Deep Vein Thrombosis Prophylaxis in Hospitalized Medical Patients: Current Recommendations, General Rates of Implementation, and Initiatives for Improvement

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Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of preventable morbidity and mortality following hospitalization.\textsuperscript{1} In the last decade, investigators have used randomized controlled trials (RCTs) to assess the efficacy and safety of various methods of VTE prevention for more than 20,000 medical patients.\textsuperscript{2} Identifying medical patients at risk for VTE and providing effective prophylaxis is now an important health care priority to reduce the burden of this morbid and sometimes fatal disease.

SCOPE OF THE PROBLEM: THE IMPORTANCE OF VENOUS THROMBOEMBOLISM IN THE MEDICAL PATIENT

As many as one-third of all cases of VTE occur in the 3 months following hospitalization\textsuperscript{3,4} and VTE accounts for approximately 10% of all in-hospital mortality.\textsuperscript{5} Of all patients diagnosed with hospital-associated VTE, half to three-quarters are medical patients without antecedent trauma or lower extremity injury\textsuperscript{6,7} and 70% to 80% of inpatient deaths due to PE occur in medical patients.\textsuperscript{8} An analysis of data from the 2003 United States Healthcare Cost and Use Project estimated that more than 8 million hospitalized patients are at risk for VTE annually, that almost 200,000 experience hospital-associated VTE, and that appropriate prophylaxis would have averted more than 110,000 of these events.\textsuperscript{9}

The absolute risk for symptomatic VTE occurring within 3 months of medical hospitalization, according to linked administrative databases, is 1.7%\textsuperscript{10}; however, this estimate includes all hospital discharges, regardless of patient VTE risk. When prospective studies have evaluated medical patients with one or more recognized VTE risk factors, the incidence of venographically detected VTE rises to 10% to 15%\textsuperscript{11,12} with even higher rates in critically ill patients.\textsuperscript{13} In the

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doi:10.1016/j.ccm.2010.07.005
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absence of prophylaxis, the rate of symptomatic proximal DVT (which is more likely to result in PE or the post-thrombotic syndrome) in medical patients with risk factors for VTE is approximately 5%. PE has been reported in 0.5% of patients.

Hospital-associated VTE carries substantial cost, similar to that incurred by stroke or myocardial infarction. Post-thrombotic syndrome occurs in approximately one-third of patients with symptomatic DVT, and is a source of additional medical cost and long-term morbidity.

These findings highlight the significant association between medical hospitalization and VTE, and the importance of effective strategies to mitigate this risk and reduce associated patient morbidity and mortality. PE is considered the most common preventable cause of hospital mortality, and its prevention has been given the highest priority among 79 interventions detailed in a report by the Agency for Health Research and Quality (AHRQ). Use of VTE prophylaxis in medical patients is cost effective, and results in net health savings that may extend for as long as 2 years following hospitalization.

PROPHYLAXIS OF VTE: IMPORTANCE TO PATIENTS AND BARRIERS TO IMPLEMENTATION

Over 3 decades, a large number of RCTs and prospective cohort studies have validated the effectiveness of various prophylactic strategies to reduce the incidence of DVT, PE, and even fatal PE that is associated with hospitalization. Studies have validated that VTE prophylaxis is safe and results in only a small excess risk for bleeding. Furthermore, implementation of an effective prophylaxis strategy results in net cost savings.

Despite the significance of these benefits, the rate of implementation of VTE prevention strategies in medical inpatients is disappointing. Multiple registries and queries of administrative data reveal rates of VTE prophylaxis in medical patients ranging from 15% to 49%. This rate is markedly lower than that reported in similar analyses of surgical patients, which have reported rates of VTE prophylaxis of as high as 90%.

Several reasons may explain the lower rate of implementation of VTE prophylaxis in medical patients. Prophylaxis decisions in surgical patients are often driven by the surgical procedure, whereas medical inpatients are a more diverse and heterogeneous population. Risk assessment for VTE in medical patients is complex, with many recognized risk factors noted in assessment tools, and a lack of precision regarding indications and contraindications for prophylaxis. In addition, concerns regarding bleeding risk and lack of clinician time have been cited as barriers to implementing prophylaxis in all patients.

IDENTIFYING PATIENTS FOR PROPHYLAXIS: VTE RISK FACTORS

Although a large majority of medical inpatients are considered at risk for VTE, pharmacologic prophylaxis incurs expense and a small increased risk for bleeding. Therefore, most practitioners select patients for prophylaxis on the basis of a sufficiently high perceived risk of VTE. Unfortunately, the list of putative risk factors for VTE in medical patients is extensive (Table 1), and there is limited validation of methods to stratify the relative contribution of individual factors or assess the additive risk when multiple factors coexist.

These limitations impede implementing an individual-based system for prophylaxis decisions, whereby a practitioner determines a patient’s individual risk for hospital-associated VTE and responds with a targeted prophylaxis decision based on this risk estimate. When assessing a medical patient for VTE risk, admission illness, activity level, and patient history may all contribute to the VTE risk profile. Admitting diagnoses of heart failure, acute stroke, chronic obstructive pulmonary disease (COPD), respiratory infection, and cancer are considered to confer a higher risk for VTE. Presence of vascular devices and location of admission (medical ward vs intensive care unit [ICU]) also influences the risk for VTE.

Heart failure has long been recognized as an admitting diagnosis associated with an increased risk for VTE. Some of the earliest studies of pharmacologic prophylaxis focused on this patient group. The risk appears to be amplified by the severity of symptoms, with higher risk observed in patients with New York Heart Association class III or IV symptoms. Other cardiovascular diseases, including myocardial infarction, have also been associated with VTE risk; however, this risk may be mitigated in many patients by the use of anticoagulant medications for treatment of acute coronary artery disease.

Respiratory disease, particularly respiratory failure, carries a strong association with increased VTE risk. COPD and severe respiratory infection have been among the inclusion criteria for several studies of pharmacologic prophylaxis. In addition to COPD and respiratory infection, acute respiratory distress syndrome, parenchymal lung disease, and pulmonary hypertension have also been associated with increased VTE risk.
Cancer is a common diagnosis or comorbidity in hospitalized medical patients. Cancer patients are as much as 6 times more likely to develop VTE than patients without cancer; moreover, VTE is one of the most common complications of malignancy and results in decreased survival. Several mechanisms contribute to this increase in risk. Many tumors have been associated with hypercoagulability through a variety of biochemical mechanisms, and this risk varies by type of malignancy. Adenocarcinomas of the abdominal and pelvic viscera and brain tumors confer a particularly strong association with VTE. In addition, certain tumors may cause venous thrombosis through mechanical compression of veins. Cancer therapy, including chemotherapy agents, radiation therapy, hormonal therapies, and use of indwelling venous catheters, also contributes to this risk. Despite these factors, cancer patients have been reported to have lower rates of VTE prophylaxis than other patient groups.

Bed rest or limited ambulation, increased patient age, and a history of prior VTE are patient-specific factors that confer higher risk. A derivation-validation of a simplified risk-assessment tool, which analyzed 18 potential risk factors in approximately 120,000 medical hospitalizations against the outcome of VTE diagnosed within 3 months of discharge, found that patient age, prior VTE, and cancer are dominant risk factors in predicting development of VTE (Woller SC and colleagues, in preparation; data obtained by personal communication, July, 2010).

The presence of a peripherally inserted central venous catheter (PICC), typically inserted in the brachial veins, is also associated with an increased risk for upper extremity VTE. A risk prediction model, derived from analysis of in-hospital DVT rates following 2014 PICC placements, revealed that a history of prior VTE (odds ratio [OR] 9.92) and increasing catheter diameter and number of lumens (OR 7.54 for 5F double-lumen; 19.50 for 6F triple-lumen) were most predictive of PICC-associated DVT (Evans RS, Sharp, JH, Linford LH and colleagues, Chest, in press data obtained by personal communication, July, 2010).

Reported rates of VTE in critically ill patients in an ICU have varied widely but with upper-range estimates far in excess of the rates reported in medical ward patients (Table 2). ICU patients

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### Table 1
**Recognized risk factors for VTE in hospitalized inpatients**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age &gt;60–65 has been used to define risk groups in controlled trials. Age &gt;40 is often used as a threshold after which the addition of other risk factors confers significant risk</td>
</tr>
<tr>
<td>Obesity</td>
<td>No threshold body mass index has clearly been defined at which significant VTE risk begins</td>
</tr>
<tr>
<td>Immobility</td>
<td>No standard definition. Bed rest or bed rest with ambulation only to bathroom has been used in prophylaxis trials to define immobility</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>Major risk factor for hospital-associated VTE</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Risk particularly high in those with paralysis or paresis of a lower limb</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Defining risk condition in many prophylaxis trials. Hospitalization with heart failure usually implies severe functional impairment</td>
</tr>
<tr>
<td>Severe respiratory disease</td>
<td>Defining risk condition in many prophylaxis trials. Hospitalization for respiratory disease usually implies severe functional impairment</td>
</tr>
<tr>
<td>Severe inflammatory disease</td>
<td>Examples include rheumatologic conditions such as systemic lupus erythematosis; flares of inflammatory bowel disease</td>
</tr>
<tr>
<td>Active cancer</td>
<td>Includes cancer under palliative care; cancer with any form of active treatment (radiation, chemotherapy, or biologic therapy), or cancer with completion of treatment in the preceding 6 months</td>
</tr>
<tr>
<td>Severe infectious disease</td>
<td>Includes pneumonia, sepsis syndromes, meningitis</td>
</tr>
<tr>
<td>Hypercoagulability and thrombophilia</td>
<td>Includes acquired and hereditary thrombophilias, as well as myeloproliferative syndromes, nephrotic syndrome, and protein-losing enteropathy</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>Generally defined as surgery under general or regional anesthesia in the preceding 3 months</td>
</tr>
</tbody>
</table>

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are likely to have multiple risk factors for VTE (see Table 1) and the ICU environment may contribute to VTE risk, in that patients are more likely to be immobilized, may be mechanically ventilated, may be medically sedated and/or paralyzed, and may be more likely to have central venous catheters.13

Several studies have attempted to develop formal risk assessment models (RAMs), containing individual risk factors, usually in combination with the patient’s admission diagnosis.40,41,43,44 None of these tools are used commonly; their implementation has likely been hampered by complexity. Furthermore, validation of these RAMs has been limited outside of the original study populations.13

TABLE 2
Rates of VTE in various groups of hospitalized patients without prophylaxis

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Rate of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>General medical ward</td>
<td>10%—20%</td>
</tr>
<tr>
<td>ICU</td>
<td>10%—80%</td>
</tr>
<tr>
<td>Stroke patients</td>
<td>20%—50%</td>
</tr>
<tr>
<td>with paralysis</td>
<td>40%—60%</td>
</tr>
</tbody>
</table>

Abbreviation: ICU, intensive care unit.

INITIATIVES FOR IMPROVEMENT: STRATEGIES TO INCREASE RATES OF PROPHYLAXIS

Initiatives to improve the uptake of VTE prophylaxis in medical patients can be separated into general and specific strategies.

General Strategies to Improve VTE Prophylaxis

General strategies to improve the use of VTE prophylaxis include (a) identification of easily identified and targeted patient groups who are likely to benefit from prophylaxis, or (b) broad application of a prophylaxis strategy to encompass all patients, except those in whom anticoagulants are contraindicated or in whom therapeutic-dose anticoagulation is being administered for other clinical indications.

With the first approach, one can target 5 large patient groups, to include congestive heart failure, respiratory disease, ischemic stroke, serious infection, and advanced cancer.13 With the second approach, all medical patients would be candidates for anticoagulant VTE prophylaxis unless they had a contraindication, such as active bleeding, or were already receiving anticoagulant therapy. The first approach has the merit that these patient groups were the dominant patient groups studied in RCTs of pharmacologic VTE prophylaxis.20,28–45 A limitation of this approach is that it may overlook some patients at increased risk for VTE. The second approach has the merit of being more inclusive and not predating prophylaxis on the basis of admission diagnosis—a more simplified approach that may optimize anticoagulant prophylaxis. Its drawbacks include possible administration of anticoagulant prophylaxis, with its inherent risks, to patients who may derive little if any benefit. The authors suggest that the approach used should depend on patient demographics at each institution. Thus, hospitals that have a high volume of less acute, less ill patients may opt for the disease-specific approach, targeting anticoagulant prophylaxis to selected higher-risk medical patients. Other hospitals, such as tertiary care facilities, which typically have a high volume of acutely ill patients, may opt for the more inclusive approach, as one would anticipate few patients who are considered “low risk.” Whichever general approach is taken, the American College of Chest Physicians (ACCP) consensus guideline recommends (Level 1A) that every hospital have an institution-wide policy for VTE prophylaxis that, ideally, should reflect the patient demographics.13

Specific Strategies to Improve VTE Prophylaxis

A variety of more specific strategies has been studied to attempt to overcome the barriers to successful implementation of VTE prophylaxis and increase rates of appropriate implementation. Strategies may be categorized as active (performance audit and feedback, reminder systems, preprinted orders) or passive (distribution of guidelines and educational sessions). Several active strategies have been shown to increase rates of prophylaxis46–50 and decrease rates of VTE diagnosed following hospitalization.51 The method of intervention chosen influences the rate of success. Kucher and colleagues51 implemented a computerized system that identified inpatients at high risk for VTE not receiving prophylaxis. The system then randomly assigned a group of providers to receive computerized alerts. The group of patients whose providers received the alert were more likely to receive VTE prophylaxis and less likely to experience VTE within 90 days of hospital discharge. However, such a system is highly dependent on the capabilities of the electronic medical record at the institution, limiting widespread use of the intervention. A second study used the same risk assessment system but provided the prophylaxis
remind the patient of the rate of response to the reminder over time.53

Simpler active strategies have also been implemented and have demonstrated increases in prophylaxis rates and VTE outcome. In a group of medical and surgical patients, Maynard and colleagues44 studied the effect of an embedded set of electronic orders that included a menu of VTE prophylaxis options. Over 3 years, the rate of prophylaxis increased from 58% to 98% and the rate of hospital-associated VTE detected by imaging review decreased by 30%. Although this intervention did not require an information system capable of automatic risk assessment and targeted alerting, it still required an electronic physician orders system that may not be widely available. Audit and feedback was also used, which requires additional resources. Paper-based systems, such as preprinted orders, have also been used. While arguably the simplest and most generalizable of the active interventions, the degree of effectiveness of such systems is more variable.50,54,55 These systems are also subject to fatigue and likely require active upkeep by personnel tasked to maintain such a system.55 Preprinted orders carry a lower level of recommendation in published guidelines.13 Features shown to predict an effective prophylaxis program include use of a multifaceted approach and a system of audit and feedback.50

By contrast, passive interventions, while much easier to implement, appear to be ineffective at changing the rate of appropriate prophylaxis. Grand rounds or lectures, distribution of published guidelines, and dedicated education programs do not appreciably change prophylaxis practices.46–56 However, such activities are often used in the creation of a program of active intervention to help increase acceptance of the active strategy, and may improve the success of implementation.57,58 Several published guidelines make recommendations to hospitals regarding the type of prophylaxis programs that should be implemented (see “Prophylaxis Recommendations: Published Guidelines and Regulatory Statements”).

PROPHYLAXIS INTERVENTIONS: OPTIONS AND EVIDENCE FOR EFFECTIVENESS

Nonpharmacologic and Mechanical Strategies

Nonpharmacologic strategies to reduce the risk of VTE include promoting patient activity through ambulation, graduated compression stockings (GCS), venous foot pumps (VFPs), and intermittent pneumatic compression devices (IPCs). These interventions are thought to prevent DVT through several mechanisms: they reduce stasis of blood in the veins through intermittent application of pressure, and enhance both local and systemic fibrinolysis, as has been shown by decreases in euglobin clot lysis time.59–62 Many investigators have suggested that tPA-activity increases despite decreases in tPA-antigen, and that PAI-1 Ag and activity drop.60,61 Others have shown decreases in Factor VIIa activity.63 Enhancement of fibrinolysis likely explains the observation that patients with a device applied to one extremity experience a reduction in DVT rate in extremities without a device.62,64 The attractiveness of these methods is that they are unlikely to increase the risk for bleeding.

Early and frequent ambulation is a simple intervention, but no studies have been performed to quantify its effectiveness as a sole method of VTE prophylaxis. The observation that most hospital-associated VTE events occur in patients who are ambulatory13 argues against the effectiveness of ambulation as a solitary intervention for VTE prophylaxis. In addition, many hospitalized patients are unable to ambulate, particularly in ICU settings.

Mechanical methods of prophylaxis, while conferring a low risk for bleeding, also have limitations. Such devices are only effective when worn by the patient, and in the case of IPCs and VFPs, when the devices are activated and functioning properly. Observational studies show substantial noncompliance with mechanical devices,65 with the highest rates of compliance in the ICU. The presence of devices also may be a barrier to patient ambulation. There are several different devices available, many of which have not been assessed in clinical trials but have achieved regulatory approval based on similarity to preexisting devices. Size, fit, pressure settings, and for IPCs, timing and mode of compression, have not been well standardized. Very obese patients may have leg circumferences that preclude being fit with any device. Furthermore, GCS can cause skin breakdown or ulceration, especially in the elderly or other patients with compromised skin integrity.66
IPCs can cause ecchymoses or other soft tissue injury when not properly fitted or if used excessively. Actual contraindications to mechanical prophylaxis include open skin lesions and preexisting DVT in the limb prior to application.

Studies in surgical populations have noted reduction in the risk of VTE when mechanical methods are the sole prophylaxis method employed, but similar studies have not been performed in medical inpatients. One study suggested that VFPs were ineffective in surgical patients when compared with full-length IPCs. It is also noteworthy that a large randomized trial reported no therapeutic benefit when mechanical antithrombotic devices were added to anticoagulant prophylaxis. Even in surgical populations, no study has affirmed a beneficial effect of mechanical prophylaxis as a sole intervention on rates of symptomatic PE or survival. Existing studies of mechanical prophylaxis tend to be less methodologically rigorous than studies of pharmacologic prophylaxis, in part due to the difficulty inherent in blinding the intervention.

Given these limitations, mechanical methods of prophylaxis should not be considered a “benign” method of prophylaxis that should be widely used, but should be reserved for medical inpatients with contraindications to pharmacologic prophylaxis, such as active bleeding, hemorrhagic stroke, or a bleeding diathesis. Even then, patients assigned to a mechanical VTE prophylaxis should be frequently reevaluated and provided with pharmacologic prophylaxis when the contraindication abates.

### Pharmacologic Prophylaxis

Prophylaxis using pharmacologic agents is the most effective means of VTE prevention in medical inpatients. A meta-analysis of studies totaling more than 20,000 medical inpatients showed that pharmacologic prophylaxis reduced symptomatic DVT by 53%, symptomatic PE by 58%, and fatal PE by 64%, although there was no improvement in all-cause mortality.

Several medications have been approved by the United States Food and Drug Administration (FDA) for prevention of VTE in medical inpatients (Table 3). All presently approved medications are anticoagulants; antiplatelet agents are not approved for this purpose. Several studies have shown limited

### Table 3
FDA-approved medications for VTE prophylaxis in medical patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Dose if ClCr ≤30 mL/min</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>5000 units SC, BID, or TID</td>
<td>Same</td>
<td>The BID and TID doses have never been directly compared in an RCT. Meta-analyses have suggested greater efficacy but greater risk of bleeding with the TID dose. Current guidelines conclude that there is insufficient evidence to recommend one dosing strategy over the other</td>
</tr>
<tr>
<td>Low Molecular Weight Heparins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40 mg SC daily</td>
<td>30 mg SC daily</td>
<td>The 30-mg SC daily dose is not FDA-approved for patients on hemodialysis Dosing of all LMWHs is less certain for severely obese patients with a BMI ≥35. Experts have advocated use of enoxaparin 30 mg SC twice daily for patients with a BMI ≥35</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5000 units SC daily</td>
<td>No specifically approved dose</td>
<td>The 5000 units SC daily dose has been studied in ICU patients with severe renal failure, but is not specifically FDA-approved in this patient group</td>
</tr>
<tr>
<td>Pentasaccharides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5 mg SC daily</td>
<td>No approved dose</td>
<td>Not labeled for patients &lt;50 kg Labeled “use with caution” when ClCr 30–50 mL/kg Very unlikely to cause HIT</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; ClCr, creatinine clearance; HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin; SC, subcutaneous; TID, 3 times daily.
beneficial effect of acetylsalicylic acid (ASA) in the prevention of VTE, largely in surgical populations, but the effect is less than that of anticoagulant medications. Additional studies have shown no beneficial effect from ASA in orthopedic surgery patients. There is no evidence that ASA is safer than anticoagulants presently employed for VTE prophylaxis in medical inpatients.

The anticoagulant medications presently approved for VTE prophylaxis are effective, reducing the rate of symptomatic VTE by nearly two-thirds when compared in large randomized trials, and confer a minimal increased risk for major bleeding. While more beneficial than nonpharmacologic strategies, pharmacologic prophylaxis has limitations. All agents presently available are administered by subcutaneous injection, which carries minor inconvenience to patients and adds a burden to hospital staff. All agents are associated with a risk for heparin-induced thrombocytopenia (HIT), although this risk is low with low molecular weight heparins (LMWHs), estimated at less than 0.1%, and has occurred with fondaparinux in only one reported case.

Contraindications include active bleeding or elevated risk of bleeding, history of HIT (particularly with persistent elevation of anti-platelet factor 4 IgG antibodies), and medication allergy. LMWHs and fondaparinux are primarily cleared by renal excretion, and renal dysfunction requires dose adjustment or use of unfractionated heparin (see “Low Molecular Weight Heparins” and “Fondaparinux”).

Unfractionated Heparin

Unfractionated heparin (UFH) is the agent with the longest history of use for VTE prophylaxis in medical inpatients, and was first studied against placebo as a method of VTE prophylaxis more than 25 years ago. In addition to being compared with placebo, UFH prophylaxis has served as the comparator group for several studies of newer anticoagulant medications.

The dosing of UFH (see Table 3) has varied in trials of medical prophylaxis, with 5000 units subcutaneously dosed either twice daily or 3 times daily. Controversy has existed over which dosing strategy is preferred. These 2 doses have never been directly compared, but the twice-daily regimen was shown to be similarly effective to enoxaparin, 20 mg subcutaneously once daily, in an RCT, whereas the same dose of enoxaparin was no better than placebo in a second trial. A meta-analysis of nearly 8000 patients showed a statistically significant increase in the rate of bleeding with the thrice-daily dose, and a nonsignificant trend toward greater VTE with the twice-daily dose. A meta-analysis of 36 trials concluded that the thrice-daily dose of UFH was more effective than the twice-daily dose for VTE prevention (relative risk, 0.27 vs 0.52). Current guidelines conclude that there is insufficient evidence to recommend one dosing strategy over the other.

UFH is a commonly used anticoagulant for VTE prophylaxis in medical inpatients. As other available agents are cleared predominantly by renal excretion, UFH may be the preferred agent in patients with severe renal dysfunction, although some LMWH preparations have been assessed in this patient group as well (see “Low Molecular Weight Heparins”). UFH is contraindicated in patients with a history of HIT, especially in those in whom persistent heparin-associated platelet factor 4 antibodies exist. In 2008, a defect in the manufacturing process resulted in the distribution of UFH contaminated with oversulfated chondroitin sulfate, leading to cases of severe anaphylactoid reaction. The FDA in the United States implemented a program to detect contaminated UFH and remove it from the United States drug supply. Recently, an update to the US Pharmacopeia (USP) heparin monograph, effective October 1, 2009, resulted in an approximate 10% reduction in heparin potency in the United States, bringing units of UFH in line with international standards. This potency change in UFH is unlikely to have any effect on UFH dosing for VTE prophylaxis, whereas higher doses may need to be administered to patients receiving therapeutic-dose UFH that is adjusted by monitoring of the activated partial thromboplastin time. Although the drug acquisition cost of UFH is less than that for other agents in the United States, the inherent expense of more frequent administration offsets this cost benefit. In addition, a cost-effectiveness study, conducted with pharmaceutical industry funding at a tertiary center, concluded that LMWH has superior cost effectiveness to UFH due to the lower rate of HIT and avoidance of related costs of HIT management. Fondaparinux has had favorable cost effectiveness when compared with enoxaparin in orthopedic patients, but cost-effectiveness data are not available for prophylaxis in medical patients.

The evidence for the effectiveness of UFH is substantial, with several studies showing benefit compared with placebo and effectiveness similar to that of LMWH including efficacy results from a pooled analysis of more than 4500 patients, which examined symptomatic and asymptomatic DVT, clinically overt PE, and death. Specific patient populations in which UFH has been studied and found to be beneficial include patients with stroke.
medical patients 65 years and older, patients with heart failure and/or severe respiratory disease, and general medical inpatients with one or more VTE risk factors. ICU patients have had similar risk reduction in several studies, but a study of the twice-daily regimen of UFH in ICU patients showed it to be no better than placebo for prevention of VTE using ultrasound-detected DVT as the clinical end point. The effect of UFH on all-cause mortality in medical patients has been the subject of two adequately powered studies. In one study, all-cause mortality was reduced from 10.9% to 7.8% but the second, larger study showed no effect on mortality. The majority of studies have not had sufficient power to assess mortality. UFH prophylaxis is associated with a low overall rate of major bleeding, although a meta-analysis of more than 4500 patients found the incidence of bleeding was higher with UFH than LMWH prophylaxis (1.2% vs 0.4%, \(P = .049\)).

**Low Molecular Weight Heparin**

Several preparations of LMWH are available for VTE prophylaxis in medical patients. LMWHs have less tendency to bind to plasma proteins and macrophages, and have a longer plasma half-life than UFH; this has led to the adoption of once-daily dose regimens for medical prophylaxis. Three LMWHs have been assessed in randomized trials for VTE prophylaxis in medical patients: enoxaparin, dalteparin, and nadroparin. Enoxaparin and dalteparin are approved by the FDA for this indication. All LMWH preparations are dosed once daily for medical prophylaxis, with dosing varying by agent. Different LMWHs have not been directly compared in randomized trials, but the effectiveness appears to be similar between available agents. In patients with severe renal insufficiency, defined as estimated creatinine clearance (CrCl) less than 30 mL/min, enoxaparin has an FDA-approved adjusted dose of 30 mg subcutaneously once daily, although to the authors’ knowledge this dose regimen has not been formally studied in clinical trials involving patients with severe renal insufficiency. This dose is not approved for dialysis-dependent patients. Dalteparin’s labeling indicates it should be used with caution in patients with severe renal insufficiency. However, a single-arm study of dalteparin, 5000 units subcutaneously once daily, was performed in ICU patients with severe renal insufficiency (CrCl <30 mL/min), and detected no evidence of excess anticoagulation from bioaccumulation, determined by anti-factor Xa level monitoring, after a mean of 7 days of treatment. This study, therefore, suggests that dalteparin 5000 units once daily is an option for DVT prophylaxis in patients with renal insufficiency. An ongoing randomized trial (PROTECT) is comparing this regimen against UFH 5000 units twice daily for VTE prophylaxis in critically ill patients, including those with severe renal insufficiency (NCT00182364).

Dosing of all LMWHs is less certain for severely obese patients with a body mass index (BMI) of 35 or greater. Open-label studies using monitored, high doses of enoxaparin (40–60 mg subcutaneously twice daily) have been performed in bariatric surgery populations; but studies of medical patients with similar degrees of obesity are lacking. Experts have advocated use of enoxaparin, 30 mg subcutaneously twice daily, for patients with a BMI of 35 or greater, which corresponds to a dose administered in high-risk surgical patients.

RCTs against placebo and against UFH have validated the effectiveness of LMWHs for prevention of VTE in medically ill inpatients. Three doses of enoxaparin have been tested against placebo. In a study of medical inpatients aged 65 years or older, enoxaparin 60 mg daily provided a relative risk reduction for VTE of two-thirds as measured by mandatory fibrinogen uptake scan. A second study of medical inpatients aged at least 40 with at least one VTE risk factor tested enoxaparin 20 mg daily and 40 mg daily against placebo. The 40-mg dose conferred a relative risk reduction of approximately 60% whereas the 20-mg daily dose did not differ from placebo. Outcomes were measured by mandatory venography or venous ultrasound.

Dalteparin was tested against placebo in one randomized trial, enrolling acutely ill medical patients at least 40 years old. Clinically important VTE (PE, symptomatic DVT, asymptomatic proximal DVT on duplex ultrasound, sudden death) was reduced by almost 50%. Enoxaparin has been tested against UFH in 3 randomized trials. A 20-mg daily dose was tested against UFH dosed twice daily in a study of medical patients 65 years and older at bed rest. There was no significant difference in VTE event rates between the 2 groups as measured by fibrinogen uptake scan. The 40-mg daily dose of enoxaparin has been compared with thrice-daily dosed UFH in 2 randomized trials of medical patients. The first enrolled patients at bed rest for at least 7 days with at least one additional VTE risk factor. The second enrolled patients with an admission diagnosis of heart failure or severe respiratory disease. In both studies there was no significant difference in the rate of VTE between the LMWH and UFH groups, although
a subgroup of patients with heart failure in the second trial derived more benefit from LMWH (rate of VTE 3.6% vs 1.5%, P < .05).

Nadroparin was similarly effective to thrice-daily dosing of UFH in a randomized trial. This medication is not available in the United States.

As noted earlier, a large meta-analysis has suggested a decrease in the rate of major bleeding for LMWH when compared with UFH, although the absolute rate of major bleeding for both strategies is very small. An additional meta-analysis of 36 studies suggested greater reduction in VTE with LMWH. There are no studies of fondaparinux with a creatinine clearance of less than 30 mL/min. As already noted, fondaparinux is extremely unlikely to cause HIT, and is the pharmacologic agent of choice in medical inpatients with a history of this condition.

A randomized trial of fondaparinux versus placebo has been conducted in acutely ill medical patients aged at least 60 years. Mandatory venography was performed to assess outcome between study days 6 and 15. Fondaparinux reduced the rate of VTE by almost 50% in this population. Major bleeding occurred in 1 patient (0.2%) in each study arm.

**Fondaparinux**

The most recent agent to gain FDA approval for VTE prophylaxis in medical patients is fondaparinux, an injectable pentasaccharide. Fondaparinux consists of a moiety of 5 saccharides, analogous to the minimum fragment of a heparin molecule capable of binding to antithrombin. The anticoagulant effect of fondaparinux is achieved through inhibition of activated factor X, and unlike UFH and LMWH it does not inhibit the effect of factor II.

Dosing of fondaparinux is similar to that of LMWH, and consists of once-daily subcutaneous injection of 2.5 mg. It has a longer pharmacologic half-life than any of the LMWH products presently available, and is cleared by renal excretion. Drug labeling suggests use with caution in patients with estimated creatinine clearance of 30 to 50 mL/min, and this drug is contraindicated in patients with a creatinine clearance of less than 30 mL/min. There is also no labeled dosing for medical prophylaxis for patients weighing less than 50 kg.

Indications for use of fondaparinux are similar to those of LMWH. There are no studies of fondaparinux in patients with severe renal insufficiency. As already noted, fondaparinux is extremely unlikely to cause HIT, and is the pharmacologic agent of choice in medical inpatients with a history of this condition.

A randomized trial of fondaparinux versus placebo has been conducted in acutely ill medical patients aged at least 60 years. Mandatory venography was performed to assess outcome between study days 6 and 15. Fondaparinux reduced the rate of VTE by almost 50% in this population. Major bleeding occurred in 1 patient (0.2%) in each study arm.

**Future Pharmacologic Agents**

Several classes of new anticoagulant medications are in ongoing trials. New oral anticoagulants, including anti-Xa inhibitors (rivaroxaban, apixaban), are being assessed in clinical trials of VTE prophylaxis in medical inpatients (NCT00571649, NCT00457002). If effective and approved by the FDA, such agents offer the benefit of more convenient oral dosing.

**DURATION OF VTE PROPHYLAXIS**

VTE prophylaxis is generally provided for the duration of hospitalization; however, the ideal duration of thromboprophylaxis in medical patients is unknown. Randomized trials have frequently assessed VTE outcomes following 7 to 14 days of pharmacologic prophylaxis. However, patients may be hospitalized for much longer than this and may be discharged to settings such as nursing facilities, in which they may have ongoing risk of VTE. Most VTE events diagnosed in association with hospitalization occur in the outpatient setting following discharge. Whereas orthopedic and cancer surgery patients have been extensively studied with regard to extended prophylaxis (continued prophylaxis past the date of hospital discharge), only limited study of this issue has occurred in medical patients. Hull and colleagues assigned 2975 patients with acute medical illness who were receiving inpatient pharmacoprophylaxis to a program of extended prophylaxis with enoxaparin, 40 mg daily for 28 ± 4 days. The comparator group of 2988 patients received placebo in the outpatient setting (initial duration of pharmacoprophylaxis was 10 ± 4 days). VTE was reduced by 40% (from 4.0% to 2.5%) and symptomatic VTE by 73% (from 1.1% to 0.3%) in the extended prophylaxis group. The major safety outcome was any bleeding, occurring in 6.3% of the extended prophylaxis group and 3.9% of the placebo group (P = .007). Major bleeding also increased from 0.3% to 0.8% absolute risk difference, 0.51% (95% CI, 0.12% to 0.89%). The protocol was modified during the trial due to lower than expected VTE events, and authors concluded that extended prophylaxis benefits only certain higher risk subgroups of patients.

Piazza and colleagues are presently engaged in a multicenter quality improvement study (NCT00853463) testing the effect of a reminder to consider extended-duration thromboprophylaxis in medical patients when hospital discharge is planned. Results of this study are not yet available.

**PROPHYLAXIS RECOMMENDATIONS: PUBLISHED GUIDELINES AND REGULATORY STATEMENTS**

Over the past 25 years, more than 20 clinical practice guidelines regarding VTE prophylaxis in
medical and surgical patients have been published by various groups. Recent guidelines of VTE prophylaxis in medical patients have been published by the ACCP in 2008.\textsuperscript{13} Six North American and European entities have issued guidelines regarding prevention and management of VTE in patients with cancer, and have published a joint consensus statement in 2009.\textsuperscript{107} A review of specific recommendations was also published by the American Heart Association in 2004.\textsuperscript{108}

In addition to scientific guidelines, entities involved in health care regulation and accreditation have issued policy statements regarding VTE prophylaxis. The US Joint Commission and the

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**Fig. 1.** Suggested algorithm for VTE prophylaxis of medical inpatients. aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; INR, international normalized ratio.
National Quality Forum (NQF) have endorsed standardized prophylaxis practices, and in May 2008 implemented a set of 6 VTE measurements as a core measure set for the ORYX program. Hospitals in the United States must select 4 such core measure sets as a component of accreditation as of May 1, 2009.\textsuperscript{109}

As mentioned earlier, the AHRQ has given VTE prevention the highest priority among 79 patient safety practices.\textsuperscript{18} In addition, the AHRQ and NQF together endorsed a practice guideline stating that all patients should have VTE risk assessed at admission and regularly thereafter, and have clinically appropriate methods of VTE prevention applied.\textsuperscript{110} The US Surgeon General issued a call to action for the prevention of VTE in a 2008 statement.\textsuperscript{111}

**SUMMARY**

A rational approach to assessing and implementing VTE prophylaxis in the medical patient, given the evidence and recommendations discussed, is summarized in Fig. 1.

VTE is a common and preventable complication of hospitalization in medical patients. All patients should be assessed for VTE risk at admission, and reassessed frequently during hospitalization. Most hospitalized medical patients are at sufficient risk of VTE to merit prophylaxis. Patient membership in certain groups, including ICU patients, the elderly, and those admitted with heart failure or severe respiratory disease, is adequate to confer high VTE risk. In other patients, the presence of individual risk factors defines sufficient risk to merit prophylaxis.

Pharmacologic prophylaxis is the mainstay of VTE prevention. It is effective, safe, and cost effective. LMWH can be considered the initial choice for prophylaxis based on its efficacy, safety, cost effectiveness, and easy-to-administer once-daily dose regimens. UFH is a reasonable alternative agent and should be initially considered in patients with severe renal insufficiency. Fondaparinux should be the initial choice in patients with a history of HIT. Mechanical prophylaxis should be used in patients in whom pharmacologic prophylaxis is contraindicated, although these devices should be used with care. The contraindication should be frequently reassessed, and pharmacologic prophylaxis should be initiated if the contraindication remits. There have been no studies to assess the use of inferior vena cava filter placement as a method of VTE prophylaxis in the medical inpatient.

Multiple scientific guidelines support VTE prophylaxis in medical patients. Regulatory and accreditation agencies have mandated that hospitals use formalized systems to assess VTE risk and provide clinically appropriate prophylaxis measures to patients at risk.

Additional research is needed to determine the optimal duration of VTE prophylaxis and to determine which patients would benefit from prophylaxis extended beyond hospital discharge.

**REFERENCES**


90. Harenberg J, Schomaker U, Flosbach CW, et al. Enoxaparin is superior to unfractionated heparin