Venous thromboembolism (VTE), comprised of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of death, disability, and economic burden worldwide. VTE afflicts millions of individuals and accounts for several hundred thousand deaths annually in the United States.\(^1\,^2\)

Despite significant advances, such as the development of novel anticoagulants and alerting systems for patients at high risk for VTE, PE remains the most common preventable cause of death in hospitalized patients.

Although VTE is a common problem, it is often difficult to diagnose. Prophylaxis is a more cost-effective strategy for preventing VTE-associated morbidity than is the treatment of established disease. VTE strikes a wide range of individuals, from teenagers\(^3\) to the elderly. VTE often complicates the course of patients who are sick and hospitalized, but it can also occur in ambulatory and otherwise healthy individuals. Although most individuals survive, VTE impairs quality of life by increasing susceptibility to chronic thromboembolic pulmonary
Table 1. Risk Factors for VTE

<table>
<thead>
<tr>
<th>Risk Factor</th>
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</thead>
<tbody>
<tr>
<td>Acute medical illness</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Central venous catheterization</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agents</td>
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<tr>
<td>Estrogen-containing and estrogen-modulating medications</td>
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<tr>
<td>Immobility</td>
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<tr>
<td>Increasing age</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Inherited or acquired thrombophilia</td>
</tr>
<tr>
<td>Myeloproliferative disorders</td>
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<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>Pregnancy and the postpartum period</td>
</tr>
<tr>
<td>Previous VTE</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Trauma</td>
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<tr>
<td>Venous compression</td>
</tr>
</tbody>
</table>

hypertension and chronic venous insufficiency.4,5 Thus, implementing an appropriate prophylaxis program is vital for patients at risk for VTE.

Effective and safe prophylactic measures against VTE exist, and formal guidelines have been formulated and published.6,7 However, despite the endorsement of multiple medical societies and the adoption of guidelines as official policy in many institutions, surveys demonstrate that implementation of VTE prophylaxis among high-risk patients continues to be suboptimal during hospitalization.8

Epidemiology of DVT and PE

INCIDENCE

VTE is the third most common cardiovascular disease behind heart attack and stroke, respectively, but it is the most preventable medical problem among patients hospitalized with other illnesses. Recent national estimates suggest that more than 600,000 symptomatic VTE events occur each year and that PE is responsible for approximately 150,000 to 200,000 deaths per year in the United States.1,2 One study reported that the incidence of DVT after discharge from a short-term hospital stay was 48 per 100,000 and the incidence of PE (with or without DVT) was 23 per 100,000.9 Additionally, a number of published studies have demonstrated that the incidence of first-time VTE rises exponentially with age, from fewer than 5 per 100,000 per year among children under 15 years of age, to 450 to 600 per 100,000 per year among those over the age of 80.9,10 The likelihood of VTE recurrence after a time-limited course of anticoagulation is approximately 30% over the ensuing 10 years.5

BURDEN TO PATIENTS

Clinical manifestations of DVT often include swelling, pain, and extremity discoloration and may lead to PE. Manifestations of PE may include dyspnea, pleuritic pain, cough, and hemoptysis, or it may be asymptomatic.11,12 VTE is associated with complications including recurrence of DVT or PE, chronic thromboembolic pulmonary hypertension, death, or lower extremity valve dysfunction. The 28-day mortality rate for a first VTE event is approximately 11%, an alarmingly high rate.13 Additionally, 3-month mortality rates for PE as high as 17% have been reported.14 The risk for VTE recurrence is greatest within 6 to 12 months after the first event, continues for at least 10 years,15 and is associated with increased mortality.16 Valve dysfunction, which can lead to venous hypertension and a chronic condition called post-thrombotic syndrome, is most often caused by a previous DVT.17 Post-thrombotic syndrome can have devastating effects on the patient’s quality of life and is associated with venous hypertension that may cause pain, edema, skin changes, varicose veins, and skin

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The cumulative incidence of the development of post-thrombotic syndrome after a VTE event is high: 17% at 1 year, 23% at 2 years, and 29% at 8 years, with 30% of these cases classified as severe.18

**BURDEN TO SOCIETY**

Direct medical costs to the US health care system related to VTE events and complications are at least $600 million annually. Bullano and colleagues estimate that managed care plans pay a median of $3,131 per incident of DVT, $6,424 per incident of PE, and $12,200 for a DVT plus PE combination event.19 A 2004 registry of 5,451 patients with ultrasound-confirmed DVT at 183 institutions in the United States revealed that DVT led to hospitalization in 80% of those who were diagnosed as outpatients. Those initially diagnosed as inpatients remained hospitalized for a median of 12 days.20

However, appropriate prophylaxis, using anticoagulants, mechanical measures, or a combination of both, can prevent most episodes of VTE.21 For example, mechanical measures as simple as “low-tech” and inexpensive graduated compression stockings are effective in reducing the risk of postoperative VTE.22-24 A Cochrane Review demonstrated that the use of graduated compression stockings reduced VTE in hospitalized patients after surgery by about 50%.24

### Risk Assessment and Evidence-based Guidelines

To improve survival, avoid recurrences, prevent complications, and reduce health care costs, VTE occurrence must be reduced. Patient risk stratification is needed to modify exposures and target primary and secondary prophylaxis to patients who would benefit most. Independent risk factors for VTE have been identified (Table 1) and can be used as a basis for risk assessment.25 Surgery is a well-identified cause of VTE in hospitalized patients. However, many medical patients also are at risk for VTE. Patients who are medically ill account for 70% to 80% of fatal PEs and 50% to 70% of symptomatic thromboembolic events.6 The high incidence of DVT and fatal PEs in medical and surgical patients highlights the importance of assessing the risk for VTE in hospitalized patients so that prophylactic strategies can be implemented.

The eighth edition of the American College of Chest Physicians (ACCP) guidelines recommend against the use of passive strategies, such as distribution of guidelines or educational events, to reduce VTE. The use of multicomponent approaches, audit, and feedback, and the use of automatic reminders, such as preprinted orders and computer reminders, have been proven to increase prophylaxis adherence and are recommended.25 However, because almost all hospitalized patients have at least 1 risk factor for VTE and approximately 40% have 3 or more, guidelines recommend implementation of institution-wide prophylaxis policies with routine prophylaxis for all patients who belong to major target groups. For example, patients undergoing major general surgery or major orthopedic surgery should be routinely placed on prophylaxis rather than individual prophylaxis prescribing based on formal risk assessment models.25

### Table 2. Levels of Thromboembolism Risk and Recommended Prophylaxis in Hospitalized Patients

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Definition</th>
<th>Approximate DVT Risk Without Prophylaxis, %</th>
<th>Prophylaxis Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Minor surgery in mobile patients, medical patients who are fully mobile</td>
<td>&lt;10</td>
<td>No prophylaxis, early and “aggressive” ambulation</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Most general, open gynecologic, or urologic surgery patients; medical patients, bed rest, or sick Moderate VTE risk plus high bleeding risk</td>
<td>10-40</td>
<td>LDUH, LMWH, fondaparinux Mechanical prophylaxis</td>
</tr>
<tr>
<td>High risk</td>
<td>Hip or knee arthroplasty, hip fracture surgery; major trauma, spinal cord injury High-risk VTE plus high bleeding risk</td>
<td>40-80</td>
<td>LMWH, fondaparinux, oral vitamin K antagonist Mechanical prophylaxis</td>
</tr>
</tbody>
</table>

LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism
Risk assessment models are used to determine a VTE composite risk estimate in each patient based on individual predisposing factors and the risk associated with patients’ current illness or procedure. The eighth edition of the ACCP guidelines recommend against using formal risk assessment models because they have not been adequately validated and are complex.

One strategy that has been proposed to decrease the complexity of the risk assessment process for surgical patients involves assigning them to 1 of 4 VTE risk levels based on the type of operation (minor, major), age (<40 years, 40 to 60 years, and >60 years), and the presence of risk factors (eg, cancer or previous VTE). Limitations to this classification strategy include risk scoring that is based on studies that are more than 25 years old, uncertainty about the influence of each factor on overall risk, lack of definitions for minor and major surgery, and arbitrary cutoffs for age and duration of surgery.

The implementation of routine group-specific prophylaxis allows clinicians to easily identify the general group of patients at risk for VTE and provides general prophylaxis recommendations (Table 2).

**Prevention**

In 1986, the ACCP released its first set of guidelines on antithrombotic therapy. The guidelines are updated regularly and provide clear and explicit evidence-based recommendations for the use of appropriate VTE prophylaxis.

**VTE Prophylaxis for Surgical Patients**

In 2008, the ACCP recommended that prophylactic strategies for surgical patients be stratified based on type of surgery and bleeding risk, with use of progressively more aggressive therapies as the degree of risk increases. Use of low-molecular-weight heparin (LMWH), fondaparinux, or a vitamin K antagonist is recommended instead of low-dose unfractionated heparin (LDUH) for patients undergoing orthopedic surgery or with trauma or spinal cord injury because these agents are more effective than LDUH in preventing VTE. However, patients undergoing general, gynecologic, or urologic surgery or neurosurgery may receive either LMWH or LDUH; both therapies are considered equally effective for prevention of VTE in these at-risk patient populations.

**VTE Prophylaxis for Medical Patients**

The 2008 ACCP guidelines recommend the use of LDUH or LMWH in medical patients who are acutely ill and who have been admitted to the hospital with congestive heart failure or severe respiratory disease or who have been confined to bed with 1 or more additional VTE risk factors. A meta-analysis of 9 randomized controlled trials comparing the efficacy of subcutaneous LDUH (5,000 units) twice daily versus 3 times daily for VTE prophylaxis in 7,978 acutely ill medical patients found a significant risk reduction for proximal DVT and PE with 3 rather than 2 daily doses (0.9 vs 2.3 events per 1,000 patient days; \(P=0.05\)). However, the use of LDUH 3 times per day was accompanied by a small but significant increase in the risk for major bleeding (0.96 vs 0.35 events per 1,000 patient days; \(P<0.001\)).

**Quality Initiatives**

Despite sophisticated alerting mechanisms and long-standing guidance on appropriate VTE prophylaxis, many international and national registry studies have identified suboptimal adoption of and adherence to guidelines for VTE prophylaxis in most at-risk populations. Although two-thirds of medical inpatients with risk factors for VTE received some form of thromboprophylaxis, less than one-fourth of these at-risk patients had thromboprophylaxis continued until hospital discharge, as recommended in the ACCP guidelines. Similarly, in a retrospective study examining VTE prophylaxis practices in patients with confirmed DVT, 29% of patients had received any form of thromboprophylaxis prior to the VTE event.

Recognition of VTE as a preventable event and evidence indicating poor adherence to guidelines has led to government-sponsored national quality initiative outreach efforts. In 2001, the Department of Health and Human Services and the Centers for Medicare & Medicaid Services (CMS) began launching quality initiatives. The goal of the quality initiative program is to improve the quality of health care provided in the United States by increasing transparency through the development of quality measures.

The CMS has recently developed a standardized approach for the development and maintenance of quality measures used in various quality initiative programs including those for VTE. The process of creating quality measures begins with clinical studies and ultimately ends in pay-for-performance (P4P) initiatives. P4P programs were developed in response to increased awareness of the need to improve quality and cost-effectiveness of health care. The P4P initiatives reward health care providers, including physicians and hospitals, for improving the quality of care they provide to patients.

The Surgical Care Improvement Project (SCIP) is aimed, in part, at preventing morbidity and mortality associated with VTE. SCIP’s goal is a 25% reduction of postoperative complications nationwide by 2010, including a reduction in postsurgical thromboembolic events. SCIP quality measures related to VTE include use of appropriate VTE prophylaxis within 24 hours of surgery and diagnosis of DVT and PE within 30 days post-surgery.
Similarly, the National Quality Forum is collaborating with the Joint Commission to develop national consensus standards for VTE prevention and treatment. These standards identify preferred practices to ensure quality care for patients with or at risk for VTE. Performance measures are being developed to evaluate the quality of care provided to patients in screening for VTE risk, the institution of prophylaxis, and effective VTE treatment. Draft measures focus on the appropriate overlap of parenteral and oral anticoagulation therapy, platelet count monitoring to detect heparin-induced thrombocytopenia, and justification for use of inferior vena cava filters instead of anticoagulation therapy, among various other aspects of VTE prevention, treatment, and outcomes. Public comments have been solicited, and the measures remain to be finalized.

Additionally, the Joint Commission has recognized that anticoagulation therapy is a common cause of adverse events. A mandate to reduce the likelihood of patient harm associated with the use of anticoagulation therapy (warfarin, unfractionated heparin, and LMWH, other anticoagulants) has been established as a 2008 Joint Commission National Patient Safety Goal.

Heparin Recall

More than 100 years ago, a medical student at John Hopkins University discovered heparin. Originally, it was created from both bovine and porcine sources, but
after decades of use, it was found that adverse reactions occurred less frequently with porcine-sourced heparin. For the last 10 years, heparin has been derived exclusively from pig intestines.

The use of appropriate prophylaxis for patients at risk for VTE recently has been complicated as a result of a recent national heparin recall. In late January 2008, risks of heparin therapy began to be reported publicly with the recall of heparin by Baxter, one of the largest manufacturers of drugs in the United States. Baxter initiated a nationwide voluntary recall of multidose vials of unfractionated heparin because of a series of adverse-event reports to the FDA’s MedWatch program. These reports suggested an increase of allergic-type reactions or episodes of hypotension. Adverse reactions have included stomach pain or discomfort; nausea; vomiting; diarrhea; low blood pressure; chest pain; fast heart rate; dizziness; fainting; unresponsiveness; shortness of breath; tachycardia; drug ineffectiveness; burning sensation; redness or paleness of skin; abnormal sensation of the skin, mouth, or lips; flushing; increased sweating; decreased skin sensitivity; headache; feeling unwell; restlessness; watery eyes; throat swelling; thirst; and difficulty opening the mouth. Some of these reactions may be severe or life threatening. The heparin recall was later extended to single-dose vials and then essentially to the entire heparin product line distributed in vials (Table 3).

The FDA initiated a series of investigations into the manufacturing sites for heparin. These investigations led to China, where the slaughterhouses that provide the pig intestines needed for the drug’s manufacture are located. In the manufacture of heparin, the intestines of pigs are collected and processed. The casings are separated and used in food manufacture, and the pulp is ultimately boiled and placed in a resin bath. The heparin product is a highly sulfated mucopolysaccharide that is ionically charged; it can be separated in that resin bath as a result. The separated product is then shipped to the United States, where it undergoes further processing in factories in New Jersey, Illinois, or Wisconsin.

The recall of heparin products extended beyond Baxter because the raw materials originated at a Chinese laboratory owned by Scientific Protein Laboratories, which supplied the materials to a number of

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/19/2007</td>
<td>First reports of allergic reactions in pediatric dialysis patients</td>
</tr>
<tr>
<td>01/04/2008</td>
<td>FDA alerted of 4 allergic reactions in dialysis patients</td>
</tr>
<tr>
<td>01/07/2008</td>
<td>CDC notified of allergic-type reactions</td>
</tr>
<tr>
<td>01/09/2008</td>
<td>CDC notifies FDA of association between Baxter heparin and allergic reactions</td>
</tr>
<tr>
<td>01/25/2008</td>
<td>Baxter issues recall of heparin 1,000 unit/mL 10- and 30-mL multidose vials</td>
</tr>
<tr>
<td>02/28/2008</td>
<td>Baxter recalls remaining heparin vial products</td>
</tr>
<tr>
<td>03/20/2008</td>
<td>American Health Packaging announces recall of approximately 1,400 units of heparin sodium vial products as part of broader Baxter recall</td>
</tr>
<tr>
<td>03/21/2008</td>
<td>B. Braun’s supplier recall of heparin active pharmaceutical ingredient prompts voluntary recall of heparin solutions</td>
</tr>
<tr>
<td>03/28/2008</td>
<td>Covidien initiates voluntary recall of prefilled syringes containing heparin</td>
</tr>
<tr>
<td>05/14/2008</td>
<td>Medtronic initiates voluntary field actions for selected heparin-coated products used during cardiopulmonary bypass</td>
</tr>
</tbody>
</table>

CDC, Centers for Disease Control and Prevention

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pharmaceutical manufacturers, including American Health Packaging, and B. Braun Medical, who, in turn, recalled their heparin products. Through the work of FDA and academic laboratories, a contaminant in the heparin vials was identified. Using electrophoresis and spectroscopy, researchers have found an additional glycosaminoglycan called oversulfated chondroitin sulfate (OSCS) present in the heparin. The contaminant mimics heparin activity so closely that routine testing did not recognize it. However, this chemical is not normally present in the manufacture of heparin. In vitro testing and animal data demonstrated a link between the OSCS isolated in heparin products and the adverse events observed after bolus dosing. These data indicated OSCS can lead to the generation of bradykinin (a vasoactive mediator) and C3 and C5a (potent anaphylatoxins), thus manifesting as an allergic reaction or hypotension. The FDA also developed an analytical method for testing heparin pharmaceutical ingredients for OSCS. The FDA has reported that contamination of the heparin supply is a worldwide problem. Contaminated heparin has been found in at least 10 countries. APP Pharmaceuticals is now the sole manufacturer of heparin products in the United States. As might be expected, a certain level of fear of shortages of heparin has arisen among pharmacists. As a result, pharmacists have been attempting to purchase as much heparin as possible to supply their patients. Paranoia that supplies will dwindle causes pharmacists to attempt to buy as much as possible, which, in turn, causes further shortages. Baxter supplied approximately half the heparin used in the United States, and APP supplied the remainder.

The original death toll from contaminated heparin was 19, but the FDA revised that number in early June. There were 246 reported deaths in patients receiving heparin on or after January 1, 2008. There were 149 reported deaths in patients that included allergic or hypotensive symptoms, with 146 reported to the FDA on or after January 1, 2008. It remains to be seen whether the number of events reported represents the full tally of events related to heparin contamination.

Today, the heparin in the marketplace, which has been sequestered, is safe. Furthermore, for patients who require anticoagulation therapy, heparin is not the only agent available. LMWHs are available, and are considered safe because of the additional purification steps they undergo. Fondaparinux, a simple, chemically synthesized pentasaccharide, is another option for patients requiring a parenteral agent. Direct thrombin inhibitors (eg, argatroban [Encysive], lepirudin [Refludan, Bayer], and bivalirudin [Angiomax, The Medicines Company]) are further options. Although heparin historically has been the chief anticoagulant in clinical practice, clinicians can use other agents today without fear of insufficient levels of anticoagulation.

**Conclusion**

VTE is a major clinical problem with significant morbidity and mortality. Despite the existence of published guidelines, consensus papers, and government support, VTE prophylaxis remains underused. Pharmacists can play an important role in the identification of patients at risk for VTE, increasing adherence to evidence-based guidelines for VTE, and educating health care providers on related issues such as the recent heparin recall.

**References**


