

# An overview of venous thromboembolism: Impact, risks, and issues in prophylaxis

## ■ ABSTRACT

Venous thromboembolism (VTE) is a major cause of cardiovascular death, and its close association with increased age portends an increasing clinical and economic impact for VTE as the US population ages. Studies show that rates of VTE prophylaxis remain inadequate both in the hospital and at the time of discharge. Health care accreditation and quality organizations are taking interest in VTE risk assessment and prophylaxis as a measure for hospital performance ratings and even reimbursement. To set the stage for the rest of this supplement, this article reviews the rationale for VTE prophylaxis, surveys current prophylaxis rates and strategies to increase those rates, and provides an overview of risk factors for VTE and therapeutic options for VTE prophylaxis.

**V**enous thromboembolism (VTE)—which comprises both deep vein thrombosis (DVT) and pulmonary embolism (PE), which can result from DVT—is the third leading cause of cardiovascular death in the United States, after myocardial infarction and stroke. The annual incidence of DVT approaches 2 million.<sup>1</sup> Silent PE constitutes approximately half of DVT cases, as suggested by studies using ventilation perfusion scanning. The true incidence of PE is not known but is estimated to be 600,000 cases annually,<sup>1</sup> with approximately one third of these cases leading to death.<sup>2</sup>

The cost of care related to VTE in the United States has been estimated at \$1.5 billion per year.<sup>1</sup> As an example of its economic impact on the individual patient level, an analysis of 2001–2002 cost data from a large private-sector medical center found that post-operative thromboembolic complications added an average of \$18,310 to total hospital costs for each patient in whom they occurred.<sup>3</sup>

Notably, the incidence of VTE rises at an exponential rate with increasing age after the second decade of life, as shown in **Figure 1**.<sup>2</sup> Given the aging of the US population, this suggests that the clinical and economic impact of VTE will only increase in the years ahead.

## ■ DESPITE ESTABLISHED BENEFITS, VTE PROPHYLAXIS REMAINS UNDERUSED

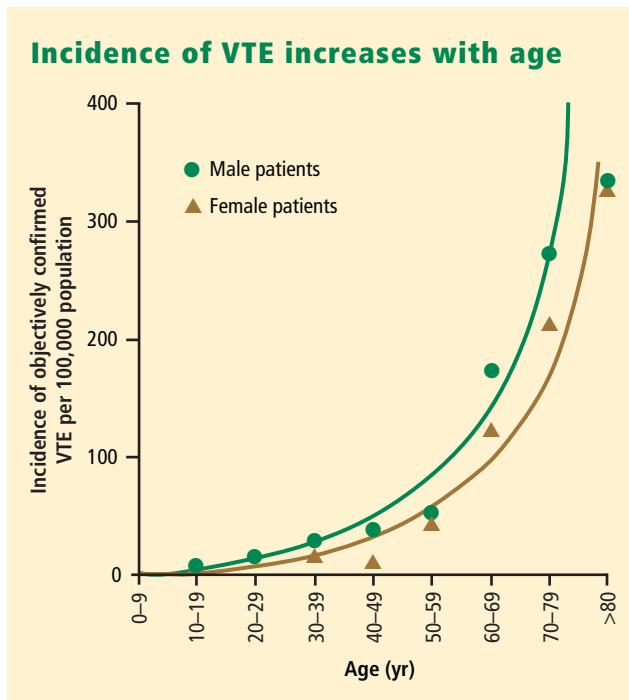
The frequency, clinical impact, and economic impact of VTE make a strong case for VTE prevention. In a 2001 analysis of patient safety practices, the Agency for Healthcare Research and Quality listed appropriate VTE prophylaxis in at-risk patients first in a rating of safety practices with the greatest strength of evidence for impact and effectiveness.<sup>4</sup>

Despite this recognition of the importance and benefit of VTE prophylaxis, prophylaxis remains highly underutilized. This has been demonstrated in numerous studies; the large epidemiologic investigation by Goldhaber et al using the DVT Free Registry is illustrative.<sup>5</sup> This prospective multicenter study enrolled 5,451 consecutive patients with acute DVT documented by venous ultrasonography over a 6-month period. Patients were classified as either outpatients or inpatients: outpatients were those who came to the emergency room and were diagnosed with DVT; inpatients were those who developed DVT in the hospital. Of the 2,726 inpatients in the registry, only 42% had received prophylaxis within 30 days prior to their diagnosis of DVT.

### Risk extends to the outpatient setting

In a recent population-based analysis, Spencer et al found a similarly low rate of VTE prophylaxis—42.8%—among 516 patients who had recently been hospitalized and subsequently developed VTE.<sup>6</sup> This study also found that VTE was three times as likely in the outpatient setting as in the inpatient setting, and that almost half of the outpatients with VTE had been recently hospitalized. Taken together, these findings indicate that VTE prevention efforts are inadequate

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**FIGURE 1.** Incidence rates of venous thromboembolism (VTE) per 100,000 population for men and women in the population-based Worcester DVT Study.<sup>2</sup> The increase in incidence for both sexes is well approximated by an exponential function of age.

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both in the hospital and at the time of discharge, when patients' risk for VTE is still elevated.<sup>6,7</sup>

### ■ VTE PROPHYLAXIS AS AN EMERGING QUALITY MEASURE

Increased recognition of the impact of VTE has prompted accreditation and quality organizations to take interest in VTE risk assessment and prophylaxis as a measure for institutional performance ratings and even reimbursement.

The Joint Commission on Accreditation of Healthcare Organizations and the National Quality Forum have launched a joint project to develop a set of standardized inpatient measures to evaluate hospitals' practices for the prevention and treatment of VTE.<sup>8</sup> The project has pilot-tested several proposed performance measures in dozens of volunteer hospitals, including measures of whether VTE risk assessment is performed and VTE prophylaxis is initiated (if indicated) within 24 hours of admission to the hospital or to the intensive care unit. Hospitals participating in the pilot program are required to report their rates of potentially preventable hospital-acquired VTE.

Similarly, the ongoing Surgical Care Improvement Project (SCIP) has targeted VTE prophylaxis as one of a handful of priority areas for reducing surgical complications. As a national quality partnership of organizations sponsored by the Centers for Medicare and Medicaid Services (CMS), SCIP set a national goal in 2005 to reduce preventable surgical morbidity and mortality by 25% by 2010.<sup>9</sup>

The stakes of the SCIP initiative are high in both clinical and financial terms. CMS mandated that hospitals report on three SCIP quality measures in 2007 in order to receive full Medicare reimbursement in 2008. Of the three measures, two involved VTE prophylaxis: (1) how often VTE prophylaxis was ordered for surgical patients when indicated, and (2) how often appropriate surgical patients received prophylaxis postoperatively. Moreover, beginning October 1, 2008, CMS will no longer reimburse hospitals for certain preventable conditions, and DVT and PE are being considered for inclusion in this list of conditions excluded from reimbursement.<sup>10</sup>

### ■ PROPHYLAXIS RATES CAN BE IMPROVED

Fortunately, there is evidence that interventions to increase awareness may increase the rate of VTE prophylaxis. Stinnett et al reported that education, in the form of hospital-specific data on VTE rates and implementation of risk-stratification guidelines, increased the use of VTE prophylaxis in high-risk hospitalized medical patients at a tertiary care center from a preintervention rate of 43% to a postintervention rate of 72%.<sup>11</sup>

In addition to educational interventions, formalized risk-assessment tools, in the form of electronic alerts, offer another strategy that may increase rates of VTE prophylaxis. The promise of this approach was demonstrated in a study at Brigham and Women's Hospital in Boston, in which 2,506 hospitalized patients at risk for VTE were randomly assigned to either an intervention group, in which physicians received a computer alert about the patient's VTE risk, or a control group, in which no alert was issued.<sup>12</sup> The rate of VTE prophylaxis was more than twice as high in the intervention group as in the control group (33.5% vs 14.5%;  $P < .001$ ), and the 90-day incidence of VTE was reduced from 8.2% in the control group to 4.9% in the intervention group ( $P = .001$ ).

### ■ WHO'S AT RISK FOR VTE?

Our understanding of the risk factors for VTE dates back more than a century to the work of the German pathologist Rudolf Virchow, who identified three broad categories of risk: circulatory stasis, endothelial

**TABLE 1**  
Risk factors for VTE

|  |                                  |
|--|----------------------------------|
| Surgery  | Infection                        |
| Trauma   | Heart failure                    |
| Immobility, paresis  | Respiratory failure              |
| Malignancy   | Inflammatory bowel disease       |
| Cancer therapy (hormonal chemotherapy or radiotherapy)         | Nephrotic syndrome               |
| Previous VTE   | Myeloproliferative disorders     |
| Increased age (especially > 75 yr)                             | Obesity                          |
| Pregnancy and postpartum status                                | Smoking                          |
| Estrogen-containing oral contraception, or HRT or SERM therapy | Varicose veins                   |
|  | Central venous catheterization   |
|  | Inherited/acquired thrombophilia |
|  | Travel                           |

VTE = venous thromboembolism; HRT = hormone replacement therapy; SERM = selective estrogen receptor modulator

injury, and hypercoagulable state. These categories manifest as a multiplicity of specific risk factors, as outlined in **Table 1**. Notably, many of these risk factors are highly prevalent in hospitalized patients. Also particularly notable is the association between increasing age and VTE, as illustrated in **Figure 1**.

### ■ OPTIONS FOR VTE PROPHYLAXIS

An ideal therapy for VTE prophylaxis would be one that is effective, safe, inexpensive, and easy to administer and monitor, and that has few side effects or complications.

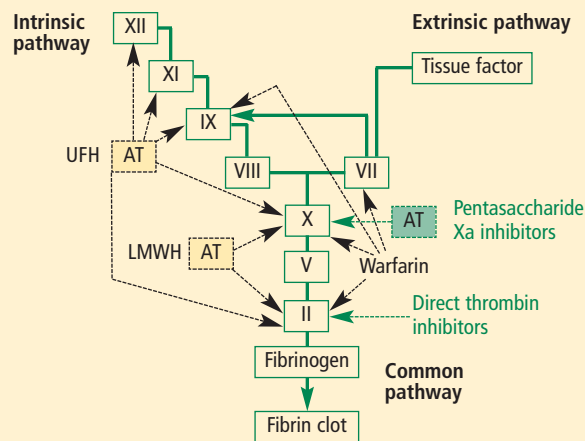
#### Mechanical prophylaxis

Mechanical forms of VTE prevention carry no risk of bleeding, are inexpensive because they can be reused, and are often effective when used properly. Mechanical forms include graduated compression stockings, intermittent pneumatic compression devices, and venous foot pumps.

The American College of Chest Physicians (ACCP), in its Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy, published in 2004,<sup>13</sup> recommends that mechanical methods be used primarily in two settings:

- In patients with a high risk of bleeding (in whom pharmacologic prophylaxis is contraindicated)
- As an adjunct to pharmacologic prophylaxis.

Because the use of mechanical forms of prophylaxis in hospitalized medical patients is not evidence-



AT = antithrombin; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin  
Roman numerals represent clotting factors.

**FIGURE 2.** The pathways of coagulation and the points of action of various classes of anticoagulant therapies.

Reprinted from Nutescu EA, et al. A pharmacologic overview of current and emerging anticoagulants. *Cleve Clin J Med* 2005; 72(Suppl 1):S2-S6.

based, mechanical prophylaxis should be reserved for those medical patients at risk for VTE who have a contraindication to pharmacologic prophylaxis.

To be effective, mechanical forms of prophylaxis must be used in accordance with the device manufacturer's guidelines, which is frequently not what happens in clinical practice. In clinical trials in which the efficacy of intermittent pneumatic compression devices was demonstrated, patients wore their devices for 14 to 15 hours per day.

#### Pharmacologic options

The pharmacologic options for prevention of VTE act at different points in the coagulation cascade (**Figure 2**), as detailed below.

**Unfractionated heparin (UFH)** inhibits factor Xa and factor IIa equally. Because it is a large heterogeneous molecule, UFH is not well absorbed in subcutaneous tissue. Its anticoagulant response is variable because of its short half-life. It must be dosed two or three times daily subcutaneously for VTE prophylaxis, and must be given intravenously for treatment of VTE. The rate of heparin-induced thrombocytopenia, a potentially catastrophic adverse drug event, is considerably higher with UFH than with low-molecular-weight heparins (3% vs 1%).<sup>14</sup> Osteopenia can develop with the use of UFH over even short periods, and osteoporosis can occur with long-term use.

**Low-molecular-weight heparins (LMWHs)** preferentially inhibit factor Xa compared to factor IIa. The LMWHs (ie, enoxaparin [Lovenox], dalteparin [Frag-

min]) are derived from UFH through a chemical depolymerization and defractionation process that results in a much smaller molecule. LMWHs are well absorbed from subcutaneous tissue and have a predictable dose response attributable to their longer half-life (relative to UFH), which allows for once-daily or twice-daily subcutaneous dosing. As noted above, LMWHs carry a much lower rate of heparin-induced thrombocytopenia compared with UFH. Because LMWHs are predominantly cleared by the kidneys, dose adjustment may be needed in patients with renal impairment.

**Fondaparinux** (Arixtra) is a synthetic pentasaccharide that acts as a pure inhibitor of factor Xa. It binds antithrombin III, causing a conformational change by which it inhibits factor Xa and thereby inhibits coagulation further downstream. Fondaparinux has a long half-life (18 to 19 hours), which enables once-daily subcutaneous dosing but which also may require administration of the costly activated factor VII (NovoSeven) to reverse its effects in cases of bleeding. Because fondaparinux is cleared entirely by the kidneys, it is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min). It is also contraindicated in patients who weigh less than 50 kg, due to increased bleeding risk.

Details on the efficacy of these agents for VTE prophylaxis in various patient groups are provided in the subsequent articles in this supplement.

### Investigational anticoagulants

The above pharmacologic options may soon be joined by several experimental anticoagulants that are currently in phase 3 trials for VTE prophylaxis—oral factor Xa inhibitors such as rivaroxaban and apixaban, and oral factor IIa (thrombin) inhibitors such as dabigatran.

### ■ AUTHOR DISCLOSURES

Dr. Jaffer reported that he has received consulting fees and honoraria for teaching/speaking from Sanofi-Aventis, consulting fees and research grant support from AstraZeneca, and consulting fees from Roche Diagnostics and Boehringer Ingelheim. He also serves on the governing board of the Society for Perioperative Assessment and Quality Improvement (SPAQI) and the board of directors of the Anticoagulation Forum.

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