With VTE now considered a chronic condition, knowing treatment options—and dosing schedules—is important. We have a chart for that.
Each year, there are approximately 10 million cases of venous thromboembolism (VTE) worldwide. Optimal treatment is vital. Recently, the American College of Chest Physicians updated its 2012 guidelines regarding antithrombotic therapy for VTE. In this 10th edition of the guideline, experts provide 53 updated recommendations for appropriate treatment of patients with VTE in a 38-page report. We combed through the guideline and selected the key new recommendations covering outpatient management of acute deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE).

I. Treatment of VTE

**Recommendation:** For DVT of the leg or PE without an associated cancer diagnosis, all direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, or edoxaban) are recommended over vitamin K antagonist (VKA) therapy or warfarin (all Grade 2B), and warfarin is recommended over low-molecular-weight heparin (LMWH; Grade 2C).

**Details:** This decision to recommend (although it is a weak recommendation) a DOAC over warfarin is a significant change from past recommendations. Until now, warfarin was the standard of care, and many practitioners were reluctant to use a DOAC for a DVT or PE preferentially over warfarin. Since the publication of the previous guideline, many large randomized trials have found them to be as effective as warfarin but cause less bleeding, especially intracranial hemorrhage. However, of the factor Xa inhibitors, only dabigatran has a reversal agent (idarucizumab or Praxbind®). Warfarin is preferred over LMWH because warfarin is not associated with a high rate of recurrence of VTE in patients with VTE without cancer, and warfarin therapy is more convenient and less expensive than injectable LMWH. Patient preference and cost should be considered when selecting an agent for treatment of DVT or PE.

**Comments:** Table 1 below summarizes the available DOACs in the U.S.

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name</strong></td>
<td>Eliquis</td>
<td>Pradaxa</td>
<td>Savaysa</td>
<td>Xarelto</td>
</tr>
<tr>
<td><strong>FDA-approved indicators for treatment of VTE</strong></td>
<td>10 mg PO twice daily for 7 days, then 5 mg PO twice daily</td>
<td>After 5 to 10 days of parenteral therapy with UH or LWMH, 150 mg PO twice daily</td>
<td>After 5 to 10 days of parenteral therapy with UH or LWMH, 60 mg PO once daily (30 mg PO once daily if ≤60 kg)</td>
<td>15 mg PO twice daily for 3 weeks, then 20 mg PO once daily</td>
</tr>
<tr>
<td><strong>Dosing in Renal Dysfunction</strong></td>
<td>Renal impairment including those on dialysis  • No dosage adjustment needed; monitor for bleeding Clcr &gt;30 mL/min  • No dosage adjustment needed; monitor for bleeding Clcr &lt;30 mL/min  • Avoid</td>
<td>Clcr &gt;50 mL/min  • No dosage adjustment needed; monitor for bleeding Clcr 15 mL/min to 50 mL/min  • 30 mg PO once daily Clcr &lt;15 mL/min  • Avoid</td>
<td>Clcr &gt;30 mL/min  • No dosage adjustment needed; monitor for bleeding Clcr &lt;30 mL/min  • Avoid</td>
<td></td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Tablets 2.5 mg, 5.0 mg</td>
<td>Capsules 75 mg, 110 mg, 150 mg</td>
<td>Capsules 75 mg, 110 mg, 150 mg</td>
<td>Tablets 10 mg, 15 mg, 20 mg</td>
</tr>
</tbody>
</table>

Abbreviations: PO= orally; UH = unfractionated heparin; LMWH = low-molecular-weight heparin
Recommendation: For VTE associated with cancer, LMWH is recommended over warfarin (Grade 2B). There is moderate-quality evidence to suggest LMWH is more effective than warfarin, and there is a high rate of recurrence of VTE in patients with cancer who receive warfarin therapy, possibly because it is harder to keep the INR within the therapeutic range in these patients. Additionally, LMWH can be used in patients with vomiting, and these agents may be easier to hold or discontinue if invasive procedures are needed or if chemotherapy-induced thrombocytopenia occurs (all Grade 2C).

Details: Although prescribing a DOAC to a patient with cancer-associated VTE would not be an “off-label use” in the United States, there is no compelling evidence that therapy with a DOAC is superior to LMWH, which is considered the current standard of care in this setting.

Comments:

Table 2 below summarizes the available LMWH products available in the U.S.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Dalteparin</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved indications for treatment of VTE</td>
<td>Extended treatment of VTE in patients with cancer: • Month 1: 200 IU/kg SC once daily • Months 2 to 6: 150 IU/kg SC once daily</td>
<td>Inpatient treatment of acute DVT with or without pulmonary embolism: • 1.0 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily Outpatient treatment of acute DVT without pulmonary embolism: • 1 mg/kg SC every 12 hours</td>
</tr>
</tbody>
</table>

Dosing in Renal Dysfunction

| Clcr 30 to 60 mL/min | No dosage adjustment needed; monitor for bleeding | Clcr 30 to 60 mL/min | No dosage adjustment needed; monitor for bleeding |
| Clcr <30 mL/min | Use with caution, target anti-Xa levels 0.5 to 1.5 IU/mL (4 hours to 6 hours after dose, after 3 to 4 days of therapy) | Clcr <30 mL/min | Use with caution, 1 mg/kg SC once daily Dialysis | Avoid, unless checking anti-Xa levels |

Abbreviations: SC = subcutaneous

Recommendation: In patients with DVT of the leg or PE who receive extended therapy, there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C).

Details: It may be appropriate for the choice of anticoagulant to change in response to changes in the patient's circumstances or preferences during long-term or extended phases of treatment. However, it is not necessary to change the anticoagulant as all recommended anticoagulants are safe and effective during extended therapy (>3 months).

Comments: Since the publication of the prior VTE guideline, information regarding the efficacy and safety of extended treatment of VTE with dabigatran has been published. Dabigatran has been found to be similarly effective but is associated with a lower risk of bleeding compared with warfarin therapy (risk of major bleeding 8 fewer per 1000 treated patients).
Similarly, extended treatment with rivaroxaban and apixaban has been shown to reduce the risk of recurrent VTE compared with placebo and without an increased risk of bleeding when compared with warfarin therapy.

II. Aspirin Therapy in the Treatment of VTE

**Recommendation:** In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, aspirin over no aspirin to prevent recurrent VTE should be used (Grade 2B).

**Details:** Aspirin is less effective at preventing recurrent VTE than are anticoagulants and is therefore not considered an alternative to anticoagulant therapy for extended therapy. However, in a patient who does not wish to continue anticoagulant therapy, aspirin should be used to prevent recurrent VTE. However, the benefits of reducing a recurrent VTE should be balanced against the risks of bleeding.

**Comments:** Previous VTE guidelines did not address use of aspirin in the treatment of VTE. Since then, however, 2 randomized controlled trials evaluated the efficacy of aspirin in patients with an initial unprovoked VTE who have received anticoagulant therapy for 3 to 18 months. In general, extended therapy with aspirin was found to be associated with a lower overall risk of recurrence of VTE by more than one-third compared with no therapy, without significantly increasing the risk of bleeding.

III. Treatment of Acute PE Out of Hospital

**Recommendation:** In patients with low-risk PE and whose home circumstances are adequate, treatment at home or early discharge over standard discharge (eg, after the first 5 days of treatment) is acceptable (Grade 2B).

**Details:** Prior VTE guidelines recommended that patients with acute PE be treated with parenteral anticoagulation (LMWH, fondaparinux, IV or subcutaneous unfractionated heparin). In the past, these agents were necessary prior to initiation of warfarin or dabigatran. However, with the introduction of newer DOACs such as rivaroxaban and apixaban, overlap is unnecessary, and some patients with PE can be treated as outpatients, without the need for hospitalization.

**Comments:** Although there are no new additional randomized controlled trials regarding outpatient treatment of PE since the publication of the previous guideline, several prospective and retrospective observational trials and meta-analyses have provided additional information. For example, one recent systematic review and meta-analysis of >1200 patients found that low-risk patients with acute PE can be safely treated as outpatients, if home circumstances are adequate.

According to the updated VTE guideline, outpatient therapy of acute PE should be considered only in patients who satisfy all of the following conditions:

- Patient is clinically stable with good cardiopulmonary reserve
- No contraindications to anticoagulation exists including recent bleeding, severe renal or hepatic dysfunction, or platelet count <70,000/m$^3$
- Patient is expected to be adherent with treatment and follow-up
- Patient feels well enough to be treated at home
IV. Management of Recurrent VTE on Anticoagulation Therapy

**Recommendation:** In patients who have recurrent VTE on warfarin therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), treatment should be changed to LMWH, at least temporarily (Grade 2C).

In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), the dose of the LMWH should be increased by about 25% to 33% (Grade 2C).

**Details:** There are no randomized controlled trials on management of patients with recurrent VTE, so management is based on low-quality evidence. Recurrence can be due to treatment factors (early in therapy, incorrect regimen, drug interactions, nonadherence, etc) or patient factors (active, undiagnosed cancer, antiphospholipid syndrome, use of concurrent medications which increase coagulability, etc).

**Comments:** Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt assessments as to whether this is truly a recurrent VTE, evaluation of adherence with anticoagulant therapy, and consideration of an underlying malignancy. A recurrence soon after starting initial therapy can be managed with a temporary switch to an LMWH, usually for at least 1 month. Moderate-quality evidence suggests that LMWH is more effective than warfarin therapy in patients with VTE and cancer, so switching to treatment doses of LMWH is adequate. If there is no reversible cause for recurrent disease and anticoagulant dosing cannot be intensified, a vena cava filter can be inserted to prevent a PE.

V. Conclusions

There has been an important conceptual change in VTE management, one that views VTE as a chronic condition. Five-year recurrence rates for unprovoked VTE are 30%. In VTE provoked by a transient non-surgical condition, rates are 15%; in the setting of cancer, rates are 15% per year. Conveying this information to patients should improve decision-making and compliance when lifelong anticoagulation is recommended.

More options are available now than ever before. DOACs allow for PE treatment without hospitalization. The possibility of avoiding parenteral therapy in PE simplifies treatment regimens. The option to avoid therapy altogether in the setting of subsegmental PE will save unnecessary treatment for many.

For unstable patients, thrombolysis and catheter-directed therapy provide lifesaving options. These guidelines are more specific than many. However, you must still be comfortable assessing such things as bleeding risk, cardiopulmonary reserve, and probability of distal DVT extension to properly incorporate the recommendations into practice. Some clinical judgment is necessary to determine risk-benefit ratios of thrombolysis and/or catheter-directed therapy in the unstable patient. Selecting patients for home-based PE treatment is likewise imprecise.

DOACs all appear equally effective. However, you must familiarize yourself with dosing schedules for each one including renal dosing. Variable dosing regimens mean educating your patients as well. Also keep in mind the requirement for antecedent parenteral therapy when using dabigatran and edoxaban.
American College of Chest Physicians (CHEST) Grading System

1A – Strong recommendation, high-quality evidence. Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies.

1B – Strong recommendation, moderate-quality evidence. Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.

1C – Strong recommendation, low- or very-low-quality evidence. Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence.

2A – Weak recommendation, high-quality evidence. Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies.

2B – Weak recommendation, moderate-quality evidence. Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or very strong evidence from observational studies.

2C – Weak recommendation, low- or very-low-quality evidence. Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence.

About the authors

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References


