUM  Emerging anticoagulants


Clinical and management challenges in preventing venous thromboembolism in health systems: A case-based panel discussion

STUART T. HAINES, WILLIAM E. DAGER, AND TOBY C. TRUJILLO

Clinicians and managers at health systems face many challenges in preventing venous thromboembolism (VTE) in their institutions. Overcoming these challenges and improving outcomes requires an understanding of clinical and management issues related to VTE prevention.

Clinical challenge 1

Dr. Haines: Mr. Vegas, a 48-year-old man who weighs 430 lb (195 kg) and is 6 feet tall, is admitted to the hospital for bariatric surgery. He has a history of deep vein thrombosis (DVT) in 2006, at which time he was treated successfully with warfarin for 3 months.

Mr. Vegas is at high risk for VTE after bariatric surgery because of his history of DVT and obesity. The American College of Chest Physicians (ACCP) guidelines recommend routine thromboprophylaxis with low molecular weight heparin (LMWH), low-dose unfractionated heparin (UFH) three times daily, fondaparinux, or a combination of one of these pharmacologic methods with optimally used intermittent pneumatic compression for patients undergoing inpatient bariatric surgery.

Purpose. To illustrate clinical and management issues in the prevention of venous thromboembolism (VTE) in health systems.

Summary. Lack of evidence to guide the choice among available anticoagulants and the dosing, timing of initiation, and duration of therapy for VTE prevention in certain clinical situations can present challenges for clinicians. Patient characteristics such as the presence of obesity, epidural catheters, renal impairment, or heparin-induced thrombocytopenia complicate the decision-making process. The introduction of new anticoagulants may overcome some of the clinical challenges associated with VTE prophylaxis, but determining whether to add new agents to the formulary and restrict their use may pose management challenges. The safety, effectiveness, ease of use, and cost of new agents compared with older agents already on the formulary are primary considerations.

Conclusion. An understanding of the clinical and management issues involved in preventing VTE is needed to improve the use of anticoagulants and reduce the incidence of VTE in health systems.
Larger-than-usual doses of UFH and LMWH, with weight-based dosing of LMWH, are recommended by ACCP for these patients. However, the ACCP guidelines do not provide detailed guidance for choosing among and dosing these anticoagulants in obese patients like Mr. Vegas who undergo bariatric surgery. Mr. Vegas has a body mass index (BMI) of 58 kg/m², making him morbidly obese (a BMI >40 kg/m² often is used to define morbid obesity). What anticoagulant therapy would you use to prevent VTE after bariatric surgery in Mr. Vegas?

**Dr. Dager:** It would be important to ascertain whether Mr. Vegas’s DVT in 2006 was idiopathic or provoked as the result of a precipitating factor, such as a long airplane flight or a surgical procedure. Nevertheless, Mr. Vegas is at higher risk for VTE than other patients undergoing bariatric surgery because of his obesity and history of DVT. My biggest concern is the increased risk for pulmonary embolism because of his obesity.

An effort to improve the diet and lose weight prior to bariatric surgery usually is recommended for patients like Mr. Vegas. Enoxaparin 40 mg subcutaneously (s.c.) every 12 hours has been used successfully to prevent VTE in patients undergoing bariatric surgery for morbid obesity. We perform a lot of bariatric surgery at the University of California (UC) Davis Medical Center. As improved surgical techniques have led to shorter lengths of stay and shorter durations of VTE prophylaxis, we subsequently observed an increase in the incidence of VTE. Therefore, we extended our dosing of enoxaparin to 40 mg s.c. every 12 hours starting preoperatively, and prophylaxis is continued for at least seven days after bariatric surgery. To date, we have not observed any VTE complications, which is consistent with a report in which bariatric surgery patients who received 3 days of prophylaxis had a higher incidence of VTE compared with patients who received enoxaparin 30 mg s.c. every 12 hours for 10 days. Fondaparinux 2.5 mg s.c. once daily is recommended by ACCP for VTE prevention in nonobese patients undergoing orthopedic or other major surgery, and the drug may have a therapeutic effect on subclinical thrombosis that develops during or after surgery. However, the appropriate dose to use for obese patients undergoing bariatric surgery is unclear. Weight-based dosing is used for VTE treatment, with fixed daily 10-mg doses for patients weighing more than 100 kg. A daily 5-mg dose might be considered for VTE prophylaxis in Mr. Vegas, although there is no evidence to support its use. This dose may be larger than is required.

An aggressive unfractionated heparin (UFH) regimen of 7500 units s.c. every eight hours might be considered for Mr. Vegas, although evidence to support this regimen also is lacking. When making the transition to warfarin therapy, a factor to consider in choosing a warfarin dose is the likelihood that Mr. Vegas may respond differently than he did three years ago. Therefore, use of the same dose of warfarin that he received in 2006 may not be optimal.

**Dr. Trujillo:** I concur with Dr. Dager. I would use enoxaparin 40 mg s.c. every 12 hours because of the available evidence of its safety and efficacy for VTE prevention after bariatric surgery in the morbidly obese patient population.

Whether an aggressive UFH dosing regimen is reasonable for Mr. Vegas is unclear. At the University of Colorado Hospital, we often have difficulty determining the proper dosage of UFH to use for VTE prophylaxis in medically ill patients who are obese. We typically use a dosage based on weight extrapolated from the Thromboembolism-Prevention in Cardiac or Respiratory Disease With Enoxaparin (PRINCE) trial. In the PRINCE trial, a fixed UFH dosage of 5000 units s.c. every eight hours was used in medically ill patients, and approximately one third of the patients were overweight. We have no evidence to support our approach to UFH dosing in medically ill patients who are obese, however.

I might dose warfarin empirically, titrating to an international normalized ratio (INR) of 2.0 to 3.0 as recommended by ACCP, rather than using the 2006 dose. This approach eliminates body weight as a consideration in dosing.

**Dr. Haines:** Would you consider using the activated partial thromboplastin time (aPTT) to guide UFH dosing (e.g., a target aPTT of 40 seconds)? There is no evidence to support this approach, but using aPTT to guide therapy would at least demonstrate that an anticoagulant effect has been achieved.

**Dr. Dager:** At UC Davis Medical Center, we might use aPTT values to guide UFH dosing for VTE prophylaxis in patients with advanced age (e.g., 80 years or older) or a low body weight (e.g., <50 kg). We would check the aPTT periodically to ensure that anticoagulation is not excessive in these patients.

We have noticed that patients with multiple acute traumas often are antithrombin deficient during the first few days after hospital admission, which we have linked to increased incidence of VTE and mortality in critically ill trauma patients. We use UFH infusions with a target aPTT of 35-45 seconds in trauma patients. We have observed low DVT rates with this approach, although it is not supported by clinical trial data.

In young pediatric patients, you might consider the possibility of the presence of a hypercoagulable state due to a hereditary deficiency in endogenous anticoagulants. This possibility might need to be taken into consideration in making decisions about anticoagulant use or dosing...
to prevent VTE in an obese pediatric patient.

Clinical challenge 2

Dr. Haines: Mrs. Carson is a 63-year-old woman who is admitted for abdominal surgery for colon cancer. She weighs 156 lb (71 kg). An epidural catheter was placed for pain control, but the surgeon would like to remove it today (postoperative day 1). Mrs. Carson has been receiving dalteparin 5000 units s.c. daily for VTE prophylaxis since she is at high risk because of her cancer and surgery.1 Spinal hematoma formation with long-term or permanent paralysis is a rare complication of the use of epidural catheters in anticoagulated patients.1 Insertion and removal of epidural catheters in patients receiving anticoagulants increases the risk of this complication. When is the best time to remove the catheter from Mrs. Carson in relation to her dalteparin therapy?

Dr. Trujillo: The timing of catheter removal in Mrs. Carson is a dilemma because of the need to remove the catheter at a time when the plasma concentration and therapeutic effect of dalteparin are low. This is best done late in the dosing interval but well before the next dose. The dosing interval in Mrs. Carson is 2 hours before the next dose. Six hours after a dose and 6 hours before the next dose. The HIT antibodies formed during the initial exposure to heparin will react if heparin is administered within 100 days (especially within 30 days).6 The HIT antibodies formed during UFH therapy often cross-react with LMWH, eliminating this class of agents as an option.7 Except for rare circumstances, fondaparinux does not cross-react with HIT antibodies, so this drug may be one option for VTE prophylaxis in patients like Mr. Genoa with strongly suspected or confirmed HIT.7 Warfarin alone is not recommended for Mr. Genoa if his platelet count is low because it could increase the risk for thrombosis and result in venous limb gangrene.7

Dr. Trujillo: I agree with Dr. Dager that it is important to check Mr. Genoa’s platelet count now. The 260,000/µL or 130,000/µL value measured one month ago could have been a laboratory error.

If the oral direct thrombin (factor IIa) inhibitor dabigatran or oral direct factor Xa inhibitor apixaban or rivaroxaban were available, I might consider using one of them. In theory, these agents should not cross-react with HIT antibodies, but this has not yet been formally studied. Moreover, clinical trials using these new drugs for VTE prophylaxis in medically ill patients like Mr. Genoa have not yet been published.

I would probably use fondaparinux in Mr. Genoa, although I would be concerned about the possibility that his CHF is severe enough to cause significant renal impairment. The elimination of fondaparinux is prolonged and the risk for bleeding is increased in patients with renal impairment.3 The drug is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min). Therefore, I would check Mr. Genoa’s renal function before initiating fondaparinux. I might use a longer dosing interval (e.g., 48 hours) for Mr. Genoa, instead of the customary 24-hour interval, if renal dysfunction is present and no other reasonable options exist.

Clinical challenge 3

Dr. Haines: Mr. Genoa is a 73-year-old woman who had hip replacement surgery four days ago. Fondaparinux 2.5 mg s.c. once daily was started eight hours after surgery for VTE prophylaxis. Mrs. Minden will be discharged to a rehabilitation facility today. For how long should fondaparinux be continued?

Dr. Haines: Mrs. Minden is a 58-year-old man who is admitted for exacerbation of congestive heart failure (CHF). During a previous admission one month ago for CHF exacerbation, he was given UFH 5000 units s.c. every eight hours for VTE prophylaxis. His platelet count had dropped from 260,000/µL to 130,000/µL at the time of discharge, but no diagnostic testing for heparin-induced thrombocytopenia (HIT) was performed. What is the best choice for anticoagulant therapy to prevent VTE in Mr. Genoa now?

Dr. Dager: The UFH therapy and 50% reduction in platelet count during the previous hospitalization suggests that HIT might have developed in Mr. Genoa, which increases his risk for thromboembolism. The platelet count should be checked. The timing of suspected HIT only one month ago creates a potential risk for rapid-onset HIT if UFH or LMWH is used now. Circulating HIT antibodies formed during the initial exposure to heparin will react if heparin is administered within 100 days (especially within 30 days).6 The HIT antibodies formed during UFH therapy often cross-react with LMWH, eliminating this class of agents as an option.7 Except for rare circumstances, fondaparinux does not cross-react with HIT antibodies, so this drug may be one option for VTE prophylaxis in patients like Mr. Genoa with strongly suspected or confirmed HIT.7 Warfarin alone is not recommended for Mr. Genoa if his platelet count is low because it could increase the risk for thrombosis and result in venous limb gangrene.7

Dr. Dager: The ACCP guidelines recommend extended prophylaxis for up to 35 days using LMWH, a vitamin K antagonist, or fondaparinux after total hip or knee replacement.1 I recommend a longer duration (e.g., six weeks) of VTE prophylaxis after hip replacement surgery for patients like Mrs. Minden because VTE usually occurs later in this patient population than in patients undergoing total knee replacement surgery.9 She could switch to warfarin and stop fondaparinux once an INR of 2.0 to 3.0 is achieved, which is the range recommended by ACCP and consistent with most published studies of patients undergoing hip or knee replacement.1
Dr. Haines: I commonly see injectable anticoagulants discontinued when the INR exceeds 1.5 during concomitant warfarin therapy for VTE prophylaxis, an approach that is not consistent with evidence-based clinical practice guidelines. Studies comparing the use of various INRs for this transition have not been conducted. I’m not sure how comfortable we should be with the use of lower INRs.

Dr. Dager: I question the adequacy of using the lower INR target ranges (e.g., 1.5 to 2.0) for the transition to warfarin alone, as done by some clinicians, although 1.5 to 3.0 was evaluated in one comparative study of patients undergoing hip or knee replacement.10 Of the other 14 comparative clinical trials in knee or hip surgery, the lowest INR target was 1.8 and the highest was 3.0. I think a compromise approach, with a target INR of at least 1.8 and a maximum of 3.0, could be considered.

Management challenge 1

Dr. Haines: The pharmacy and therapeutics (P&T) committee at Virginia City Hospital is evaluating several new anticoagulants—apixaban, dabigatran, idraparinux, and rivaroxaban—for addition to the formulary. What considerations should enter into the deliberations and formulary decisions?

Dr. Trujillo: The safety, effectiveness, ease of use, and cost of the new agents compared with older agents already on the formulary are primary concerns. Cost analyses should take into consideration the costs of managing adverse effects, particularly bleeding and thromboembolic events.

An oral route of administration and infrequent dosing are associated with ease of use. Idabiotapatranix is a biotinylated form of the indirect factor Xa inhibitor idraparinux with a long half-life that permits weekly administration.11 It is given by s.c. injection. The oral direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban and rivaroxaban are administered orally once or twice daily. These oral agents have a rapid onset of action, which circumvents the need for bridge therapy while waiting for a therapeutic INR to be achieved before discontinuing injectable anticoagulation when warfarin is initiated for VTE treatment.

Greater ease of use may be an advantage of newer anticoagulants over older agents. Their availability may promote practitioner adherence to VTE prophylaxis guidelines, increase patient adherence to therapy, and ultimately lead to improved effectiveness and outcomes. The weight given to each consideration will vary among health systems, depending on their institutional priorities and culture. Performance and outcomes reporting and pay-for-performance requirements pertaining to anticoagulant use for VTE prevention may influence formulary decisions involving new anticoagulants at Virginia City Hospital and other institutions.

Management challenge 2

Dr. Haines: Dr. Henderson, a cardiologist at Virginia City Hospital, has requested the addition of dabigatran to the formulary for stroke prevention in patients with atrial fibrillation. The drug has been associated with lower rates of stroke and systemic embolism and similar rates of major hemorrhage compared with warfarin in this patient population.12 Dr. Reno, an orthopedic surgeon at the same institution, has requested the addition of apixaban to the formulary for VTE prevention on the basis of limited safety and efficacy data in patients undergoing major orthopedic surgery.13,14 What formulary additions should be made at this institution at this time? The acquisition costs of the drugs probably will be high. Should use of the new agents be restricted to cases of therapeutic failure of less expensive agents?

Dr. Trujillo: Decisions about adding new anticoagulants to the formulary depend on formulary openness, P&T committee dynamics, and institutional characteristics and needs. The introduction of new anticoagulants will pose a dilemma to P&T committees. I would not restrict the use of new anticoagulants to cases of therapeutic failure of established agents, but I would restrict the prescribing to specific physician groups and indications to avoid widespread use in patient populations in which the drug may not yet have been found safe and effective.

Dabigatran might be added to the formulary for both stroke prevention in patients with atrial fibrillation and VTE prevention in patients undergoing major orthopedic surgery. Safety and efficacy data are available for use of the drug in this surgical population, although the efficacy data are mixed.15-17 Published data are not yet available for the use of apixaban for stroke prevention in patients with atrial fibrillation. Therefore, its use should be limited to VTE prevention in patients undergoing major orthopedic surgery if the drug is added to the formulary.

While not formally requested, rivaroxaban should be considered in conjunction with the requests by Drs. Henderson and Reno at Virginia City Hospital as part of a comprehensive review of the entire class of medications. Published safety and efficacy data are available for the use of rivaroxaban for VTE prevention in patients undergoing major orthopedic surgery.18-21 The formulary status of new anticoagulants should be re-evaluated as additional safety and efficacy data become available.

Conclusion

Certain patients at risk for VTE can present a clinical challenge. The introduction of new anticoagulants
may pose a management challenge in determining whether to add the agents to the formulary and restrict their use. The availability of new anticoagulants may help overcome some clinical challenges in preventing VTE and improve patient outcomes.

References


Improving anticoagulant use for prevention of venous thromboembolism

Article #204-000-10-429-H01P
Knowledge-based activity
Qualifies for 2.5 hours (0.25 CEU) of continuing-education credit

Learning objectives
After studying these articles, the reader should be able to

1. Describe the risk factors for venous thromboembolism (VTE).
2. Explain the evolution of quality improvement efforts as they pertain to VTE prevention.
3. Describe strategies that health-system pharmacists can use to close the cultural gap between 20th- and 21st-century medicine and improve anticoagulant use and outcomes in patients at risk for VTE.
4. Identify a cause of difficulty in assessing and reducing VTE risk, and recommend a strategy for the use of drug therapy for VTE prophylaxis in a patient with unique characteristics that require special consideration.
5. Discuss the shortcomings of currently available anticoagulants and the characteristics of the ideal anticoagulant, and compare and contrast the mechanisms of action, pharmacokinetics, administration, efficacy, safety, and potential for drug interactions from currently available and emerging anticoagulants for VTE prevention.
6. Explain a clinical or management challenge associated with VTE prevention, and outline a practical approach to overcoming the challenge.

Self-assessment questions
For each question there is only one best answer.

1. Which of the following components of Virchow's triad does factor V Leiden reflect?
   a. A hypercoagulable state alone.
   b. Endothelial injury alone.
   c. Circulatory stasis alone.
   d. Endothelial injury and circulatory stasis.

2. Which of the following is a risk factor for venous thromboembolism (VTE) commonly found in hospitalized patients?
   a. Diabetes mellitus.
   b. Hyperlipidemia.
   c. Peptic ulcer disease.
   d. Prolonged immobility.

3. Which of the following is the most important and therefore must occur first in the quality-of-care continuum?
   a. Clinical studies.
   b. Evidence-based guidelines.
   c. Mandatory practice and outcomes reporting.
   d. Pay-for-performance requirements.

4. Which of the following parts of the quality-of-care continuum is represented by “never event” reimbursement policies established by the Centers for Medicare and Medicaid Services for VTE after total hip or knee replacement surgery?
   a. Evidence-based guidelines.
   b. Hospital/physician quality measures.
   c. Mandatory practice and outcomes reporting.
   d. Pay-for-performance requirements.

5. Which of the following should health-system pharmacists avoid in order to improve the quality of care and address the needs of patients at risk for VTE?
   a. Group decision making.
   b. Multidisciplinary input.
   c. Autonomous problem solving.
   d. Teamwork.

6. Which of the following is a common reason for failure to adhere to clinical practice guidelines for VTE prophylaxis?
   a. Excessive reliance on hematologists to perform the risk assessment.
   b. Excessive reliance on clinical practice guidelines.
   c. A lack of standardized methods for measuring and defining clinical trial outcomes.
   d. A lack of awareness of the impact of VTE on morbidity and mortality.

7. There is a lack of consensus among health care practitioners and controversy surrounds use of which of the following drug therapies for VTE prophylaxis?
   a. Aspirin.
   b. Low molecular weight heparin (LMWH).
   c. Unfractionated heparin (UFH).
   d. Warfarin.
8. Which of the following durations of VTE prophylaxis is recommended after total hip replacement surgery?
   a. 1 week.
   b. 6 weeks.
   c. 10 weeks.
   d. 6 months.

9. Which of the following enoxaparin dosage adjustments should be made for patients with morbid obesity undergoing knee replacement surgery?
   a. The dosage should be decreased to 20 mg every 24 hours.
   b. The dosage should be decreased to 30 mg every 24 hours.
   c. The dosage should be increased to 40 mg every 12 hours.
   d. The dosage should be increased to 50 mg every 12 hours.

10. For which of the following issues is consensus lacking among clinicians in the prevention of VTE?
    a. The need to maintain the INR during warfarin therapy between 2 and 3.
    b. The need to avoid initiating fondaparinux therapy less than six hours after surgery.
    c. The need for smaller-than-usual LMWH doses in critically ill patients.
    d. The need to avoid removing an epidural catheter during periods of peak anticoagulant activity.

11. Which of the following statements about the use of ultrasound screening for deep vein thrombosis before hospital discharge of asymptomatic patients after surgery is correct?
    a. It is routinely recommended only after major orthopedic surgery.
    b. It is routinely recommended only for morbidly obese patients.

12. Which of the following is a characteristic of the ideal anticoagulant for VTE prevention?
    a. Narrow therapeutic index.
    b. Irreversible action.
    c. Oral route of administration.
    d. Available in a single dosage strength.

13. Which of the following is a new oral vitamin K antagonist that is not metabolized by cytochrome P-450 enzymes?
    a. Apixaban.
    b. Dabigatran etexilate.
    c. Rivaroxaban.
    d. Tecarfarin.

14. Which of the following is an emerging oral anticoagulant that might interact with proton pump inhibitors and other drugs that lower gastric pH?
    a. Apixaban.
    b. Dabigatran etexilate.
    c. Idrabiotaparinux.
    d. Rivaroxaban.

15. Which of the following is an emerging oral anticoagulant that might be particularly useful for VTE prevention in patients with renal impairment?
    a. Apixaban.
    b. Dabigatran etexilate.
    c. Idrabiotaparinux.
    d. Rivaroxaban.

16. Which of the following must be considered in comparing the results of clinical trials of oral direct thrombin (factor IIa) and factor Xa inhibitors for VTE prevention in patients undergoing major orthopedic surgery?
    a. Differences in the primary endpoint and comparator used.
    b. Differences in the duration of treatment and enoxaparin dosing regimen used.
    c. Differences in the duration of treatment and comparator used.
    d. The results of clinical trials should never be compared.
19. The use of anticoagulant therapy for VTE prophylaxis is a concern in surgical patients with epidural catheters for postoperative analgesia because of the risk of
   a. Catheter-related sepsis.
   b. Spinal hematoma.
   c. Inadequate analgesia.
   d. Thrombocytopenia.

20. Which of the following factors should be considered and valued in making formulary decisions about new anticoagulants for VTE prophylaxis?
   a. Cost.
   b. Ease of use.
   c. Efficacy and safety.
   d. Safety, effectiveness, ease of use, and cost.

AJHP Continuing Education

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CE Credit: 2.5 hours (0.25 CEU)
Expiration Date: May 15, 2013

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Instructions

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