Cancer-associated thrombosis

Advances in diagnosis and treatment

Kraaijpoel, N.

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Chapter 2

VENOUS THROMBOEMBOLISM: ADVANCES IN DIAGNOSIS AND TREATMENT

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*both authors contributed equally

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ABSTRACT

Importance: Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal disease.

Objective: To summarize the advances in diagnosis and treatment of VTE of the past 5 years.

Evidence review: A systematic search was conducted in EMBASE Classic, EMBASE, Ovid MEDLINE, and other non-indexed citations, using broad terms for diagnosis and treatment of VTE, to find systematic reviews and meta-analyses, randomized trials, and prospective cohort studies published between January 1st, 2013, and July 31st, 2018. The tenth edition of the American College of Chest Physicians Antithrombotic Therapy Guidelines was screened to identify additional studies. Screening of titles, abstracts, and subsequently full-text articles was performed in duplicate, as well as data extraction and risk of bias assessment of the included articles.

Findings: Thirty-two articles were included in this review. The application of an age-adjusted D-dimer threshold in patients with suspected PE has increased the number of patients in whom imaging can be withheld. The Pulmonary Embolism Rule-out Criteria safely exclude PE when the pretest probability is low. The introduction of direct oral anticoagulants has allowed for a simplified treatment of VTE with a lower risk of bleeding regardless of etiology or extent of the VTE (except for massive PE), and made extended secondary prevention more acceptable. Thrombolysis is best reserved for patients with massive PE or those with DVT and threatened limb loss. Insertion of inferior vena cava filters should be avoided, unless anticoagulation is absolutely contraindicated in patients with recent acute VTE. Graduated compression stockings are no longer recommended to treat DVT, but may be used when acute or chronic symptoms are present. Anticoagulation may no longer be indicated for patients with isolated distal DVT at low risk of recurrence.

Conclusions and relevance: Over the past five years, substantial progress has been made in VTE management, allowing for diagnostic and therapeutic strategies tailored to individual patient characteristics, preferences, and values.
INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal disease. The estimated incidence of a first acute VTE is 0.7 to 1.4 per 1000 person-years and is mostly observed in patients older than 55 years. While the incidence of DVT has remained constant over time, hospital admissions for PE in the United States more than doubled over the last decades, partly due to the widespread use of sensitive imaging techniques detecting smaller, potentially insignificant emboli. Even though the in-hospital case-fatality rate of PE has decreased in the United States between 1999 and 2008, about 30% of patients with PE die within the first year after diagnosis. VTE’s socioeconomic effect is significant, with estimated annual costs ranging from US $13.5 to 27.2 billion in the United States.

Clinical signs and symptoms of DVT include unilateral leg pain, redness, swelling, edema, warmth, and tenderness. Pulmonary embolism may present with dyspnea, chest pain, cough, hemoptysis, syncope, tachycardia, and hypotension. The clinical presentation of VTE is often not specific, and DVT can be indistinguishable from cellulitis, hematoma, superficial thrombophlebitis and congestive failure. Pulmonary embolism presents similarly to myocardial infarction, congestive heart failure and other diseases. Consequently, imaging is needed to confirm the diagnosis of VTE. The diagnosis of VTE is made in a sequence of steps including assessment of the pretest probability, followed by D-dimer testing, and imaging, as appropriate (Figure 1). When VTE is diagnosed, immediate initiation of anticoagulant therapy is imperative. The choice between different anticoagulant agents and the duration of treatment are based on the clinical presentation, the etiology of the VTE event, bleeding risk, and patient preference. This review will focus on the advances in diagnosis and treatment of VTE of the past 5 years.

METHODS

A systematic search was conducted in EMBASE Classic, EMBASE, Ovid MEDLINE, and other non-indexed citations from January 1st, 2013, to July 31st, 2018, combining terms for diagnosis and treatment of VTE, to find prospective cohort studies, randomized trials, systematic reviews and meta-analyses (eAppendix in the Supplement). Articles were restricted to humans, adults, and
studies published in English, French, Dutch, German, and Italian. In addition, the tenth edition of the American College of Chest Physicians Antithrombotic Therapy Guidelines was screened for studies not found by the initial search. Titles, abstracts, and subsequently full text articles were screened independently by two authors (TT and NK) for eligibility. Data extraction and quality assessment was independently performed in duplicate (TT and NK) using the AMSTAR tool for systematic reviews and meta-analyses, and the SIGN-50 tool for randomized trials and cohort studies; disagreements were resolved by discussion.

To be eligible, studies had to be rated as at least medium quality by the AMSTAR tool or acceptable quality by the SIGN-50 tool. When multiple systematic reviews or meta-analyses covered the same topic, the study with

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**Figure 1.** Diagnostic management of patients with suspected deep vein thrombosis or pulmonary embolism

| Patient with suspected venous thromboembolism (VTE) |
| Symptoms of deep vein thrombosis (DVT): |
| unilateral leg pain, redness, swelling, warmth, and tenderness |
| Symptoms of pulmonary embolism (PE): |
| dyspnea, chest pain, hemoptysis, syncope, tachycardia, and hypotension |

---

| Clinical decision rule³ |
| VTE unlikely |
| VTE likely |

- **Perform D-dimer testing⁴**
  - Negative
  - Positive

- **Compression ultrasonography for DVT or Computed tomography pulmonary angiography for PE**
  - Negative⁵
  - Positive

---

Abbreviations: CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism.

³ Wells score for suspected deep vein thrombosis and Wells score or revised Geneva score for suspected pulmonary embolism.

⁴ Age-adjusted D-dimer threshold, calculated as the patient’s age multiplied by 10 ng/mL (fibrinogen equivalent units) for patients older than 50 years with suspected pulmonary embolism.

⁵ Repeat compression ultrasonography 1 week after initially normal finding in patients with high clinical probability and positive D-dimer levels if initial imaging was not whole-leg ultrasonography.
the best methodological quality was included and in case of similar quality the most recent study was selected. If advances were not covered by a systematic review or meta-analysis, we included randomized trials or prospective cohort management studies.

RESULTS

Of the 2009 citations identified by the literature search, 32 articles were included in the review (eFigure in the Supplement). Characteristics and results of the included studies are provided in Table 1 and Table 2, quality assessment of included studies in eTable 1, eTable 2, and eTable 3 (in the Supplement).

Major diagnostic advances

DVT and PE cannot be diagnosed based on signs and symptoms alone. Prompt and accurate diagnosis is crucial to provide appropriate treatment and avoid thrombus extension or embolization, disease-related morbidity, and mortality. However, as VTE diagnosis is frequently suspected but confirmed in fewer than 20% of suspected cases,\textsuperscript{13,14} it is not ideal to perform imaging in every suspected case. Overall, VTE can be excluded in 29% (95% confidence interval [CI], 20 to 40%) of patients with suspected DVT and 28% (95% CI, 20 to 37%) of those with suspected PE using diagnostic algorithms including pretest probability assessment and D-dimer testing (Figure 1).\textsuperscript{15,16} The remaining patients will require compression ultrasonography or computed tomography pulmonary angiography (CTPA) to determine whether or not VTE is present.\textsuperscript{17-20}

Clinical decision rules

In settings with low VTE prevalence (e.g. emergency departments in the United States), an alternative approach to patients with suspected PE was proposed with the introduction of the Pulmonary Embolism Rule-out Criteria (PERC) rule, which aimed to rule out PE without testing.\textsuperscript{21} The 8 PERC criteria are (1) age 50 years or older; (2) pulse rate equal to or higher than 100 beats/minute; (3) pulse oximetry oxygen saturation of less than 95%; (4) unilateral leg swelling; (5) hemoptysis; (6) recent surgery or trauma; (7) prior PE or DVT; and (8) exogenous estrogen use.\textsuperscript{21} When none of these are present in a patient with suspected PE, the PERC rule safely excludes PE with a false negative rate of less than 1%, a sensitivity of 97% (95% CI, 96% to 98%), and a specificity of 22%
### Table 1. Major diagnostic advances in venous thromboembolism

<table>
<thead>
<tr>
<th>Source by category</th>
<th>Type of evidence</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Diagnostic management</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical decision rules</strong></td>
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<tr>
<td>Singh et al,22 2013</td>
<td>Meta-analysis</td>
<td>12</td>
<td>14,844</td>
<td>PERC rule</td>
<td>PERC can safely rule out PE in low clinical probability populations</td>
</tr>
<tr>
<td>Penaloza et al,25 2017</td>
<td>Cohort</td>
<td>1</td>
<td>1,773</td>
<td>PERC rule</td>
<td>PERC may safely rule out PE in patients with low implicit clinical probability in a European setting</td>
</tr>
<tr>
<td>Freund et al,26 2018</td>
<td>Cluster randomized trial</td>
<td>1</td>
<td>1,916</td>
<td>PERC rule</td>
<td>PERC safely rules out PE in patients with low implicit clinical probability in a European setting.</td>
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<tr>
<td><strong>D-dimer testing</strong></td>
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<tr>
<td>Van Es et al,16 2016</td>
<td>Meta-analysis</td>
<td>6</td>
<td>7,268</td>
<td>Conventional vs age-adjusted D-dimer threshold</td>
<td>Age-adjusted D-dimer threshold increases proportion of patients in whom imaging can be withheld, also in high-risk subgroups</td>
</tr>
<tr>
<td><strong>Diagnostic algorithm</strong></td>
<td></td>
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<tr>
<td>Van der Hulle et al,27 2017</td>
<td>Cohort</td>
<td>1</td>
<td>3,465</td>
<td>Diagnostic algorithm</td>
<td>YEARS diagnostic algorithm can safely rule out PE</td>
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<tr>
<td><strong>Imaging for suspected DVT</strong></td>
<td></td>
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<tr>
<td>Pomero et al,28 2013</td>
<td>Meta-analysis</td>
<td>16</td>
<td>2,379</td>
<td>Emergency physician-performed ultrasonography</td>
<td>Emergency physician-performed ultrasonography has a high sensitivity and specificity for the diagnosis of DVT</td>
</tr>
<tr>
<td>Abdalla et al,29 2015</td>
<td>Meta-analysis</td>
<td>23</td>
<td>1,121</td>
<td>Magnetic resonance venography</td>
<td>Magnetic resonance venography potential alternative for diagnosis of DVT when ultrasonography is not feasible</td>
</tr>
<tr>
<td><strong>Imaging for suspected PE</strong></td>
<td></td>
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<tr>
<td>Da Costa Rodrigues et al,30 2016</td>
<td>Meta-analysis</td>
<td>15</td>
<td>6,991</td>
<td>Lower limb ultrasonography</td>
<td>Proximal lower limb ultrasonography can confirm but cannot rule out PE</td>
</tr>
<tr>
<td>Squizzato et al,31 2017</td>
<td>Meta-analysis</td>
<td>13</td>
<td>1,170</td>
<td>Magnetic resonance imaging</td>
<td>Magnetic resonance imaging has high specificity but limited sensitivity for diagnosis of PE, and one-fifth of results are inconclusive.</td>
</tr>
<tr>
<td>Phillips et al,32 2015</td>
<td>Meta-analysis</td>
<td>19</td>
<td>5,923</td>
<td>V/Q SPECT</td>
<td>V/Q SPECT and CTPA have similar performance and are both superior to planar V/Q imaging</td>
</tr>
</tbody>
</table>

Abbreviations: CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism; PERC, Pulmonary Embolism Rule-out Criteria; V/Q, ventilation/perfusion; SPECT, single-photon emission computed tomography; VTE, venous thromboembolism.
<table>
<thead>
<tr>
<th>Source by category</th>
<th>Type of evidence</th>
<th>No. of studies</th>
<th>No. of patients (% with PE)</th>
<th>Phase of treatment</th>
<th>Intervention</th>
<th>Control</th>
<th>Occurrence or relative risk / hazard ratio for primary outcome (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Oral anticoagulants</strong></td>
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<tr>
<td>Gomez et al., 2014</td>
<td>Meta-analysis</td>
<td>6</td>
<td>27,127 (43%)</td>
<td>Initial and long-term</td>
<td>DOAC</td>
<td>LMWH/VKA</td>
<td>Recurrent VTE: 0.91 (0.79-1.06) Major bleeding: 0.62 (0.45-0.85)</td>
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<tr>
<td>Gomez et al., 2015</td>
<td>Meta-analysis</td>
<td>6</td>
<td>27,127 (NR)</td>
<td>Initial and long-term</td>
<td>DOAC</td>
<td>LMWH/VKA</td>
<td>Case fatality recurrent VTE: 1.09 (0.77-1.55) Case fatality major bleeding: 0.57 (0.25-1.30)</td>
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<td>4</td>
<td>5,036 (NR)</td>
<td>Extended</td>
<td>DOAC</td>
<td>VKA or Placebo</td>
<td>Case fatality recurrent VTE: 2.02 (0.75-5.43) No fatal bleeding during extended treatment</td>
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<tr>
<td>Garcia et al., 2016</td>
<td>Meta-analysis</td>
<td>3</td>
<td>383 (NR)</td>
<td>Initial</td>
<td>10-mg nomogram</td>
<td>5-mg nomogram</td>
<td>Therapeutic INR by day 5: 1.27 (1.05-1.54)</td>
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<tr>
<td>Li et al., 2015</td>
<td>Meta-analysis</td>
<td>6</td>
<td>2,029c</td>
<td>Initial</td>
<td>Pharmaco-genetic testing</td>
<td>Standard AC strategy</td>
<td>Thromboembolic events: 0.38 (0.17-0.85) Major bleeding: 0.57 (0.37-0.90) %TTR: 4.65 (0.01-9.29)d INR &gt;4: 0.92 (0.81-1.06)</td>
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<td></td>
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<td>6</td>
<td>2,029c</td>
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<td></td>
<td></td>
<td>9</td>
<td>2,278c</td>
<td></td>
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<td></td>
<td></td>
<td>6</td>
<td>2,043c</td>
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<tr>
<td>Marik et al., 2015</td>
<td>Meta-analysis</td>
<td>2</td>
<td>533 (78%)</td>
<td>Extended</td>
<td>VKA</td>
<td>Placebo</td>
<td>Recurrent VTE: 0.09 (0.03-0.25) Major bleeding: 5.13 (0.87-30.15)</td>
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<tr>
<td></td>
<td></td>
<td>3</td>
<td>5,021 (36%)</td>
<td></td>
<td>DOAC</td>
<td>Placebo</td>
<td>Recurrent VTE: 0.16 (0.11-0.24) Major bleeding: 1.88 (0.19-18.06)</td>
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<td></td>
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<td>2</td>
<td>1,224 (41%)</td>
<td></td>
<td>Aspirin</td>
<td>Placebo</td>
<td>Recurrent VTE: 0.62 (0.44-0.87) Major bleeding: 1.28 (0.47-3.48)</td>
</tr>
<tr>
<td>Schulman et al., 2013</td>
<td>RCT</td>
<td>1</td>
<td>2,856 (35%)</td>
<td>Extended</td>
<td>Dabigatran</td>
<td>VKA</td>
<td>Recurrent VTE: 1.44 (0.78-2.64) Major bleeding: 0.52 (0.27-1.02)</td>
</tr>
<tr>
<td>Weitz et al., 2017</td>
<td>RCT</td>
<td>1</td>
<td>3,365 (50%)</td>
<td>Extended</td>
<td>Rivaroxaban 20 mg/d</td>
<td>Rivaroxaban 10 mg/d</td>
<td>Recurrent VTE: 0.34 (0.20-0.59) Major bleeding: 2.01 (0.50-8.04) Recurrent VTE: 0.26 (0.14-0.47) Major bleeding: 1.64 (0.39-6.84)</td>
</tr>
<tr>
<td>Source by category</td>
<td>Type of evidence</td>
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<td>No. of patients (% with PE)</td>
<td>Phase of treatment</td>
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<td>Occurrence or relative risk / hazard ratio for primary outcome (95% CI)</td>
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<tr>
<td><strong>Thrombolysis</strong></td>
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<tr>
<td>Watson et al, 2016</td>
<td>Meta-analysis</td>
<td>9</td>
<td>529 (0%)</td>
<td>Initial</td>
<td>Thrombolysis plus AC</td>
<td>AC</td>
<td>All-cause mortality: 0.76 (0.31-1.89) Major bleeding: 2.23 (1.41-3.52) PTS: 0.66 (0.53-0.81)</td>
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<tr>
<td></td>
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<td>17</td>
<td>1,103 (0%)</td>
<td></td>
<td>AC</td>
<td></td>
<td>PTS: 0.96 (0.82-1.11)</td>
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<td></td>
<td></td>
<td>3</td>
<td>306 (0%)</td>
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<tr>
<td>Vedantham et al, 2017</td>
<td>RCT</td>
<td>1</td>
<td>692 (0%)</td>
<td>Initial</td>
<td>CDT</td>
<td>AC</td>
<td>Percentage of thrombus load reduction: 55% vs 54% (P=.91)</td>
</tr>
<tr>
<td>Engelberger et al, 2015</td>
<td>RCT</td>
<td>1</td>
<td>48 (0%)</td>
<td>Initial</td>
<td>USAT</td>
<td>CDT</td>
<td>Venous patency: 100% vs 100% (P=.91)</td>
</tr>
<tr>
<td>Engelberger et al, 2017</td>
<td>RCT</td>
<td>1</td>
<td>45 (0%)</td>
<td>Initial</td>
<td>USAT</td>
<td>CDT</td>
<td>PTS: 17% vs 5% (P=.47) QIVIQ-20 score: 29 points vs 26 points (P=.30)</td>
</tr>
<tr>
<td>Hao et al, 2015</td>
<td>Meta-analysis</td>
<td>10</td>
<td>1,841 (100%)</td>
<td>Initial</td>
<td>Thrombolysis plus AC</td>
<td>AC</td>
<td>All-cause mortality: 0.60 (0.36-1.01) Recurrent PE: 0.39 (0.17-0.86) Major bleeding: 3.35 (2.06-5.45)</td>
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<td>8</td>
<td>1,707 (100%)</td>
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<td>AC</td>
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<td>1,699 (100%)</td>
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<tr>
<td>Konstantinides et al, 2017</td>
<td>RCT</td>
<td>1</td>
<td>709 (100%)</td>
<td>Initial</td>
<td>Thrombolysis plus AC</td>
<td>Placebo plus AC</td>
<td>All-cause mortality: 20% vs 18% (P=.43) Clinical symptoms: 36% vs 30% (P=.23) Right ventricular dysfunction: 44% vs 37% (P=.20)</td>
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<tr>
<td><strong>Vena cava filters</strong></td>
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<tr>
<td>Mismetti et al, 2015</td>
<td>RCT</td>
<td>1</td>
<td>399 (100%)</td>
<td>Initial</td>
<td>IVCF plus AC</td>
<td>AC</td>
<td>Recurrent PE: 2.00 (0.51-7.89)</td>
</tr>
<tr>
<td><strong>Compression stockings</strong></td>
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<tr>
<td>Subbiah et al, 2016</td>
<td>Meta-analysis</td>
<td>6</td>
<td>1,462 (0%)</td>
<td>Initial and long-term</td>
<td>Compression stockings</td>
<td>No stockings/placebo</td>
<td>PTS: 0.56 (0.27-1.16)</td>
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<td><strong>Cancer-associated VTE</strong></td>
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<tr>
<td>Raskob et al, 2017</td>
<td>RCT</td>
<td>1</td>
<td>1046 (63%)</td>
<td>Initial and long-term</td>
<td>LMWH/Edoxaban</td>
<td>Dalteparin</td>
<td>Recurrent VTE or major bleeding: 0.97 (0.70-1.36)</td>
</tr>
<tr>
<td>Young et al, 2018</td>
<td>RCT</td>
<td>1</td>
<td>406 (73%)</td>
<td>Initial</td>
<td>Rivaroxaban</td>
<td>Dalteparin</td>
<td>Recurrent VTE: 0.43 (0.19-0.99) Major bleeding: 1.83 (0.68-4.96)</td>
</tr>
</tbody>
</table>
## Table 2. Continued

<table>
<thead>
<tr>
<th>Source by category</th>
<th>Type of evidence</th>
<th>No. of studies</th>
<th>No. of patients (% with PE)</th>
<th>Phase of treatment</th>
<th>Intervention</th>
<th>Control</th>
<th>Occurrence or relative risk / hazard ratio for primary outcome (95% CI)</th>
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<td><strong>Isolated Distal DVT</strong></td>
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</tr>
</tbody>
</table>
| Franco et al,
  59 2017               | Meta-analysis    | 20             | 2,936 (100%)                | Initial and long-term | AC           | No treatment        | Recurrent VTE: 0.50 (0.31-0.79) Major bleeding: 0.64 (0.15-2.73)       |
| Righini et al,
  60 2016               | RCT              | 1              | 259 (100%)                  | Initial and long-term | LMWH         | Placebo             | Proximal clot extension, contralateral proximal DVT, or symptomatic PE: 3% vs 5% (P=.54) Major bleeding or CRNMB: 4% vs 0% (P=.26) |
| **Unprovoked VTE**       |                  |                |                            |                    |              |                     |                                                                        |
| Palareti et al,
  61 2014              | Cohort           | 1              | 1,010 (46%)                 | Extended           | D-dimer testing | N/A                 | Recurrent VTE in patients with negative D-dimer and no AC: 3.0% per patient year (2.2-4.4%) |
| Kearon et al,
  62 2015              | Cohort           | 1              | 410 (55%)                   | Extended           | D-dimer testing | N/A                 | Recurrent VTE in patients with negative D-dimer and no AC: 6.7% per patient year (4.8-9.0%) |
| Rodger et al,
  64 2017              | Cohort           | 1              | 2,747 (55%)                 | Extended           | HERDOO2 rule   | N/A                 | Recurrent VTE in low-risk women and no AC: 3.0% per patient year (1.8-4.8%) |

Abbreviations: AC, anticoagulation; CDT, catheter-directed thrombolysis; CI, confidence interval; CRNMB, clinically relevant nonmajor bleeding; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; FXa inhibitors, factor Xa inhibitors include apixaban, rivaroxaban, and edoxaban; INR, international normalized ratio; IVCF, inferior vena cava filter; LMWH, low-molecular-weight heparin; N/A, not applicable; NR, not reported; PE, pulmonary embolism; PTS, postthrombotic syndrome; QIVIQ, Chronic Venous Insufficiency Questionnaire; RCT, randomized controlled trial; USAT, ultrasound-assisted catheter-directed thrombolysis; VKA, vitamin K antagonist; VTE, venous thromboembolism.

*Sensitivity analysis excluding patients treated with ximelagatran.*

*Subgroup analysis of patients with submassive PE only.*

*Indication for anticoagulation included VTE, atrial fibrillation/flutter, preoperative orthopedic, heart valves replacement, thromboembolic disease, congestive heart failure, rheumatic heart disease.*

*Mean difference.*
(95% CI, 22% to 23%). When the prevalence of PE is high, as occurs in many European emergency departments (>20%), the PERC should only be applied when the treating clinician believes that the probability for PE is low. PERC has been validated in a cluster-randomized trial, but it should only be used in low prevalence settings or for patients considered to have a low probability of PE.

**D-dimer testing**

D-dimer is a sensitive marker for VTE and excludes VTE without the need for further testing for patients having a low clinical probability for PE. D-dimer levels greater than 500 ng/mL suggest the presence of PE. However, as D-dimer increases with age, older patients more often have false positive test results, which lowers the test’s specificity in these patients. The false positive rate can be reduced by using an age-adjusted D-dimer threshold, calculated as the patient’s age multiplied by 10 ng/mL (fibrinogen equivalent units) for patients older than 50 years. When tested, the proportion of patients in whom imaging could safely be withheld based on a ‘PE-unlikely’ Wells score and age-adjusted normal D-dimer levels increased from 28% to 33%. Age-adjusted D-dimer testing is useful when PE is suspected, although this approach appears to be less successful for inpatients and patients with a previous VTE or cancer. Prospective validation of the age-adjusted D-dimer threshold to rule out DVT is currently ongoing (ClinicalTrials.gov; NCT02384135).

**Diagnostic strategies for suspected PE**

Aiming to simplify the diagnostic management of suspected PE, the YEARS diagnostic algorithm presence of clinical signs of DVT, presence of hemoptysis, determination of PE to be the most likely diagnosis, and D-dimer level at 2 different thresholds. Pulmonary embolism is excluded if none of these criteria are present and the D-dimer level is less than 1,000 ng/mL or if there are 1 or more criteria present and the D-Dimer level is less than 500 ng/mL. When YEARS was tested in a Netherlands-based multicenter cohort study, 48% could be managed without imaging with a false negative rate lower than 1%. However, the D-dimer was acquired before the clinical assessment was performed, hemoptysis was uncommon, and the a priori knowledge of the existing clinical prediction rules may have influenced the determination of PE as the most likely diagnosis. Further validation is needed before YEARS is employed in clinical practice.
**Imaging for suspected DVT**

**Emergency-physician performed ultrasonography**

Ultrasonography is time consuming and generally performed by dedicated, trained technicians. This requirement and lack of 24-hour availability has led to bedside testing by emergency physicians. Emergency-physicians can perform compression ultrasonography of the proximal veins within 15 minutes with good overall diagnostic accuracy: the pooled sensitivity is 96% and specificity is 97% for DVT diagnosis, suggesting potential clinical utility with the caveat that the diagnostic accuracy is operator dependent. 28

**Magnetic resonance venography**

Magnetic resonance venography may be a valuable alternative test for those in whom ultrasonography results are inconclusive and DVT cannot be ruled out. A meta-analysis reported a promising diagnostic accuracy with a summary estimate sensitivity and specificity of 93% and 96% for DVT, respectively. 29 However, the heterogeneity and quality of the included studies, as well as the small number of patients evaluated, warrant caution. Furthermore, magnetic resonance venography has not been validated in a management study so it cannot be recommended for routine use. 17,18,20 It may benefit specific populations in whom ultrasonography is not feasible, for example morbidly obese patients.

**Imaging for suspected PE**

Computed tomography pulmonary angiography has a good diagnostic accuracy for PE, is widely available, relatively easy to perform, and therefore, in most situations has replaced ventilation/perfusion (V/Q) scintigraphy and pulmonary angiography as the first-choice imaging test for suspected PE. 18,19 However, it exposes patients to ionizing radiation and contrast medium is contraindicated in patients with severe renal impairment, and has the risk of renal toxicity and allergic reactions. Alternative tests may overcome these disadvantages.

**Compression ultrasonography of the lower limb**

Since a confirmed diagnosis of proximal DVT in patients with suspected PE is highly predictive of PE and warrants anticoagulant treatment, compression ultrasonography may also be used to establish a diagnosis of PE. 19 Importantly, a negative result does not exclude PE and requires further investigation, confirmed by a meta-analysis in which the sensitivity of proximal ultrasonography was low (41%), although specificity was high (96%). 30
Magnetic resonance imaging

Magnetic resonance imaging (MRI) avoids ionizing radiation and intravenous contrast providing a theoretical advantage over CTPA. A meta-analysis assessing the efficacy of MRI for establishing the diagnosis of PE showed the test to be inconclusive in 19% of cases limiting its ability for use in diagnosing PE.\textsuperscript{19,31}

V/Q scintigraphy and V/Q single-photon emission computed tomography

V/Q single-photon emission computed tomography is an emerging technique resulting in considerably less radiation exposure than CTPA and avoids the need for intravenous contrast. The diagnostic accuracy for PE in terms of sensitivity and specificity is similar to CTPA and both perform better than planar V/Q scintigraphy.\textsuperscript{32} However, the efficiency and safety of this technology has not been sufficiently validated for use in routine clinical practice.

Major therapeutic advances

There are 3 phases of VTE treatment: the initial (first 5-10 days), long-term (from end of acute treatment to 3-6 months), and extended (beyond 3-6 months) periods. The benefits from anticoagulation, including prevention of clot extension, PE, recurrent VTE, hemodynamic collapse and death, should be carefully weighed against the risk of bleeding to determine the choice of anticoagulant and the duration of therapy. Most patients with DVT and many with PE can be treated as outpatients (Figure 2 and Figure 3).\textsuperscript{33-36} To estimate the risk of recurrent VTE and guide decisions on treatment duration, VTE events are classified as being “provoked” by a transient or persistent risk factor, or as “unprovoked” in the absence of any identifiable risk factors for VTE.\textsuperscript{37} In patients with VTE provoked by surgery, the risk of recurrence after treatment is low (<1% after 1 year and 3% after 5 years); those with VTE caused by a nonsurgical transient risk factor, such as immobilization, pregnancy, or estrogen therapy, have an intermediate risk of recurrent VTE (5% after 1 year and 15% after 5 years).\textsuperscript{10} In both situations, anticoagulation is recommended for only 3 months, as previous randomized trials showed that major bleeding risk during extended anticoagulant treatment beyond this period outweighed the risk of recurrent VTE.\textsuperscript{10,18-20} Patients with cancer-associated VTE have a high risk of recurrence (15% annualized), and therapy may be given until the cancer is cured,\textsuperscript{10,18-20} although clinical trials supporting this recommendation are lacking. When a patient does not have any identifiable risk factor for VTE, the event is classified as unprovoked. Patients with a first unprovoked VTE have a high risk
Figure 2. Approach to initial treatment of venous thromboembolism (onset through days 5 to 10)

Abbreviations: DVT, deep vein thrombosis; IVCF, inferior vena cava filter; PE, pulmonary embolism.

a Assessment of 30-day mortality risk with the Pulmonary Embolism Severity Index score or its simplified version or use the Hestia Criteria.

b Initiate treatment with direct oral anticoagulants (rivaroxaban or apixaban, or initial low-molecular-weight heparin followed by dabigatran or edoxaban). Vitamin K antagonists, following a low-molecular-weight heparin lead-in, is indicated for those with a creatinine clearance of less than 30 ml per min, and those with concomitant use of potent P-glycoprotein inhibitors or cytochrome P450 3A4 inhibitors or inducers.

c Catheter-directed thrombolysis for deep vein thrombosis and systemic thrombolysis for pulmonary embolism.

d Active bleeding, high risk of bleeding, or other contraindication to anticoagulant therapy.
Figure 3. Approach to long-term and extended treatment of venous thromboembolism (after initial treatment)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

* Anticoagulation with direct oral anticoagulants (rivaroxaban or apixaban, or initial low-molecular-weight heparin followed by dabigatran or edoxaban). Vitamin K antagonists are indicated for those with a creatinine clearance of less than 30 ml per min, and those with concomitant use of potent P-glycoprotein inhibitors or cytochrome P450 3A4 inhibitors or inducers.

* Low-risk women according to the HERDOO2 rule.

* If transient risk factor is nonsurgical, e.g. immobilization, pregnancy, or estrogen therapy, extended treatment can be considered given the safety profile of direct oral anticoagulants.

* Edoxaban or low-molecular-weight heparin.
of recurrence of VTE (10% after 1 year and 30% at 5 years) and should therefore receive indefinite therapy, unless bleeding risk is high. The risk in men is at least double that in women.

**Initial and long-term treatment of VTE**

**Oral anticoagulants**

Over the past decade, direct oral anticoagulants (DOACs), including the direct thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, have been studied and are now recommended by the 2016 American College of Chest Physicians and 2014 and 2017 European Society of Cardiology guidelines for both DVT and PE. These anticoagulant agents have several advantages over vitamin K antagonists (VKAs), including a rapid onset of action and predictable pharmacokinetic profile, which allows for simplified drug administration in a standardized dose and avoids the need for laboratory monitoring and dose-adjustments. Dabigatran and edoxaban were studied for treatment of acute VTE following initial low-molecular-weight heparin (LMWH) treatment for at least 5 days, and rivaroxaban and apixaban without antecedent LMWH. There has been no direct comparison of DOACs with one another and the choice for one drug over the other is based on the different treatment regimens, patient characteristics, and patient preference. Vitamin K antagonists remain the preferred treatment for patients with severe renal impairment. Similarly, DOACs are generally avoided in patients with concomitant use of potent P-glycoprotein inhibitors or cytochrome P450-3A4 inhibitors or inducers, including azole antimycotics (e.g., ketoconazole), several protease inhibitors used for human immunodeficiency virus treatment (e.g., ritonavir) and antiepileptic drugs (in particular phenytoin and carbamazepine), since they can alter plasma levels of DOACs.

Compared with initial LMWH followed by long-term VKA treatment, DOACs are non-inferior for recurrent VTE and are associated with a lower risk of major bleeding, as defined by the International Society on Thrombosis and Haemostasis, (absolute risk, 1.1% vs 1.8%; risk ratio, 0.62; 95% CI, 0.45 to 0.85) in the first months of VTE treatment. All-cause-mortality, and case-fatality rates of recurrent VTE or major bleeding with DOACs are comparable to LMWH/VKA. DOAC therapy is currently more expensive than treatment with VKAs. Monthly costs range between $333 and $419 with DOACs, whereas generic VKAs cost $8 per month.

In patients treated with VKA after initiation of parenteral anticoagulant therapy, the use of a 10-mg warfarin nomogram, i.e., a loading dose of 10 mg
warfarin on day 1 and 2 with subsequent doses depending on the international normalized ratio (INR) value on day 3, more rapidly achieves therapeutic INR on day 5 than a 5-mg nomogram without adverse outcomes.\textsuperscript{42}

Pharmacogenetic testing for variations of cytochrome P450 2C9 and vitamin K epoxide reductase complex subunit 1 genes in patients initiating VKA therapy may have the potential to reduce thromboembolic events and major bleeding compared with a standard dosing strategy,\textsuperscript{43} but adequate comparisons to validated dose response nomograms have not been performed and pharmacogenetic testing is unlikely to be cost-effective.\textsuperscript{44}

**Thrombolysis**

*Deep vein thrombosis*

Catheter-directed thrombolysis as initial treatment of acute DVT is currently only recommended for patients with threatened limb loss.\textsuperscript{10} A Cochrane review including patients with acute proximal DVT showed that thrombolysis plus anticoagulation compared with anticoagulation alone may reduce post-thrombotic syndrome by a third (risk ratio 0.66; 95% CI, 0.53 to 0.81).\textsuperscript{45} However, thrombolysis appeared to have no effect on the occurrence of PE, recurrent DVT, or death, and moreover has an increased bleeding risk.\textsuperscript{39} Results did not differ between thrombolytic agents or route of administration (systemic vs. loco-regional vs. catheter-directed).\textsuperscript{45} The recent randomized ATTRACT trial confirmed these findings as pharmacomechanical catheter-directed thrombolysis (i.e., local administration of thrombolytic agent with concomitant thrombus aspiration or maceration) compared with anticoagulation alone did not lead to better results with regard to VTE recurrence or mortality, and led to an increased risk of major bleeding in the first 10 days.\textsuperscript{46} Notably, the occurrence of post-thrombotic syndrome after 24 months was similar in both treatment groups, suggesting no role for catheter-directed thrombolysis in routine management of DVT.\textsuperscript{46} Similarly, as ultrasound-assisted thrombolysis appears to have no benefit over conventional catheter-directed thrombolysis, it should not be used.\textsuperscript{47,48} Whether any subgroup of DVT patients without threatened limb loss may benefit from systemic or catheter-directed thrombolysis remains to be determined.

*Pulmonary embolism*

Systemic thrombolysis as initial therapy is currently only recommended by the 2016 American College of Chest Physicians and 2014 European Society of Cardiology guidelines for patients with acute massive or high-risk PE, i.e.,
those presenting with hemodynamic compromise broadly defined as a systolic blood pressure of less than 90 mmHg. For patients with intermediate-risk or submassive PE, i.e., hemodynamically stable patients with signs of right ventricular dysfunction on imaging and elevated cardiac biomarkers, thrombolysis is not recommended, as in these patients the benefits from reperfusion are counterbalanced by the high risk of intracranial hemorrhage and non-intracranial major bleeding. Systemic administration of thrombolysis plus heparin compared to heparin reduced the risk of recurrent PE at the expense of an increase in major bleeding. Conflicting results have been published with regard to overall mortality and a lack of evidence limits comparison of PE-related mortality. Two-year follow-up of the large PEITHO study in patients with intermediate risk PE in which systemic thrombolysis plus heparin was compared to placebo plus heparin, showed no difference with regard to all-cause mortality or right ventricular dysfunction confirming thrombolysis should not be used in non-high risk patients.

**Vena cava filters**

Inferior vena cava filters may be used in patients with proximal DVT or PE who have an absolute contraindication to anticoagulant therapy, but are not recommended in those who can be anticoagulated. The use of a retrievable inferior vena cava filter for 3 months in addition to standard anticoagulation compared to anticoagulation alone was recently evaluated in a randomized trial including 399 hospitalized patients with severe acute PE. There was no reduction in recurrent PE or death at 3 and 6-month follow-up. The use of inferior vena cava filters in patients with a contraindication to anticoagulation remains controversial. Recent retrospective data suggest that in these patients, inferior vena cava filters are associated with an increased 30-day mortality rate. Despite compelling evidence, guideline recommendations, and the US Food and Drug Administration warning about filter complications in 2010, usage rates across the United States remain high.

**Compression stockings**

The use of graduated compression stockings after an acute proximal DVT does not reduce the incidence of post-thrombotic syndrome compared with placebo or no stockings. Accordingly, compression stockings are only recommended as symptomatic treatment in patients with acute or chronic symptoms, such as swelling and discomfort.
Cancer-associated VTE

Cancer patients have an increased risk for both recurrent VTE and bleeding complications. The 2016 American College of Chest Physicians and 2014 and 2017 European Society of Cardiology guidelines recommend long-term daily subcutaneous LMWH as first-choice drug in patients with cancer-associated VTE.\(^{10,18,19}\) Recently, two randomized trials compared DOACs with LMWH for the treatment of VTE in cancer patients. The Hokusai VTE Cancer trial showed that the once daily factor Xa inhibitor edoxaban, which is given orally, was noninferior to the LMWH dalteparin which is given as a subcutaneous injection once daily for the composite outcome of recurrent VTE or major bleeding.\(^{56}\) The absolute rate of recurrent VTE at 12 months was lower with edoxaban (7.9% vs. 11.3%; hazard ratio [HR] 0.71, 95% CI, 0.48 to 1.06; \(P=0.09\)), while the absolute rate of major bleeding was higher (6.9% vs. 4.0%; HR 1.77, 95% CI, 1.03 to 3.04; \(P=0.04\)), mainly due to upper gastrointestinal bleeds in patients with gastrointestinal cancer. The SELECT-D pilot trial, in which rivaroxaban was compared with dalteparin for the treatment of cancer-associated VTE, reported similar results.\(^{57}\) The absolute rate of recurrent VTE at 6 months was lower with rivaroxaban (4% vs. 11%; HR 0.43, 95% CI, 0.19 to 0.99) at the expense of a higher major bleeding rate (6% vs. 4%; HR 1.83, 95% CI, 0.68 to 4.96).\(^{57}\) The 2018 guidance of the International Society on Thrombosis and Haemostasis suggests specific DOACs (edoxaban or rivaroxaban) for the treatment of cancer-associated VTE in patients with a low risk of bleeding and no drug-drug interactions with DOACs.\(^{58}\) In the United States, Edoxaban costs $337, rivaroxaban $333 and dalteparin $3527 per month,\(^{41}\) so in addition to having similar efficacy, these DOACs are less expensive than dalteparin. Apixaban is currently being evaluated in cancer-associated VTE (ClinicalTrials.gov; NCT03045406, NCT03080883).

Isolated distal DVT

The 2016 American College of Chest Physicians guidelines suggest ultrasound surveillance of isolated distal DVT to monitor for thrombus extension to the proximal veins is preferred over anticoagulation in patients having a low risk of extension.\(^{10}\) However, a meta-analysis suggested anticoagulation may reduce the risk of VTE recurrence, without increasing the risk of bleeding.\(^{59}\) This meta-analysis was limited by the substantial heterogeneity across the included studies, mainly due to differences in study design, patient characteristics, and treatment regimens. In contrast, the only double-blind randomized placebo-controlled trial to date examining this question showed that LMWH therapy for 6 weeks was not superior to placebo in reducing the risk of proximal extension,
contralateral DVT, or symptomatic PE in low-risk outpatients with symptomatic distal DVT, and the risk of bleeding was increased with LMWH. This study was prematurely terminated due to slow recruitment, expiration of the study drug, and lack of funding to manufacture new study drug batches, precluding arriving at definitive conclusions about the best approach for managing isolated distal DVT.

**Extended treatment**

**Unprovoked VTE**

Extended treatment for long-term prevention of recurrent VTE is indicated for patients with unprovoked VTE, unless bleeding risk is high.

Negative (normal) D-dimer levels measured serially after stopping anticoagulation are associated with a low risk of recurrent VTE and may be used to guide the decision to stop anticoagulant treatment in women but not in men, since they have an unacceptable high risk of recurrent VTE even if D-dimer levels are normal (9.7% per patient-year; CI, 6.7 to 13.7%). However, the requirement for measurement of D-dimmers off-treatment, the use of different cutoffs to define a normal test and the use of different D-dimer assays in the validation studies call into question the utility of this approach.

The HERDOO2 clinical decision rule was developed to identify patients with a first unprovoked VTE who have a low recurrence risk that may not require extended anticoagulation. Women with 0 or 1 of the following criteria have a low risk for recurrent VTE: signs of post-thrombotic syndrome in either leg (hyperpigmentation, edema, or redness), VIDAS® D-dimer level ≥250 µg/L on anticoagulation 6 months after initiation of treatment, body mass index ≥30 kg/m², and age 65 years or older. Women with scores of 2 or more have a high risk for recurrent VTE. HERDOO2 cannot be applied to men since when it was developed, no subgroup of men with unprovoked VTE had an annual VTE recurrence risk of less than 3%. A recent prospective management study demonstrated that HERDOO2 effectively predicted a low risk of recurrence for women who had an unprovoked VTE and subsequently had a less than 3.0% annual risk of recurrent VTE off anticoagulant treatment. The DASH and Vienna prediction scores for recurrent VTE have not been externally validated in prospective management studies limiting their utility.

**Oral anticoagulants**

The 2016 American College of Chest Physicians and 2014 and 2017 European Society of Cardiology guidelines suggest extended therapy with DOACs over
VKAs or low-dose aspirin in patients without cancer.\textsuperscript{10, 19, 20} Compared with placebo or aspirin, extended therapy with DOACs or VKAs significantly reduces the risk of recurrent VTE.\textsuperscript{67-70} Compared with VKAs, dabigatran and edoxaban are as effective and associated with a lower risk of major bleeding (0.9\% vs. 1.8\%; HR 0.52, 95\% CI, 0.27 to 1.02 for dabigatran; 0.3\% vs. 0.7\%; HR 0.45, 95\% CI, 0.22 to 0.92 for edoxaban).\textsuperscript{69-71} In contrast to extended treatment with VKAs,\textsuperscript{72} the introduction of DOACs has enabled to continue anticoagulant therapy at a lower dose, as apixaban and rivaroxaban at a prophylactic dose (10 mg once daily and 2.5 mg twice daily, respectively) are associated with a similar efficacy as a therapeutic dose (20 mg once daily and 5 mg twice daily, respectively) and a bleeding risk comparable with placebo and aspirin (absolute risk of major bleeding <0.5\% per year).\textsuperscript{68, 73}

**DISCUSSION**

Improvement of existing diagnostic algorithms to reduce the number of unnecessary imaging exams is desirable, since the widespread use of advanced imaging techniques may lead to detection of clinically insignificant clots, resulting in patients being anticoagulated with the risks of treatment outweighing the benefits. There is a particular need to improve the specificity of clinical decision rules and D-dimer thresholds for inpatients, or patients with cancer or a previous VTE who are prone to false positive imaging results. An ongoing study is evaluating which predictors may improve existing clinical prediction rules for patients with prior VTE who have a suspected recurrence (ClinicalTrials.gov; NCT02297373).

Evidence for withholding anticoagulant therapy in specific subgroups is emerging, especially for those with small VTE. As for patients with isolated distal DVT, the most recent American College of Chest Physicians Antithrombotic Therapy Guidelines suggest that patients with isolated subsegmental PE at low risk of progression or recurrence may not require anticoagulation.\textsuperscript{10} The safety of withholding anticoagulation in patients with subsegmental PE and a negative bilateral ultrasonography of the proximal leg veins is currently under investigation (ClinicalTrials.gov; NCT01455818).

To better guide decisions on the duration of anticoagulant therapy in patients with unprovoked VTE, the lack of a bleeding risk score that has been prospectively validated in a management study remains an important knowledge gap. In the forthcoming years, bleeding risk assessment should be improved to
tailor individual treatment strategies. However, given the lower bleeding risk with DOACs, the benefit-risk profile of anticoagulant treatment may have shifted and patients with an intermediate risk of recurrent VTE, such as patients with VTE provoked by a nonsurgical transient risk factor, may now benefit from extended treatment as the bleeding risk may no longer exceed the risk of recurrence.

One of the concerns regarding the DOACs is the lack of agents to reverse the anticoagulant effect. Idarucizumab has been approved for reversal of dabigatran and andexanet alfa for reversal of apixaban and rivaroxaban, but the need for these products will be difficult to evaluate. Given the short half-life of DOACs, cessation of the drug and supportive care may be sufficient for the vast majority of bleeding cases. Despite no specific reversal agents for the thousands of patients in the original trials of DOACs in VTE and atrial fibrillation patients, the risk of death from major bleeds was substantially less than those that occurred on VKAs.

Direct oral anticoagulants are currently associated with higher treatment costs than VKAs and may therefore not be affordable to all patients.

There is currently insufficient evidence to support the use of DOACs in patients with significant renal impairment, antiphospholipid syndrome, heparin-induced thrombocytopenia, or venous thrombosis at unusual sites, such as splanchnic vein thrombosis. Large trials that assess the efficacy and safety of DOACs in these specific patient populations are ongoing.

CONCLUSIONS

In the past 5 years, substantial progress has been made in the management of VTE, allowing for diagnostic and therapeutic strategies tailored to individual patient characteristics, preferences, and values. Further studies should aim at improving VTE management and will need to target specific issues as outlined in this review.
REFERENCES


