Clinical Experience With the New Oral Anticoagulants for Treatment of Venous Thromboembolism

Farzana Bacchus, Sam Schulman

Abstract—Four non–vitamin K antagonist oral anticoagulants, apixaban, dabigatran, edoxaban, and rivaroxaban, have been evaluated in phase III clinical trials for the treatment of acute venous thromboembolism, and all except edoxaban have also been studied for extended secondary prophylaxis after venous thromboembolism. Rivaroxaban, and recently also dabigatran, has been approved for this indication, and it is therefore timely to review the characteristics, efficacy, and safety of these drugs with emphasis on patients with venous thromboembolism. This review focuses on the clinical results from the phase III trials, separately for each of the drugs as compared with vitamin K antagonists. We also address the results from meta-analyses that were published recently. Finally, the results in some special groups of interest—renal impairment, elderly patients, and patients with cancer—are reviewed, although they only comprised small minorities of the study populations. All 4 drugs demonstrated noninferiority against vitamin K antagonists in the acute treatment and clear superiority against placebo in the extended treatment (not performed with edoxaban). The risk of bleeding was generally lower with non–vitamin K antagonist oral anticoagulants, and the reduction of risk of intracranial hemorrhage seems to mirror the experience from atrial fibrillation trials. In conclusion, during the past 30 years we have moved from a week of hospitalization and intravenous heparin therapy, via low-molecular-weight heparin injections subcutaneously and early discharge from the hospital, to the possibility of only oral outpatient therapy without coagulation monitoring, yet safe for patients with acute venous thromboembolism. (Arterioscler Thromb Vasc Biol. 2015;35:513-519. DOI: 10.1161/ATVBAHA.114.303396.)

Key Words: hemorrhage • pulmonary embolism • recurrence • venous thrombosis

Venous thromboembolic disease is a common cause of morbidity and mortality in the Western world. Pulmonary embolism (PE) and deep vein thrombosis (DVT) occur in 1 in 1000 individuals.1 The mainstay of treatment is with anticoagulant drugs. Until recently, the standard of care was to initiate parenteral therapy with unfractionated heparin or low-molecular-weight heparin (LMWH) and then usually bridge to oral therapy. For decades, vitamin K antagonists (VKAs) have been the only oral anticoagulants available for treatment and prevention of venous thromboembolism (VTE). VKAs pose several issues, including numerous dietary and drug interactions, need for frequent coagulation monitoring, and frequent dosage changes. In recent years, there has been an abundance of research to produce non-VKA oral anticoagulants (NOACs) with more favorable characteristics. It is formulated with tartaric acid because the absorption improves in an acidic environment. Dabigatran etexilate was developed as the prodrug, with better absorption owing to its more lipophilic characteristics. It is formulated with tartaric acid because the absorption improves in an acidic environment. Dabigatran etexilate was converted to the active component, dabigatran, on absorption. The bioavailability is only 6% to 7%, and it has peak activity at 1.5 hours.3 Excretion of dabigatran is primarily (80%) via the kidneys. The half-life is 12 to 17 hours in healthy individuals with normal renal function.3 Dabigatran has been demonstrated to have predictable pharmacokinetics without need for routine coagulation monitoring.5 There are no significant food or drug interactions because dabigatran is not metabolized by the P450 cytochrome, but it is a substrate for permeability glycoprotein (P-gp).3 Strong inducers and inhibitors of the P-gp transporter should be avoided (Table 1).

Rivaroxaban is a small, reversible, oral, direct inhibitor of factor X, which is crucial for thrombin generation. Rivaroxaban inhibits factor Xa in both the free and prothrombinase-bound state.5 Rivaroxaban is rapidly absorbed, has good bioavailability (≤80%), and reaches peak concentration at ≈3 hours. The half-life is 5 to 9 hours in healthy individuals.6 One third of rivaroxaban is eliminated unchanged by the kidney, whereas the remainder of the drug is excreted by the biliary system.7 Rivaroxaban is metabolized by the

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Pharmacology

Dabigatran is a potent and reversible oral, direct thrombin inhibitor, which specifically inhibits clot-bound and free thrombin.2 It is a hydrophilic compound with poor oral absorption. Thus, dabigatran etexilate was developed as the prodrug, with better absorption owing to its more lipophilic characteristics. It is formulated with tartaric acid because the absorption improves in an acidic environment. Dabigatran etexilate was converted to the active component, dabigatran, on absorption. The bioavailability is only 6% to 7%, and it has peak activity at 1.5 hours.3 Excretion of dabigatran is primarily (80%) via the kidneys. The half-life is 12 to 17 hours in healthy individuals with normal renal function.3 Dabigatran has been demonstrated to have predictable pharmacokinetics without need for routine coagulation monitoring.5 There are no significant food or drug interactions because dabigatran is not metabolized by the P450 cytochrome, but it is a substrate for permeability glycoprotein (P-gp).3 Strong inducers and inhibitors of the P-gp transporter should be avoided (Table 1).

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cytochrome P450 (CYP) 3A4 enzyme and P-gp. As such, strong inhibitors of these enzymes lead to less clearance of rivaroxaban and increased levels of the drug. Similarly, strong CYP3A4 inducers should be avoided because there may be increased clearance of the drug. There are no specific food interactions, but does ≥15 mg should be taken with food to improve absorption (Table 1).

Apixaban is also a direct inhibitor of factor Xa, both clot-bound and unbound. It is a small, oral, rapidly acting drug with predictable pharmacokinetics. The time to peak plasma concentration varies from 1 to 3 hours, and it has a half-life of 8 to 15 hours. It is predominantly excreted by the liver via both CYP3A4-dependent and CYP3A4-independent mechanisms. Only 25% of the drug is renally excreted. Avoidance of strong inhibitors of CYP3A4 and P-gp is recommended. Concomitant administration of the CYP3A4 and P-gp inducer rifampicin leads to a 54% reduction of the apixaban area under the curve, and this drug as well as phenytoin, carbamazepine, phenobarbital, and St John’s Wort should be avoided (Table 1).

Efficacy and Safety in Treatment of Acute VE

Each of the 4 NOACs has been studied in large randomized controlled trials (RCTs), demonstrating their efficacy and safety in treatment of acute VTE. They have also been studied in the setting of stroke prevention in atrial fibrillation, in which there is evidence to support their safety and efficacy. The RCTs of dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment of acute VTE have all used VKAs (mainly warfarin) as the comparator.

A large, double-blind, double-dummy RCT (RE-COVER) compared dabigatran with warfarin for the treatment of acute VTE. In all, 2564 patients who had acute, symptomatic, proximal DVT of the legs or PE were randomized to dose-adjusted warfarin with a therapeutic international normalized ratio (INR) range of 2 to 3 (n=1265), or dabigatran 150 mg twice daily (n=1274). Both groups initially received parenteral anticoagulation for a median of 9 days and were treated for 6 months. The primary outcome of recurrent VTE or death related to recurrent VTE was found in 2.4% of the dabigatran group and 2.1% of the warfarin group, which demonstrated noninferiority of dabigatran (Table 2). There was no significant difference between the groups for the secondary outcomes of symptomatic DVT, symptomatic nonfatal PE, death related to VTE, and all deaths. The warfarin group maintained an INR in the therapeutic range 60% of the time, which is consistent with INR monitoring in other studies. There are no data to support its use as monotherapy, without a heparin or LMWH initiation.

RE-COVER II similarly demonstrated that dabigatran is noninferior to warfarin for the treatment of acute VTE. A pooled analysis of both studies showed no significant difference in recurrent VTE. There was a trend toward lower efficacy with dabigatran in patients aged <60 years, although this was not statistically significant. Safety analysis demonstrated a significantly lower rate of any bleeding event in the dabigatran group compared with warfarin (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.61–0.79). There was also a significantly lower rate of combined major or clinically relevant bleeding (HR, 0.62; 95% CI, 0.50–0.76) in the dabigatran group (Table 3). There was a trend to higher risk reduction of bleeding with warfarin at age >85 years. No significant difference was noted for major bleeding events when the entire treatment regimens were compared, but when analyzing only the treatment period on dabigatran (versus warfarin), there was a significant reduction of the risk of major bleeding.

Dabigatran showed a trend toward more gastrointestinal bleeding, but lower rates for all other anatomic sites including intracranial hemorrhages. However, these were not statistically analyzed. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study in patients with atrial fibrillation demonstrated for the dabigatran 150 mg twice a day dose, which was used in the VTE trials, similar bleeding rates with a decrease in intracranial hemorrhages compared with warfarin. Similar to the RE-LY trial, in the RE-COVER studies there were more acute coronary events in the dabigatran group (compared with warfarin), although this was not statistically significant. The only other adverse event to note is increased dyspepsia with dabigatran (2.9%) compared with warfarin (0.6%; P<0.001). Dyspepsia seems to be reduced by instructing patients to take the medication with food.

The efficacy and safety of rivaroxaban has been studied in the EINSTEIN program. The Acute DVT Study randomized patients with acute, symptomatic, proximal DVT, without symptomatic PE, to rivaroxaban or enoxaparin and VKA. Rivaroxaban was given at 15 mg twice daily for the first 21 days without a heparin lead-in, then 20 mg once daily for the remainder of the treatment. The time in therapeutic range for the VKA group was 58%. The primary efficacy outcome of recurrent VTE showed noninferiority for rivaroxaban (2.1%) compared with warfarin (3.0%; HR, 0.68; 95% CI, 0.44–1.04; P<0.001). The primary safety outcome was first major or clinically relevant nonmajor bleeding. There was no significant difference between the groups for the primary safety outcome (HR, 0.97; 95% CI, 0.76–1.22), or for major bleeding (HR, 0.65; 95% CI, 0.33–1.30). Total deaths were not significantly different between the groups, although there was a trend in favor of rivaroxaban.

The PE arm of the EINSTEIN study randomized patients with acute PE to the same treatment regimen of rivaroxaban.
The primary efficacy and safety outcomes were the same as in the DVT arm of the study. Analysis of the rate of recurrent VTE for rivaroxaban (2.1%) compared with VKA (1.8%; HR, 1.12; 95% CI, 0.75–1.68; P=0.003) showed noninferiority. First episode of major or clinically relevant nonmajor bleeding was not significantly different. However, major bleeding was less frequent in the rivaroxaban group (1.1%) compared with the VKA group (2.2%; HR, 0.49; 95% CI, 0.31–0.79; P=0.003).17

The Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) study randomized patients with VTE, either DVT or PE, to apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily compared with conventional treatment with LMWH and warfarin.18 There was no use of parenteral anticoagulants in the apixaban group after randomization, similar to the rivaroxaban studies. The time in therapeutic range for warfarin was 61%. The primary efficacy outcome was the composite of recurrent symptomatic VTE or death related to VTE. Apixaban was found to be noninferior to warfarin for this efficacy outcome (2.3% versus 2.7%; P<0.001; Table 2). The primary safety outcome was major bleeding. Apixaban had a significantly lower risk of bleeding (0.6%) than warfarin (1.8%; relative risk [RR], 0.31; 95% CI, 0.17–0.55; P<0.001; Table 3), with a trend toward less intracranial and gastrointestinal bleeding. There was also significantly less major bleeding or clinically relevant nonmajor bleeding in the apixaban group (P<0.001). Subgroup analysis demonstrated that monotherapy with apixaban was as efficacious in patients with extensive pulmonary disease compared with those with lower thrombus burden, demonstrating its generalizability and use.

Edoxaban was similarly studied in a large, double-blind RCT for treatment of acute, symptomatic VTE.19 Different from the other studies, the Hokusai-VTE study encouraged inclusion of patients with extensive PE who had right ventricular strain and measurements of brain natriuretic peptide. This was to evaluate the more generalized use of the drug. Unlike the other oral direct anti-Xa inhibitors, the Hokusai-VTE study used parenteral anticoagulation for all patients before starting either edoxaban or warfarin. The primary efficacy outcome of symptomatic, recurrent VTE was not statistically different between the edoxaban and warfarin groups (3.2% versus 3.5%; P<0.001; Table 2). Among the patients with extensive PE, the edoxaban group had fewer recurrent events than the warfarin group. The primary safety outcome of first major or clinically relevant nonmajor bleeding occurred in 9.5% of the edoxaban group and 10.3% of the warfarin group (HR, 0.81; 95% CI, 0.71–0.94; P=0.004) for superiority of edoxaban over warfarin for bleeding (Table 3). There was a trend toward less intracranial bleeding in the edoxaban group, although this was not statistically significant. Major bleeding was not statistically different, although clinically relevant nonmajor bleeding was significantly less frequent in the edoxaban group.19

### Indirect Comparisons of New Oral Anticoagulants in Acute Treatment of VTE

The efficacy of new oral agents, with or without initial parenteral therapy, is generally noninferior but not superior to VKA (Table 2). On the contrary, risk estimates for any bleeding outcome, except for the subset of gastrointestinal bleeding, are never favoring VKA, and many of the estimates show a significant reduction with NOACs (Table 3).

A few direct and indirect meta-analyses to compare the efficacy and safety of new anticoagulants against each other or against VKA have been performed, and the results vary somewhat.20–22 This depends mainly on which studies were included. One analysis included also phase II trials and studies on ximelagatran,23 which was withdrawn from the market in 2006. For 2 analyses, the results of the most recently published phase III trials were not available.21,22 Thus, in 1 analysis, rivaroxaban turned out to be the only drug that reduced the risk of major bleeding compared with VKA (RR, 0.57; 95% CI, 0.39–0.84),22 although this was driven by the positive result in the Einstein PE study and with only 1 phase II trial included for apixaban.21 The lack of significant difference between NOACs in efficacy or mortality was supported by the 2 subsequent meta-analyses,20,21 but I found an increased risk of major bleeding for dabigatran and edoxaban in comparison with apixaban (RR, 2.69; 95% CI, 1.19–6.07; RR, 2.74; 95% CI, 1.40–5.39, respectively).20

### Extended Treatment for Prevention of VTE

The risk of recurrent VTE may be ≤10% the first year after discontinuing anticoagulation.23 For decades, after the period

### Table 1. Characteristics and Pharmacokinetics of the Non–Vitamin K Antagonist Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug target</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to maximum effects</td>
<td>1.5–2 h</td>
<td>2 h</td>
<td>3–4 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>12–17 h</td>
<td>5–9 h</td>
<td>8–15 h</td>
<td>8–10 h</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>60–70 L</td>
<td>50 L</td>
<td>Low</td>
<td>&gt;300 L</td>
</tr>
</tbody>
</table>

CYP indicates cytochrome P450; and P-gp, permeability glycoprotein.

### Table 2. Efficacy Outcome of Recurrent VTE with Use of Non–Vitamin K Antagonist Oral Anticoagulants in Comparison With Vitamin K Antagonists in the Treatment of Acute VTE

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Recurrent VTE or VTE-related death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>0.89 (0.70–1.13)</td>
</tr>
<tr>
<td>Rivaroxaban†</td>
<td>0.90 (0.68–1.20)</td>
</tr>
</tbody>
</table>

**CI** indicates confidence interval; RR, relative risk; and VTE, venous thromboembolism.

*RR was recalculated from the hazard ratio for optimal comparison (dabigatran [from RE-COVER II pooled analysis], edoxaban, and rivaroxaban [combined data from EINSTEIN-DVT and EINSTEIN-PE study]).

†Efficacy outcome for EINSTEIN studies was recurrent VTE, and not combined recurrent VTE or VTE-related death.
of acute treatment of VTE, the only practical option for continuation of oral anticoagulation was with VKAs. However, because of the numerous issues of inconvenient laboratory monitoring and drug and dietary interactions, the patients may not prefer continuation of warfarin. The NOACs have been studied in the extended treatment of VTE. They may offer additional options for extended treatment or prevention of VTE beyond the initial treatment period.

For extended treatment of VTE, dabigatran was studied in 2 RCTs at a dose of 150 mg twice daily, after ≥3 months of initial anticoagulant treatment.24 In RE-SONATE, patients received dabigatran compared with placebo. Dabigatran had a lower rate of recurrent VTE (0.4%) compared with placebo (5.6%; HR, 0.08; 95% CI, 0.02–0.25; P<0.001), but with a significantly higher rate of major and clinically relevant bleeding (5.3% versus 1.8%; HR, 2.92; 95% CI, 1.52–5.60), driven by the excess of nonmajor clinically relevant bleeding. Lower gastrointestinal bleeding was more frequent in the dabigatran group than in the warfarin group (5.6% versus 10.2%; HR, 0.63 (0.51–0.77). There was less frequent major or clinically relevant bleeding in the dabigatran group, similar to that seen with dabigatran in RE-LY.15

Rivaroxaban was studied in EINSTEIN’s Continued Treatment Study after 6 to 12 months of oral anticoagulation for treatment of acute VTE.16 Rivaroxaban was administered at a dose of 20 mg once daily compared with placebo. The rivaroxaban group demonstrated a significant reduction in recurrent VTE compared with placebo (1.3% versus 7.3%; HR, 0.18; 95% CI, 0.09–0.39; P<0.001). However, similar to dabigatran compared with placebo, major bleeding and clinically relevant nonmajor bleeding was more frequent in the rivaroxaban group compared with placebo (6.0% versus 1.2%; HR, 5.19; 95% CI, 2.3–11.7; P<0.001).16 Rivaroxaban has not been studied in extended treatment as compared with warfarin.

Apixaban was similarly studied in patients who had completed 6 to 12 months of anticoagulation for VTE in the AMPLIFY-EXT study.25 The study design uniquely randomized patients to different doses of apixaban, 5 mg twice daily or 2.5 mg twice daily, or to placebo. The lower dose of apixaban has been shown to provide effective thromboprophylaxis in previous orthopedic studies. The primary efficacy outcome of symptomatic recurrent VTE or death was significantly lower with both doses of apixaban (RR, 0.33 for apixaban 2.5 mg versus placebo; RR, 0.36 for apixaban 5 mg versus placebo), compared with placebo. The primary safety outcome of major bleeding occurred in 0.5% in the placebo group, 0.2% in the apixaban 2.5 mg group, and 0.1% in the apixaban 5 mg group. As such, there was no increased risk of major bleeding for either dose of apixaban compared with placebo (RR, 0.49 and 0.25, respectively, although not statistically significant).25

The secondary prevention trials have also been subjected to a network meta-analysis, which included studies on NOACs, warfarin or aspirin versus placebo/control and dabigatran versus warfarin.26 Warfarin, which was well controlled, showed the best efficacy (odds ratio [OR], 0.07; 95% CI, 0.03–0.15), closely followed by dabigatran (OR, 0.09; 95% CI, 0.04–0.21), and aspirin had the least effect (OR, 0.65; 95% CI, 0.39–1.03). All anticoagulants reduced the risk of recurrent VTE in comparison with aspirin. Warfarin adjusted at an INR of 2.0 to 3.0 conferred the highest risk of major bleeding (OR, 5.24; 95% CI, 1.78–18.25), and apixaban was associated with the lowest risk of bleeding, but risk estimates were uncertain because of a very small number of events.26

Above, we reviewed the evidence to support the use, efficacy, and safety of the NOACs compared with VKA or placebo. Studies have previously shown the benefit of extended duration of treatment with warfarin.23 However, dabigatran is the only NOAC that has been directly compared with warfarin in this setting, demonstrating noninferiority, with a decreased bleeding risk. Although apixaban was not compared directly with warfarin, it has shown superiority to placebo and, possibly more important, offers a lower risk of bleeding than both dabigatran and rivaroxaban compared with placebo. Rivaroxaban and dabigatran have been approved in the United States and in Europe for use as extended treatment for prevention of VTE.

### Special Populations

#### Renal Impairment

All of the studies assessing NOACs in the treatment of acute VTE excluded patients with severe renal impairment, usually

### Table 3. Safety Outcomes of Bleeding With Use of Non–Vitamin K Antagonist Oral Anticoagulants in Comparison With Vitamin K Antagonists in the Treatment of Acute Venous Thromboembolism

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Major Bleeding or Clinically Relevant Nonmajor Bleeding</th>
<th>Major Bleeding</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence, n/N (%)</td>
<td>RR* (95% CI)</td>
<td>Incidence, n/N (%)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>115/2691 (4.3)</td>
<td>0.44 (0.36–0.55)</td>
<td>15/2691 (0.6)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>136/2553 (5.3)</td>
<td>0.63 (0.51–0.77)</td>
<td>37/2553 (1.4)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>349/4118 (8.5)</td>
<td>0.81 (0.71–0.94)</td>
<td>56/4118 (1.4)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>388/4150 (9.3)</td>
<td>0.94 (0.82–1.07)</td>
<td>40/4150 (1.0)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ICH, intracranial hemorrhage; and RR, relative risk.

*RR recalculated from the hazard ratio for optimal comparison (dabigatran [from RE-COVER II pooled analysis], edoxaban, and rivaroxaban [combined data from EINSTEIN-DVT and EINSTEIN-PE study]). ICH includes both fatal and nonfatal ICH with RR calculated from each study.
defined as a calculated creatinine clearance (CrCl) <30 mL/min. The apixaban study excluded patients with CrCl <25 mL/min or a serum creatinine >220 μmol/L; this is because of its low dependence on renal elimination.28 In RE-COVER, 90% of the participants had a CrCl >50 mL/min, making it difficult to establish an evidence-based decision about the use and dose of NOACs in the moderately renal impaired group.12 The pooled analysis of RE-COVER and RE-COVER II showed that bleeding events were more frequent when renal function declined, but that there was no difference between the treatment groups of dabigatran and warfarin.29 This suggests that no dose change is required for mild to moderate renal dysfunction. Similarly, the rivaroxaban and apixaban trials had few participants with CrCl <50 mL/min. In the EINSTEIN study, the renal dysfunction subgroup analysis showed no difference in efficacy and safety between rivaroxaban and VKA. Both rivaroxaban and apixaban need further studies in the moderate renal impairment population. A systematic review was conducted to assess the efficacy and safety of NOACs in chronic kidney disease.30 There were no differences in the rate of recurrent VTE or bleeding events between NOACs and VKAs. Currently, none of the published studies concluded with a recommendation for dose adjustment in moderate renal impairment. However, the European Medicines Agency and Health Canada approved dabigatran for the treatment of VTE at the studied dose of 150 mg twice daily but also at the reduced dose of 110 mg twice daily, which only has been evaluated in the atrial fibrillation population. Practically speaking, for patients with CrCl <50 mL/min, many physicians decrease the dose of dabigatran (from 150 mg) to 110 mg twice daily, rivaroxaban (from 20 mg) to 15 mg once daily, and apixaban (from 5 mg) to 2.5 mg twice daily in patients with atrial fibrillation. In patients with end-stage renal disease or requiring hemodialysis, NOACs are generally avoided, because this patient population has not been studied. Future RCTs are needed to assess the safety of NOACs, in particular apixaban, in patients with severe renal impairment.

Elderly Patients
The average age of patients in each RCT was <60 years. As such, there may be limitations in the interpretation of results and applicability to the elderly population. This is particularly important because of the fact that the incidence of VTE increases with age, but patients are generally at higher risk of bleeding and falls at an older age. In a recent meta-analysis of studies only on the acute treatment of VTE with NOACs including all the 6 phase III trials, for patients aged ≥75 years the efficacy of NOACs was superior to that of standard therapy (RR, 0.56; 95% CI, 0.38–0.82).31 This is most likely explained by higher concentrations of active drug because of reduced glomerular filtration rate compared with younger patients. Nevertheless, the risk of major bleeding was not increased overall in the elderly patients (RR, 0.49; 95% CI, 0.25–0.96), although as mentioned above this is somewhat different for dabigatran, which is the most dependent on renal elimination. Another meta-analysis of NOACs in patients aged >75 years with treatment of VTE or atrial fibrillation included 10 RCTs with >25,000 patients. The risk of major or clinically relevant bleeding was not significantly higher with NOACs compared with conventional therapy (OR, 1.02, 95% CI, 0.73–1.43). NOACs were equally or more effective in the prevention of strokes and recurrent VTE in the respective trials.32 The EINSTEIN investigators performed subgroup analysis of risk of recurrent VTE and major bleeding in fragile patients. Fragility was defined as age ≥75 years, weight <50 kg, CrCl <50 mL/min. Fragile patients were found to have a higher risk of major bleeding compared with nonfragile patients. In fragile patients, there was significantly less major bleeding in the rivaroxaban group compared with the warfarin group (1.1% versus 3.6%; HR, 0.27; 95% CI, 0.07–0.96). Thus, old age should not be a principal reason to avoid NOACs. European and Canadian regulatory authorities have recommended a reduction of dabigatran from 150 mg to 110 mg twice daily for patients with atrial fibrillation indication and ≥80 years and both followed this also for the label for treatment of VTE. Although this is based on pharmacokinetic modeling, there is a clear difference in thrombosis burden, regarding its size between cardioembolism and VTE. Time will tell if this is an optimal recommendation. For rivaroxaban there is no recommendation to change the dose for elderly patients with VTE.

Cancer
NOACs have not been specifically studied in the active cancer population with VTE. Given the Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial results demonstrating superiority of LMWH to warfarin for the first 6 months of treatment for cancer-associated VTE,33 NOACs would need to be compared with LMWH for efficacy and safety in this population. In the CLOT trial, the recurrent VTE rate was 15.8% in the warfarin group with 4% major bleeding.33 Each of the 6 large NOAC trials included 4% to 10% of participants with active cancer, which may be a select group of patients. Indeed, the recurrence rate for patients with cancer in the pooled VKA groups was only 6.0% (and major bleed rate was 3.7%).31 A prespecified subgroup analysis of the pooled analysis for RE-COVER and RE-COVER II showed that there is a significantly higher risk of VTE, VTE-related death, and major and clinical relevant bleeding in patients with active cancer as compared with those without cancer.34 However, the efficacy and safety of dabigatran compared with warfarin did not seem to differ. The Acute DVT arm of the EINSTEIN study also describes similar efficacy and safety in the active cancer and noncancer populations. The AMPLIFY study only included 5% of participants with active cancer, and detailed results from this subset have not been presented yet. A meta-analysis of phase III trials on acute treatment of VTE with dabigatran, edoxaban, and rivaroxaban showed that the RR for recurrent VTE was 0.66 (95% CI, 0.38–1.2) compared with VKA, and the risk of bleeding was virtually identical for the 2 alternatives.35 It is evident that NOACs for treatment of cancer-related VTE need further study, preferably in comparison with LMWH.

Conclusions
Four NOACs have completed the clinical trial programs for approval on the indication acute treatment of VTE. Rivaroxaban and dabigatran have been approved for acute treatment and for extended treatment for 6 months. Apixaban
is in the final stages of assessment by the regulatory authorities at the time of writing. As for edoxaban, it is likely that the manufacturer will await the result of a new study in patients with acute VTE for whom edoxaban will be given without initial parenteral anticoagulation. A study on the extended treatment is also missing, and without that the labeling might be limited to treatment for 6 (or 12) months.

We are thus entering into an era with several choices for oral anticoagulation in patients with VTE. The vast majority of these patients are warfarin-naïve, and it takes many weeks until the INR stabilizes. The convenience of new agents is substantial during this initial period, when some patients also might have pain and reduced mobility. For patients with smaller DVT or with limited symptoms from DVT or PE and who do not need hospitalization, rivaroxaban has become an attractive agent that can be prescribed in the emergency room and the patient can be discharged with instructions that certainly take a shorter time to provide than for warfarin and for injections with LMWH. For large DVTs and for many patients with PE who deserve some days of hospitalization, unfractionated heparin or LMWH is still a good choice, and this can, on discharge, be switched to dabigatran 150 mg twice daily without any further adjustment or to rivaroxaban 15 mg twice daily, which after a total treatment period of 3 weeks is changed to 20 mg daily. For patients with high risk of recurrent DVT, extended prophylaxis can be given with warfarin, rivaroxaban, or dabigatran long term. When NOACs are prescribed long term, the physician must make sure renal function, with calculation of CrCl, is reassessed periodically and reasonably on an annual basis and perhaps more frequently for those at risk of severe renal impairment. The NOACs offer the same efficacy with a lower risk of bleeding compared with warfarin and with superior convenience. For patients with severe renal dysfunction or mechanical heart valves, the new agents are contraindicated.

Disclosures
Dr Schulman has received honoraria from Boehringer Ingelheim, Merck, Actelion, and research grants from Bayer, Baxter, Octapharma, and Boehringer Ingelheim. Dr Bacchus reports no conflicts.

References
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**Significance**

This review of the non–vitamin K antagonist oral anticoagulants for the treatment of venous thromboembolism highlights the similar efficacy compared with vitamin K antagonists and the lower risk of bleeding with the new agents, with apixaban possibly showing the best bleeding profile. All non–vitamin K antagonist oral anticoagulants are very effective in the extended prophylaxis against recurrent venous thromboembolism with a small or no increase in the risk of nonmajor, clinically relevant bleeding. Population subgroups at higher risk of bleeding or recurrent venous thromboembolism (elderly patients, moderate renal failure, active cancer) have also been studied. In meta-analyses, the non–vitamin K antagonist oral anticoagulants maintain their efficacy without a significant increase in risk of bleeding compared with vitamin K antagonists. A dose reduction of dabigatran has been recommended in Europe and Canada for elderly patients with venous thromboembolism, but the 110 mg twice daily regimen was not studied in the trials. It might be suboptimal for the initial treatment of patients with a large thrombotic burden. Postmarketing studies are much needed in this respect.