CLINICAL FOCUS: PULMONARY/VASCULAR MANAGEMENT: VTE/DVT/PE

A Review of Venous Thromboembolism Prophylaxis for Hospitalized Medical Patients

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Abstract: In the last decade, greater focus has been directed toward venous thromboembolism (VTE) prophylaxis in hospitalized, non-surgical patients. Both deep venous thrombosis and pulmonary embolism are potentially preventable causes of patient morbidity and mortality related to hospitalization. Despite the availability of high-quality, evidence-based guidelines for VTE prevention, there is compelling evidence that many hospitalized patients do not receive appropriate VTE prevention measures. Hospitalists play an important role in the implementation of appropriate VTE prophylaxis measures for this patient population; thus, knowledge of updated recommendations is vital to their practice, as well as patient safety. We provide a comprehensive evidence-based clinical review of VTE prophylaxis for nonsurgical hospitalized patients, including risk factors and risk assessment, indications for prophylaxis, recommended therapeutic options, and updates from recently released practice guidelines by the American College of Physicians and the American College of Chest Physicians, published in 2011 and 2012, respectively.

Keywords: Deep venous thrombosis; pulmonary embolism; venous thromboembolism; thromboprophylaxis; prophylaxis.

Introduction

Venous thromboembolism (VTE)—including deep venous thrombosis (DVT) and pulmonary embolism (PE)—is a common and potentially preventable complication of hospitalization, which carries significant incidences of patient morbidity and mortality.1-3 Population-based studies estimate that nearly 170,000 cases of VTE occur in the United States annually.3,4 Hospitalization for a medical illness in itself carries approximately an 8-fold increase in patient risk of developing VTE.1 Lack of VTE prophylaxis puts patients at substantial risk for symptomatic DVT, PE, chronic postthrombotic syndrome, and elevated risk of recurrent VTE. The most critical consequence of PE is mortality, which is potentially preventable in hospitalized patients with use of prophylactic anticoagulant therapy; however, the evidence for use of routine thromboprophylaxis in hospitalized medical patients is based on randomized trials that predominantly use asymptomatic DVT as their primary endpoint.5-9 Use of asymptomatic DVT as a primary endpoint could, in theory, exaggerate estimates of effectiveness, as there are currently no available data to suggest that use of VTE prophylaxis in medical patients is associated with a lower incidence of mortality.10

After recognizing the importance of VTE prevention, The Joint Commission and National Quality Forum formally began implementing VTE prevention measures in 2005. This resulted in a shift in practice to implementation of universal VTE prophylaxis in all hospitalized patients, regardless of underlying risk.11 The Joint Commission continues to monitor VTE prophylaxis as a core performance measure,
contributing to the routine use of preventative measures against VTE in the hospital setting, even in low-risk patients in whom the use of thromboprophylaxis may be inappropriate and may result in patient harm.11

Despite shifts in practice promoting increased use of VTE thromboprophylaxis and the availability of evidence-based guidelines for VTE prevention, there is compelling evidence that many nonsurgical inpatients do not receive appropriate preventative measures.12–15 The Venous Thromboembolism Study to Assess the Rate of Thromboprophylaxis (VTE START)14 revealed that 36.8% of at-risk patients (as determined by the American College of Chest Physicians [ACCP] 7th edition guidelines, which supported routine prophylaxis for all patients of major target groups) received no thromboprophylaxis at all. Of the at-risk patients who received VTE prophylaxis, nearly half received inappropriately prescribed therapy in terms of dosage, frequency, or duration.14 Additionally, medical patients were less likely than surgical patients to receive appropriate thromboprophylaxis.14 Similar observations were seen in the Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers (IMPROVE) study,15 where only 50% of hospitalized medical patients received pharmacologic and/or mechanical VTE prophylaxis. Both VTE START and the IMPROVE study demonstrated that there is a critical need to increase awareness among physicians and advance implementation of appropriate use of VTE prophylaxis for hospitalized nonsurgical patients.

The American College of Physicians (ACP) and ACCP have addressed the appropriateness of VTE prophylaxis in the release of updated practice guidelines published in 2011 and 2012, respectively.10,16 The ACP and ACCP guidelines urge physicians to perform risk stratification prior to initiating prophylaxis and place an emphasis on selective prevention for those patients at highest risk for VTE. We provide a comprehensive evidence-based clinical review of VTE prophylaxis for hospitalized medical patients, including risk factors and risk assessment, indications for prophylaxis, recommended therapeutic options, and a summary of updates from recently released practice guidelines, focusing on hospitalists as the target audience. Throughout the article, individual recommendations from each organization guideline will be followed by the rated quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation framework provided by each respective organization. The recommendations from the ACP and ACCP guidelines are summarized in Table 1.

Materials and Methods
A comprehensive literature search of the available evidence on VTE prophylaxis was performed by the authors using PubMed, MEDLINE, and Cochrane Database (English language). Articles were critically evaluated by the authors and/or were independently rated as high quality by an established evaluation process, such as Cochrane Collaboration, or cited in evidence-based consensus guidelines from the ACP or ACCP.

Evidence for the Benefit of VTE Prophylaxis
The authors of the 2012 ACCP guidelines comprehensively evaluated the available literature for VTE prophylaxis in hospitalized medical patients and concluded that use of prophylactic anticoagulants in at-risk, nonsurgical inpatients led to a reduction in fatal PE by approximately 2 events per 1000 patients treated (relative risk [RR], 0.41; 95% CI, 0.22–0.76).10 In high-risk medical inpatients, use of VTE prophylaxis reduced the incidence of symptomatic DVT by approximately 34 events per 1000 patients treated (RR, 0.47; 95% CI, 0.22–1.0).10 Both the ACP and ACCP guidelines agree that use of VTE prophylaxis does not significantly reduce all-cause mortality rate nor significantly increase incidence of major bleeding. However, the benefit of VTE prophylaxis on patient mortality rate outcomes may not have been recognized in prior studies due to lack of power in sample size that would be required for this particular outcome. Furthermore, VTE prophylaxis in low-risk patients may not significantly reduce incidence of symptomatic DVT or PE (including fatal PE).10,16

Risk Factors and Risk Assessment for VTE
Hospitalization for medical illness in itself carries a nearly 8-fold increased risk for VTE and autopsy studies have shown that approximately 10% of inpatient deaths can be attributed to PE.1,3 More than half of all VTE events occur in hospitalized, acutely ill medical patients, and 3 of every 4 fatal PEs occur in patients admitted to inpatient medical services.17–19 Furthermore, when compared with surgical inpatients, nonsurgical inpatients are less likely to receive appropriate VTE thromboprophylaxis.12 Although the benefits of VTE prophylaxis on outcomes in hospitalized medical patients are not as clear cut as they are in surgical patients (especially in terms of mortality), it is recommended that both populations undergo routine assessment at admission to determine the
The risk factors for VTE identified in the PPS are 11 common VTE risk factors. In the PPS risk-assessment model (Table 3), hospitalized medical patients are categorized as low risk (<4 points) or high risk (≥4 points) for occurrence of VTE based on the presence of underlying risk factors. Currently, insufficient evidence exists to recommend a specific RAM for this purpose because most RAMs available for this purpose lack prospective validation with adequate follow-up time. Because the risk for VTE and risk for bleeding may change for individual patients during their hospital stay, it is recommended that risk assessment should be repeated every 24 to 48 hours to determine the addition and/or discontinuation of VTE prophylaxis.

One available risk-assessment model is the Padua Prediction Score (PPS), which assigns points for the presence of 11 common VTE risk factors. In the PPS risk-assessment model (Table 3), hospitalized medical patients are categorized as low risk (<4 points) or high risk (≥4 points) for occurrence of VTE based on the presence of underlying risk factors. The risk factors for VTE identified in the PPS are consistent with those described by the most recent ACCP guidelines. An alternative resource for risk prediction is currently insufficient evidence exists to recommend a specific RAM for this purpose because most RAMs available for this purpose lack prospective validation with adequate follow-up time. Because the risk for VTE and risk for bleeding may change for individual patients during their hospital stay, it is recommended that risk assessment should be repeated every 24 to 48 hours to determine the addition and/or discontinuation of VTE prophylaxis.
Table 2. Risk Factors for VTE

| Strong risk factors (OR > 10) | | Moderate risk factors (OR 2–9) | | Weak risk factors (OR < 2) |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Fracture (hip or leg)       | Arthroscopic knee surgery   | Bed rest > 3 days           |
| Hip or knee replacement     | Central venous lines        | Immobility due to sitting   |
| Major general surgery       | Chemotherapy                | (eg, prolonged car or air travel) |
| Major trauma                | Congestive heart or respiratory failure | Increasing age |
|                            | Hormone replacement therapy | Laparoscopic surgery (eg, cholecystectomy) |
|                            | Malignancy                  | Obesity                      |
|                            | Oral contraceptive therapy  | Pregnancy/postpartum         |
|                            | Paralytic stroke            | Previous venous thromboembolism | |
|                            | Pregnancy/postpartum        | Thrombophilia                |
|                            | Varicose stroke             | | |

Table 3. Risk Assessment Model (high risk of VTE: ≥ 4 points)

<table>
<thead>
<tr>
<th>Baseline features</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer§</td>
<td>3</td>
</tr>
<tr>
<td>Previous VTE (with the exclusion of superficial vein thrombosis)</td>
<td>3</td>
</tr>
<tr>
<td>Reduced mobility¶</td>
<td>3</td>
</tr>
<tr>
<td>Known thrombophilic condition‡</td>
<td>3</td>
</tr>
<tr>
<td>Recent (≤ 1 month) trauma and/or surgery</td>
<td>2</td>
</tr>
<tr>
<td>Elderly (age ≥ 70 years)</td>
<td>1</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30 kg/m²)</td>
<td>1</td>
</tr>
<tr>
<td>Heart and/or respiratory failure</td>
<td>1</td>
</tr>
<tr>
<td>Acute myocardial infarction or ischemic stroke</td>
<td>1</td>
</tr>
<tr>
<td>Acute infection and/or rheumatologic disorder</td>
<td>1</td>
</tr>
<tr>
<td>Ongoing hormonal treatment</td>
<td>1</td>
</tr>
</tbody>
</table>

§Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months. †Anticipated bed rest with bathroom privileges (either because of patient’s limitations or on physician’s order) for ≥ 3 days. ‡Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210 A prothrombin mutation, antiphospholipid syndrome.


Abbreviations: BMI, body mass index; VTE, venous thromboembolism.

Therapeutic Options for VTE Prophylaxis

There are a number of safe, cost-effective methods available for VTE prophylaxis. Pharmacologic options recommended by the ACP and ACCP guidelines for use in at-risk medical patients are given in Table 5. When choosing pharmacologic options, it is recommended that the risks of thrombosis and bleeding be weighed individually for each patient (ACP Grade: strong recommendation, moderate-quality evidence). Nonpharmacologic modalities include graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCs), and venous foot pumps (VFPs). Both sets of guidelines recommend the use of low-dose unfractionated heparin (UFH), low-dose low-molecular-weight heparin (LMWH; eg, enoxaparin or dalteparin), or fondaparinux for thromboprophylaxis in at-risk patients (ACCP Grade 1B) and suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (ACCP Grade 1B). Of note, the ACCP guidelines recommend against the use of aspirin for VTE prophylaxis in hospitalized medical patients. Data from trials evaluating use of aspirin as VTE thromboprophylaxis in hospitalized medical patients are limited in number and direct evidence of benefit in this patient population is lacking. Furthermore, there have been no studies directly comparing antiplatelet therapy with traditional anticoagulants for the prevention of VTE in acutely ill medical patients.

Low-Molecular-Weight Heparins

Low-molecular-weight heparins generally used for VTE prophylaxis include enoxaparin and dalteparin. Patients may prefer use of LMWH due to its long half-life, which allows for once-daily dosing. The Medical Patients With Enoxaparin (MEDENOX) study, a randomized controlled trial involving 1102 hospitalized nonsurgical patients at risk for VTE, compared enoxaparin, 40 mg daily, given prophylactically, with placebo and found treatment with enoxaparin to be associated with a significant reduction in VTE incidence by nearly two-thirds (5.5% in the enoxaparin group vs 14.9% in the placebo
Table 4. IMPROVE Combined VTE and Bleeding Risk Factors

<table>
<thead>
<tr>
<th>VTE Risk Factors</th>
<th>HR (95% CI)</th>
<th>Bleeding Risk Factors*</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>4.7 (3.0–7.2)</td>
<td>Active gastro-duodenal ulcer</td>
<td>4.15 (2.21–7.77)</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>3.5 (1.1–11)</td>
<td>Bleeding in 3 months prior to admission</td>
<td>3.64 (2.21–5.99)</td>
</tr>
<tr>
<td>Lower limb paralysis</td>
<td>3.0 (1.6–5.7)</td>
<td>Admission platelet count &lt; 10 x 10^5 cells/L</td>
<td>3.37 (1.84–6.18)</td>
</tr>
<tr>
<td>Current Cancer</td>
<td>2.8 (1.9–4.2)</td>
<td>Age ≥ 85 (vs &lt; 40 years)</td>
<td>2.96 (1.43–6.15)</td>
</tr>
<tr>
<td>Immobilization ≥ 7 days</td>
<td>1.9 (1.3–2.7)</td>
<td>Hepatic failure (INR &gt; 1.5)</td>
<td>2.18 (1.10–4.33)</td>
</tr>
<tr>
<td>Admission to ICU or CCU</td>
<td>1.8 (1.1–2.9)</td>
<td>Severe renal failure (GFR &lt; 30 mL/min/m²)</td>
<td>2.14 (1.44–3.20)</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>1.7 (1.1–2.6)</td>
<td>Central venous catheter</td>
<td>1.85 (1.18–2.90)</td>
</tr>
</tbody>
</table>

*Refer to Appendix A for a description of major bleeding and non-major–bleeding definitions.

IMPROVE Combined Risk Calculator: [http://www.outcomes.umassmed.org/IMPROVERisk_score/index.html](http://www.outcomes.umassmed.org/IMPROVERisk_score/index.html)

Identified risk factors can be entered into the IMPROVE Combined Risk Calculator to derive a prognostic score that will estimate patient VTE and bleeding risks at hospital admission. Combining the 2 risk profiles gives physicians useful data that can be readily applied when considering the risk-to-benefit ratio for use of anticoagulant thromboprophylaxis in hospitalized medical patients. Patients with a score of ≥ 2 during hospitalization may benefit from thromboprophylaxis, which is supported by an average clinically observed VTE event rate of 2.4%. Patients with a score of < 2 may not necessarily benefit from thromboprophylaxis, as supported by a clinical VTE rate of 0.7%. Data were obtained by multiple logistic regression analysis for characteristics at admission independently associated with VTE or in-hospital bleeding.

Abbreviations: CCU, coronary care unit; GFR, glomerular filtration rate; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; OR, odds ratio; VTE, venous thromboembolism.

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**Low-Dose UFH**

Unfractionated heparin has been shown to be superior to placebo in preventing VTE in hospitalized medical patients; however, its use has not been shown to significantly lower patient mortality. A recently published prospective trial compared enoxaparin therapy in standard fixed dose (40 mg/day) with low-weight-based dosing (0.4 mg/kg/day), and high-weight-based dosing (0.5 mg/kg/day) for VTE prophylaxis in morbidly obese medical patients. The study findings suggested that use of high-weight-based dosing of enoxaparin is more effective in reaching target anti–factor Xa levels for VTE prophylaxis in obese medical patients, without an increase in patient complications. Of note, no study has evaluated whether or not these dosing strategies correlate with improvement in clinically relevant patient outcomes.
trials, comparing patient prophylaxis with UFH 5000 units, given twice daily or 3 times daily for thromboprophylaxis, found more benefit with dosing 3 times daily but an increased risk of patient bleeding. The authors suggest that practitioners should determine individual patient characteristics, risk for VTE, and risk for bleeding complications to help guide the appropriate choice of pharmacologic prevention methods. Either of the 2 dosing regimens of UFH appears to be a reasonable strategy for VTE prevention in nonsurgical inpatients. Use of UFH for thromboprophylaxis may be preferred in patients with or at high risk for renal insufficiency due to the potential for bioaccumulation with LMWH or fondaparinux.

**Fondaparinux**

Fondaparinux is a synthetic factor Xa inhibitor that can be used for VTE prophylaxis. The Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS) evaluated the use of fondaparinux (2.5 mg daily) for VTE prophylaxis in high-risk medical patients and found its use associated with a significant reduction in the incidence of both symptomatic and asymptomatic VTE compared with placebo (5.6% in the fondaparinux-treated group vs 10.5% with placebo; relative risk reduction, 47%; $P = 0.03$). There was also a non-significant reduction in mortality in the fondaparinux-treated group. A meta-analysis of thromboprophylaxis studies comparing fondaparinux with LMWH use in patients undergoing orthopedic surgery found the safety profile of fondaparinux similar to that of LMWH with regard to efficacy and major bleeding.

Fondaparinux also carries the advantage of potential off-label use for VTE prophylaxis in patients with a history of HIT. It is administered subcutaneously, similarly to other pharmacologic agents available for prophylaxis, and it has a long half-life, allowing for once-daily dosing. There is no reversal agent currently available for fondaparinux and it is not recommended for use in patients with a creatinine clearance < 30 mL/min/m² (contraindicated per US labeling).

**Contraindications to Use of Anticoagulants for VTE Prophylaxis**

Prior to initiating an anticoagulant for VTE prophylaxis, it should be determined if the patient has any existing contraindications to anticoagulants (eg, active bleeding or high risk of bleeding complications, allergy to heparin agents or pork products, history of HIT). The risk-benefit ratio of prophylactic anticoagulation should be individualized in each patient. In general, bleeding that complicates prophylactic anticoagulation involves the central nervous system (ie, intracranial hemorrhage) or other vital organs.

In a large systematic review of hospitalized medical patients compared with no heparin, use of heparin (including fondaparinux) and LMWH was associated with a significant reduction in the incidence of both symptomatic and asymptomatic VTE compared with placebo (5.6% vs 10.5%; $P = 0.03$). There was also a non-significant reduction in mortality in the fondaparinux-treated group. A meta-analysis of thromboprophylaxis studies comparing fondaparinux with LMWH use in patients undergoing orthopedic surgery found the safety profile of fondaparinux similar to that of LMWH with regard to efficacy and major bleeding.

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**Table 5. Preferred Therapeutic Options for VTE Prophylaxis in Medical Patients**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency (daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin*</td>
<td>5000 units</td>
<td>SC</td>
<td>2 or 3 times</td>
</tr>
<tr>
<td>Enoxaparin Can</td>
<td>40 mg</td>
<td>SC</td>
<td>Once</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5 mg</td>
<td>SC</td>
<td>Once</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5000 units</td>
<td>SC</td>
<td>Once</td>
</tr>
</tbody>
</table>

*Consider twice daily dosing for elderly (age ≥ 70) and those at elevated risk of bleeding.

**Table 6. Potential Contraindications to Anticoagulant Thromboprophylaxis**

<table>
<thead>
<tr>
<th>Active or suspected major bleeding</th>
<th>General surgery within 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia (platelets &lt; 50,000/µL)</td>
<td>Recent brain, spinal, or ophthalmologic surgery/ intervention</td>
</tr>
<tr>
<td>Active ulcerative or angiodysplastic gastrointestinal disease</td>
<td>Suspected intracranial hemorrhage</td>
</tr>
<tr>
<td>Coagulopathy (INR &gt; 1.5 or aPTT &gt; 40 sec)</td>
<td>Severely uncontrolled hypertension</td>
</tr>
<tr>
<td>Concomitant use of platelet inhibitors or other anticoagulants</td>
<td>Conditions with increased risk of hemorrhage (eg, bacterial endocarditis, hemorrhagic stroke, congenital or acquired bleeding disorders)</td>
</tr>
<tr>
<td>History of HIT</td>
<td></td>
</tr>
</tbody>
</table>

*Does not necessarily apply to patients with liver disease or antiphospholipid antibody syndrome, both of which carry an elevated risk for thrombosis; it does not necessarily apply if anticoagulated with warfarin.

**Abbreviations:** aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio.
ing UFH, LMWH, or fondaparinux) resulted in fewer PEs (absolute reduction of 4 events per 1000 patients treated) but resulted in more bleeding events (absolute increase of 9 events per 1000 patients treated) with no effect on mortality. In most hospitalized acutely ill medical patients at elevated risk for VTE, the clinical benefit of reduction of PEs likely outweighs the harm of increased risk for bleeding events. Potential contraindications to the use of anticoagulants for VTE prophylaxis are outlined in Table 6. Additionally, a small risk of HIT occurrence may exist for patients with use of UFH or LMWH. As mentioned, fondaparinux has been successfully used off-label for VTE prophylaxis in patients with a history of HIT.

**Risk Factors for Bleeding With Anticoagulants for VTE Prophylaxis**

In the IMPROVE study, the strongest risk factors (OR > 3.0; P < 0.05) for inhospital patient bleeding included active gastroduodenal ulcer (OR 4.15; 95% CI, 2.21–7.77), bleeding within 3 months prior to admission (OR 3.64; 95% CI, 2.21–5.99) and blood platelet count < 50 x 10^9 cells/L (OR 3.37; 95% CI, 18.4–6.18). Other patient risk factors for bleeding included aged > 85 years, hepatic failure, renal failure, central venous catheter, rheumatic disease, cancer, intensive care unit (ICU) stay, and male sex. Determining a patient’s baseline risk of bleeding remains a difficult task; however, use of tools such as the IMPROVE Combined Risk Calculator can assist physicians when weighing the risks and benefits associated with anticoagulant thromboprophylaxis.

Both the ACCP and ACP guidelines recommend against anticoagulant thromboprophylaxis in patients actively bleeding or at high risk for bleeding. The ACCP suggests that mechanical thromboprophylaxis with GCS (ACCP Grade 2C) or IPC (ACCP Grade 2C) for patients at increased risk for thrombosis who are actively bleeding or at high risk for bleeding. The ACP guidelines differ slightly in this regard, recommending against the use of GCS in patients at high risk for bleeding or in whom heparin use is contraindicated for other reasons (ACP Grade: strong recommendation, moderate-quality evidence). The recommendation against the use of GCS is based on the lack of evidence supporting their use in prevention of VTE and evidence supporting clinically important lower extremity skin damage caused by their use. The ACP suggests IPC should be used (rather than GCS) because of evidence supporting their usefulness in surgical patients. Risk of patient bleeding complications should be continually assessed during hospitalization and anticoagulant prophylaxis should be started as soon as bleeding risk is considered low, if VTE risk persists.

**Non-Pharmacologic (Mechanical) Methods of VTE Prophylaxis**

There are 3 major methods of mechanical prophylaxis for VTE: GCS, IPC, and VFP. The ACP and ACCP guidelines differ slightly regarding the use of mechanical thromboprophylaxis. The ACP recommends against the use of mechanical prophylaxis with GCS for prevention of VTE for patients in whom heparin can be used (ACP Grade: strong recommendation, moderate-quality evidence) because of their unclear benefit and potential for harm (eg, skin breaks, ulcers). Alternatively, ACP suggests IPC should be used for patients at elevated risk for VTE with contraindications to heparin use, whereas the ACCP suggests use of GCS or IPCs in patients with risk factors for VTE and at high risk for bleeding (ACCP Grade 2C).

In hospitalized medical patients, there are no studies that have compared mechanical compression with anticoagulant treatment for the prevention of VTE. Studies evaluating the effectiveness of mechanical methods have been performed primarily in surgical patient populations. Pooled analysis of 3 trials evaluating the effectiveness of thigh-length GCS in medical patients failed to demonstrate or exclude a beneficial effect on symptomatic DVT or PE. Moreover, caution must be exercised with use of graduated compression devices due to their potential to increase the risk of skin breaks/ulcers, particularly in patients who have experienced stroke. Although there is a lack of evidence to support it, the ACCP guidelines express that it is reasonable to expect a similar risk for skin breaks/ulcers with use of IPCs as with GCS. Possible contraindications to use of IPCs and GCS include lower extremity edema, severe peripheral vascular disease, or local conditions, which may be worsened by mechanical compression. Mechanical thromboprophylaxis is recommended for patients at increased risk of VTE who are bleeding or at high risk for major bleeding (ACCP Grade 2C).

**Critically Ill Medical Patients**

Venous thromboembolism is a very serious complication of critical illness and critically ill patients represent a unique population of hospitalized acutely ill medical patients who are at high risk for VTE but frequently develop bleeding complications when given thromboprophylaxis. The Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT) compared the effect of LMWH
(dalteparin) with UFH in critically ill patients and found no significant differences in rates of proximal leg DVT (5.1% vs 5.8%), which was the primary endpoint. Rates of catheter-related thrombosis, major bleeding, VTE, and mortality were similar in both study groups. Use of dalteparin was associated with significantly fewer pulmonary emboli (1.3% vs 2.3%), with a number needed to treat of 100 patients. Dalteparin was the chosen therapeutic agent for the trial based on prior research implying an absence of bioaccumulation with its use in critically ill patients, including patients with renal insufficiency.

Observational evidence suggests that omission of thromboprophylaxis in critically ill patients is common (as high as 16%) and is associated with an increased risk of mortality (3.9%–15.4%), after adjustment for multiple confounding variables. A large observational study involving > 400,000 patients found higher mortality rates in critically ill patients when thromboprophylaxis was delayed > 24 hours after hospital admission. Thus, prompt administration of thromboprophylaxis in critically ill patients is important and should be initiated within 24 hours of admission to the ICU. The ACCP guidelines suggest using LMWH or UFH thromboprophylaxis over no prophylaxis in critically ill patients (ACCP Grade 2C). Mechanical thromboprophylaxis with GCS or IPC is suggested for critically ill patients who are bleeding or at high risk for bleeding (ACCP Grade 2C). Patients should be continually assessed for bleeding risk and once bleeding risk decreases, pharmacologic thromboprophylaxis can be substituted for mechanical thromboprophylaxis (ACCP Grade 2B).

Summary of Updated Recommendations
Both the ACP and ACCP guidelines recommend against universal use of VTE prophylaxis in non-critically ill medical inpatients. A new focus has been placed on assessment of individual patient baseline risk of developing VTE and bleeding risks associated with VTE prophylaxis prior to initiating prophylaxis in non-critically ill medical inpatients (ACP Grade: strong recommendation, moderate-quality evidence), although none of the currently available risk- assessment models have been properly validated for this purpose. Both guidelines agree that in patients at low risk of VTE, prophylaxis aside from early ambulation is not routinely recommended (ACCP Grade 1B). In patients with elevated risk of VTE (but no increased risk of bleeding), VTE prophylaxis is suggested with UFH (either 2 or 3 times daily), LMWH, or fondaparinux (ACCP Grade 1B). The guidelines suggest that the choice of drug therapy should be based on cost, convenience, and side-effects profile. When drug therapy cannot be used in patients with high risk of VTE due to increased risk of bleeding or other contraindications to heparin use, both guidelines agree that use of IPC may be a reasonable option.

Conclusion
Venous thromboembolism remains a serious potential complication of hospitalization, with multiple cost-effective and safe modalities available for its prevention. It is evident that VTE prophylaxis may be inappropriately utilized. Hospitalists serve an important role in the implementation of updated evidence-based consensus guidelines and patient safety. Current evidence no longer supports universal thromboprophylaxis for VTE prevention; however, hospitalists will likely face challenges implementing appropriate use of VTE prophylaxis as many regulatory agencies and payer sources have backed existing quality measures put in place by JCAHO, which could potentially result in patient harm.

Individualized risk assessment for VTE should take place routinely for all medical patients requiring hospitalization, including those with stroke. In the absence of contraindications, patients at elevated risk for VTE should receive thromboprophylaxis with LMWH, UFH, or fondaparinux. In at-risk patients with contraindications to pharmacologic thromboprophylaxis (ie, active bleeding), mechanical devices may serve as a reasonable alternative. For low-risk patients, no prophylaxis is needed, with the exception of early ambulation.

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Conflict of Interest Statement
Andrew L. Bozarth, MD, Navin Bajaj, MD, and Asem Abdeljalil, MD, FCCP, ABSM, disclose no conflicts of interest.
References


Appendix A

Bleeding was defined as either major bleeding or non-major (but clinically relevant) bleeding. Major bleeding includes bleeding events contributing to death or a decrease in hemoglobin level of ≥ 2 g/dL or leading to transfusion of ≥ 2 units of packed RBCs, or bleeding involving a critical organ (intracranial, retroperitoneal, intraocular, adrenal gland, spinal, or pericardial). Non-major bleeding includes overt GI bleeding (excluding hemorrhoidal bleeding), gross hematuria, epistaxis requiring intervention, hematoma > 5 cm in diameter, intraarticular bleeding (documented by aspiration), menorrhagia or metorrhagia (increased quantity or duration), or other bleeding important enough to be documented in the patient’s chart.24