Deep vein thrombosis (DVT) of the lower extremities is the most common manifestation of venous thromboembolism (VTE), and is particularly troublesome in the older adult population. The risk of VTE and DVT increases exponentially with advancing age: the annual incidence rises from 30 cases for every 100,000 patients at age 40, to 90 cases at age 60, and 260 cases at age 80 years. Additional risk factors for VTE are presented in Box 1 below.

### Box 1. Risk Factors for Venous Thromboembolism

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Acute medical illness</td>
<td>Immobilization</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>Inherited/acquired hypercoagulable state</td>
</tr>
<tr>
<td>Cancer</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td>Previous VTE</td>
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<tr>
<td>Frailty</td>
<td>Venous trauma</td>
</tr>
</tbody>
</table>

Adapted from Reardon et al

This month’s article continues our series that will summarize and synthesize clinical practice guidelines for a number of important disease states. These topics were identified by PharMerica Corporation, and are prepared by the clinical faculty at Creighton University’s Center for Drug Information & Evidence-Based Practice.

You can view archived newsletters, including last month’s issue on chronic kidney disease, on our website: [www.creighton.edu/pharmerica](http://www.creighton.edu/pharmerica).
Rates of VTE and DVT are also significantly higher in institutionalized patients compared to the community-dwelling elderly. In the nursing home population, the incidence of VTE has been estimated at 1.2 to 3.7 diagnosed cases per 100 patient-years.\(^1\) Experts agree that most studies underestimate the true risk of VTE, as many cases go undiagnosed. The prevalence of asymptomatic proximal DVT in nursing home patients was 18% in one recent study.\(^1\) Despite this, little is known about how DVT is managed in the long-term care (LTC) setting.

Common cardiovascular conditions, including atherosclerotic vascular disease, atrial fibrillation, ischemic heart disease and valvular disease, have a relationship to thrombosis. Most patients in the LTC setting with one or more of these disorders will require antithrombotic therapy; however, older adults have a higher risk of anticoagulant-associated bleeding compared to younger patients.\(^2\) With these increased bleeding rates, it can be difficult to determine whether there is a net benefit when anticoagulation is employed in geriatric patients.

The American College of Chest Physicians (CHEST) published the 9\(^{th}\) edition of the Antithrombotic Therapy and Prevention of Thrombosis Evidence-Based Clinical Practice Guidelines in 2012. Pharmacologic recommendations for the prevention and management of VTE in nonsurgical patients, select non-orthopedic surgical patients, and orthopedic surgical patients are summarized in the article that follows. In addition, clinical evidence that addresses DVT prophylaxis and treatment in the geriatric and LTC settings will be reviewed.

**Prevention of DVT**

According to the CHEST guidelines, **acutely ill medical patients** who are hospitalized and at an increased risk of thrombosis should receive anticoagulation with a low-molecular weight heparin (LMWH), low dose unfractionated heparin (LDUH), or fondaparinux. Choice of drug therapy should be made in consideration of patient preference, compliance, ease of administration, and cost. Patients who are bleeding or at a high risk for bleeding should not receive pharmacologic thromboprophylaxis.\(^3\)
Due to the lack of adequately designed randomized controlled trials in a long-term care population, there is insufficient evidence to determine whether the benefits of thromboprophylaxis with anticoagulants outweigh the risks of therapy. In a cross-sectional analysis of over 1600 elderly post-acute care patients, LMWH did not significantly reduce the risk of proximal DVT (4% vs. 5.7% in patients who did not receive LMWH, p=0.16). On the basis of this and other data, the CHEST guidelines recommend against the routine use of thromboprophylaxis in chronically immobilized nursing home residents.

Patients undergoing general or abdominal-pelvic surgery who are at moderate risk for VTE and who are not at high risk for major bleeding should receive thromboprophylaxis with LMWH, LDUH, or mechanical prophylaxis. For those at high risk for VTE, LMWH or LDUH is recommended in combination with mechanical prophylaxis. If LMWH and LDUH are contraindicated in these high risk patients, low-dose aspirin, fondaparinux, or mechanical prophylaxis should be used.

LMWH are recommended as first-line therapy for the prevention of venous thromboembolism (VTE) in patients undergoing total hip or total knee arthroplasty. If LMWH is unavailable or if the patient has a history of heparin-induced thrombocytopenia, alternative therapies include apixaban, dabigatran, rivaroxaban, vitamin K antagonist (VKA), fondaparinux, or aspirin in combination with mechanical prophylaxis. In patients undergoing hip fracture surgery, LWMH is the preferred agent for thromboprophylaxis. Fondaparinux, LDUH, adjusted-dose VKA, and aspirin are alternative therapies. In patients undergoing any of these major orthopedic surgeries who are uncooperative with injections or an intermittent pneumatic compression device, the CHEST guidelines recommend apixaban or dabigatran. This recommendation is based primarily on the oral availability of these agents, which may improve compliance, as well as data that suggests an increased risk of bleeding with rivaroxaban and VKA. If apixaban and dabigatran are not available, rivaroxaban or VKA therapy can be considered.

Treatment of DVT
The CHEST guidelines recommend LMWH or fondaparinux as first-line therapy for the initial treatment of acute DVT of the leg. In selecting between these two options, factors including cost, availability, and clinical experience should be considered. Unfractionated heparin is an alternative choice of therapy, and may be the most appropriate option for patients with renal impairment.
In patients without cancer who require extended anticoagulant therapy for VTE, VKA is recommended as first-line. If VKA is not used, LMWH should be recommended over dabigatran or rivaroxaban. In patients with cancer, LMWH is recommended over VKA, which is preferred over dabigatran or rivaroxaban. This preference for LMWH or VKA over therapy with dabigatran or rivaroxaban receives a weak recommendation. The CHEST guidelines acknowledge that treatment with dabigatran or rivaroxaban may be associated with better clinical outcomes, but post-marketing safety data was lacking at the time of publication. Apixaban is not addressed in this section of the CHEST guidelines; it was not approved for the treatment of VTE in the United States at the time the guidelines were prepared.

Since the publication of the CHEST guidelines, critical appraisals of the available evidence have demonstrated that dabigatran, rivaroxaban, and apixaban are effective for the treatment of acute VTE, with no significant increase in the risk of major bleeding compared to conventional therapy. For the primary outcome of recurrent symptomatic VTE and related deaths, dabigatran was non-inferior to warfarin (2.4% vs. 2.1%, p<0.0001 for non-inferiority) in the RE-COVER and RE-COVER II studies. Episodes of major bleeding did not differ significantly between the treatments (HR=0.69 for dabigatran, 95% CI 0.36-1.32). Rivaroxaban therapy reduced thrombotic burden at 21 days by 43.8-53.0%, compared to 45.9% for treatment with enoxaparin and VKA. Rates of major bleeding with rivaroxaban varied widely across clinical trials (from 1.7%-10.3%), but remained similar to rates in the conventional treatment groups across all studies. Finally, the BOTTICELLI DVT study compared apixaban to treatment with LWMH or fondaparinux followed by VKA over 3 months. The composite primary efficacy outcome included symptomatic recurrence of VTE, deterioration of bilateral compression ultrasound, or deterioration of perfusion lung scan. The primary outcome occurred in 4.7% of apixaban patients and 4.2% of conventional therapy patients (p value not reported). Major or clinically relevant non-major bleeding occurred in 7.3% of patients treated with apixaban and 7.9% of patients treated with conventional therapy.

All phase III studies evaluating treatment of acute VTE were conducted as non-inferiority studies comparing the new oral anticoagulants to VKA. Therefore, they were not designed to determine superiority of one regimen over another, nor do they provide direct comparison data among the new oral anticoagulants. In the absence of head-to-head studies, an indirect comparison was performed which evaluated rivaroxaban, apixaban, and dabigatran for the treatment of acute VTE. Six randomized trials, encompassing over 27,000 patients, were included in the analysis.
The results demonstrated that the new oral anticoagulants did not differ significantly with respect to the risk of mortality, recurrent VTE, recurrent PE, or recurrent DVT. However, dabigatran significantly increased the risk of major bleeding compared to apixaban (RR=2.74, 95% CI 1.40-5.39). Apixaban also decreased the risk of bleeding compared to rivaroxaban, but this difference was not statistically significant (RR=1.80 for rivaroxaban, 95% CI 0.95-3.57). Rivaroxaban and dabigatran demonstrated similar rates of major bleeding (RR=0.73, 95% CI 0.41-1.30).

The ability to draw conclusions based on this indirect comparison is limited, but the data suggests apixaban may be safer than its comparators with respect to rates of major bleeding. As the body of evidence supporting the efficacy and safety of these agents grows, researchers and clinicians have speculated that the new oral anticoagulants will become the treatment of choice in VTE.

Conclusion
Recommendations from the American College of Chest Physicians guide anticoagulant therapy for the management of venous thromboembolism. In general, LMWH are preferred for the prevention of DVT. Apixaban, dabigatran, fondaparinux, rivaroxaban, and warfarin are appropriate alternatives; patient-specific factors should be considered when selecting an alternative. LMWH and fondaparinux are recommended as first-line therapy for the initial treatment of DVT. Emerging evidence suggests that the new oral anticoagulants may become the treatment of choice in the future; however, there remains concern about the lack of antidotes for these agents. (At the current time, only dabigatran has a specific reversal agent.) While the CHEST guidelines provide significant evidence-based guidance on the management of DVT, patient-specific factors and the clinician’s judgment should ultimately dictate an appropriate care plan.

For More Information...

An update to the CHEST Guidelines is expected this year; however, revisions were not available at the time this newsletter was prepared. Readers are advised to visit the CHEST Journal website in anticipation of updated therapeutic recommendations.

9th edition - Prevention in Nonsurgical Patients
9th edition - Prevention in Nonorthopedic Surgical Patients
9th edition - Prevention in Orthopedic Surgical Patients
9th edition - Treatment of VTE
References


