Treatment of Venous Thromboembolism With New Anticoagulant Agents

Cecilia Becattini, MD, PhD, Giancarlo Agnelli, MD

ABSTRACT

Venous thromboembolism (VTE) is a common disease associated with high risk for recurrences, death, and late sequelae, accounting for substantial health care costs. Anticoagulant agents are the mainstay of treatment for deep vein thrombosis and pulmonary embolism. The recent availability of oral anticoagulant agents that can be administered in fixed doses, without laboratory monitoring and dose adjustment, is a landmark change in the treatment of VTE. In Phase III trials, rivaroxaban, apixaban, edoxaban (antifactor Xa agents), and dabigatran (an antithrombin agent) were noninferior and probably safer than conventional anticoagulation therapy (low-molecular-weight heparin followed by vitamin K antagonists). These favorable results were confirmed in specific patient subgroups, such as the elderly and fragile. However, some patients, such as those with cancer or with intermediate- to high-risk pulmonary embolism, were underrepresented in the Phase III trials. Further clinical research is required before new oral anticoagulant agents can be considered standard of care for the full spectrum of patients with VTE. (J Am Coll Cardiol 2016;67:1941–55)

EPIDEMIOLOGY AND CLINICAL COURSE OF VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism, is one of the most common cardiovascular diseases (1-3). A systematic review on the disease burden of VTE reported annual incidences ranging from 0.75 to 2.69 per 1,000 subjects, which increased to between 2.0 and 7.0 per 1,000 among subjects ≥70 years of age (4).

VTE is a main cause of health care expenditure (5), and hospitalization accounts for the majority of the health care costs (6,7). In the United States, the rate of hospitalization for VTE per 100,000 subjects age ≥60 years increased from 581 in 2001 to 739 in 2010 (6), with an average length of stay in 2011 of 4.7 days for patients with DVT and 5.1 days for patients with pulmonary embolism (8).

The 30-day and 1-year case-fatality rates after VTE were found to be 10.6% (95% confidence interval [CI]: 10.4 to 10.8) and 23.0% (95% CI: 22.8 to 23.3), respectively (2). The 30-day mortality rates for patients with first-time DVT or pulmonary embolism were 3.0% and 31%, respectively (9).

After a first episode, VTE tends to recur, with an expected 10-year cumulative incidence rate of recurrence of approximately 25% (1). Recurrence rate peaks in the first 6 months (11% patient-years), then decreases slowly to stabilize after 3 years, remaining at about 2% per patient-year up to 10 years after the acute event. The risk for recurrence is similar after DVT or pulmonary embolism (hazard ratio [HR]: 1.19; 95% CI: 0.87 to 1.63) (10). However, pulmonary embolism tends to recur as pulmonary embolism and DVT as DVT (10,11).

The long-term sequelae of VTE are post-thrombotic syndrome, which occurs in 20% to 50% of patients after DVT, and chronic thromboembolic pulmonary hypertension, which occurs in 0.1% to 3.8% of patients after pulmonary embolism (12,13). These
Anticoagulant treatment of VTE includes 3 phases: an initial phase; a long-term or chronic phase; and an extended phase (20,21). Traditionally, in the initial treatment of VTE, rapid-onset parenteral anticoagulant agents are used to quickly achieve therapeutic anticoagulation and reduce early recurrences and mortality (22–24). For several decades, long-term and extended treatments were performed with oral vitamin K antagonists. In patients with cancer-associated thrombosis, low-molecular-weight heparin (LMWH) is recommended over vitamin K antagonists (20).

The rate of recurrent VTE during well-conducted anticoagulation is estimated to be about 2% (20) and that of major bleeding 2.2% (95% CI: 2.05 to 2.42) at 90 days (25,26). After anticoagulant treatment is stopped, the recurrence rate is low (about 3% per year or lower) in patients with VTE associated with major trauma or surgery, and it is particularly high in patients with cancer-associated VTE (about 10% per year) (27–29). Patients treated for unprovoked VTE (no identifiable risk factors) have a recurrence rate of 15% in the 2 years after treatment discontinuation (30). Although the rate of major bleeding during long-term anticoagulant treatment seems to decrease over time, the related case fatality rate remains stable and higher than the case fatality rate associated with recurrent VTE after anticoagulant treatment is stopped (26).

Anticoagulant treatment is usually withdrawn after 3 months in patients with VTE associated with major temporary risk factors (e.g., surgery, trauma) and is continued indefinitely in the case of recurrence of VTE or in patients with cancer-associated thromboembolism. The optimal duration of anticoagulant treatment after the first unprovoked VTE remains unclear (20). In these patients, prolonging anticoagulation for a definite time frame beyond the initial 3 months simply delays recurrences, without reducing the risk for this event once anticoagulation is withdrawn (11,30). After an unprovoked VTE, the nature of the initial thromboembolism (DVT or pulmonary embolism), clinical risk scores, the persistence of thrombosis in the lower limbs, or right ventricular dilation and elevated D-dimer have been proposed as methods for identifying patients at high risk for recurrence (20,31); how these results translate to the duration of treatment was not fully evaluated, however.

Parenteral anticoagulation during the initial treatment and the need for laboratory monitoring and dose adjustment during long-term treatment are the main limitations of conventional anticoagulation, in addition to a high number of drug-drug interactions.

**THE NEW ORAL ANTICOAGULANT AGENTS**

Two classes of oral direct anticoagulant agents were introduced in clinical practice to overcome the limits of conventional anticoagulation. These agents are synthetic, selective, and reversible inhibitors of factor Xa (rivaroxaban, apixaban, and edoxaban) or thrombin (dabigatran) (32–35). The predictable anticoagulant effect allows these agents to be administered in fixed doses, with no need for laboratory monitoring or dose adjustment. The short half-life of the new anticoagulant agents (NOACs) may make clinical management of situations requiring reversal of anticoagulation (needed for invasive procedures and bleeding complications) easier. Rivaroxaban and edoxaban offer the possibility of once-daily administration.

Dabigatran is a prodruk with a bioavailability of approximately 6.5%; circulating esterases rapidly convert the prodrug to the active form, 80% of which is eliminated by the kidneys (32). None of the factor Xa inhibitors is a prodruk, and all have oral bioavailability >50% (33–35). The kidneys excrete one-third of rivaroxaban as active drug; the liver metabolizes two-thirds of the drug to an inactive form, one-half of which is eliminated in the urine and one-half via the hepatobiliary route (33). Apixaban is eliminated via the intestinal (about 75%) and renal (about 25%) routes (34). Approximately one-half of edobaxan is eliminated via the renal route (35). Time to peak concentration is similar for all of these agents, ranging from 1 to 4 h, with half-lives ranging from 6 to 17 h. Half-lives can be influenced by renal clearance, and this scenario is particularly true for dabigatran. Care should be taken when using all NOACs in patients with impaired renal function (36). Reduced doses of rivaroxaban, apixaban, and edoxaban have been tested in patients with atrial fibrillation and impaired renal function; reduced doses of NOACs were not tested in patients with VTE, with the exception of edoxaban.

No data are currently available on the use of NOACs in pregnancy, breastfeeding women, and children. Clinical studies (mainly dose-finding trials) have
started or are about to start on the use of dabigatran (NCT01895777, NCT02197416, NCT02223260, and NCT01083722), rivaroxaban (NCT02497716, NCT02309411, and NCT02234843), apixaban (NCT01707394, NCT02464969 and NCT02369653), and edoxaban (NCT02303430) in children.

**NOACs for the Initial and Long-term Treatment of VTE**

**Design of the Clinical Trials.** Overall, in the initial and long-term treatment of patients with VTE, 6 randomized trials have been performed: 2 studies with dabigatran, 2 studies with rivaroxaban, and 1 study each with apixaban and edoxaban (Table 1) (37–42). The study designs of these trials reveal similarities and differences. All the trials were designed to demonstrate noninferior efficacy compared with conventional anticoagulant treatment (LMWH followed by vitamin K antagonists). Noninferiority was deemed to be a satisfactory achievement, as the main advantage of these agents over conventional treatment with NOACs as a real breakthrough to cause some clinicians to refrain from considering treatment with NOACs as a real breakthrough to be transferred to clinical practice. However, the advantages observed in terms of bleeding complications, as well as the drugs’ improved practicality, confer clinical value to these noninferiority results. Different criteria for definitions of noninferiority were used across the studies (upper 95% CI: 2.75 for dabigatran, 2.0 for rivaroxaban, 1.8 for apixaban, and 1.5 for edoxaban). These criteria contributed to different sample size estimations (2,550 patients in each study with dabigatran, 3,000 patients with rivaroxaban in the pulmonary embolism and DVT studies, 5,400 patients with apixaban, and 7,500 patients with edoxaban).

All the studies used recurrence and VTE-related death as the primary efficacy outcome. The rivaroxaban and edoxaban studies followed an event-driven design on the basis of efficacy outcomes. Major bleeding was the primary safety outcome in the apixaban trial, whereas the composite of major and clinically relevant nonmajor bleeding (clinically relevant bleeding) was the primary safety outcome in the remaining trials. Four trials enrolled patients with either DVT or pulmonary embolism, whereas the rivaroxaban program comprised 2 separate studies (1 for patients with DVT and 1 for patients with pulmonary embolism). The trials were double-blind, except for those with rivaroxaban (39,40). In the Hokusai trial, edoxaban was given as a 60-mg daily

<table>
<thead>
<tr>
<th><strong>Table 1</strong> Efficacy and Safety of NOACs for the Treatment of VTE: Results From Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Name (Ref. #)</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>RE-COVER, 2009 (37)</td>
</tr>
<tr>
<td>RE-COVER II, 2011 (38)</td>
</tr>
<tr>
<td>EINSTEIN-DVT, 2010 (39)</td>
</tr>
<tr>
<td>EINSTEIN-PE, 2012 (40)</td>
</tr>
<tr>
<td>AMPLIFY, 2013 (41)</td>
</tr>
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<td>Hokusai, 2013 (42)</td>
</tr>
</tbody>
</table>

**AMPLIFY** = Efficacy and Safety Study of Apixaban for the Treatment of Deep Vein Thrombosis or Pulmonary Embolism; bid = once daily; DB = double-blind; DVT = deep vein thrombosis; enoxa = enoxaparin; EINSTEIN-DVT = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN-PE = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; Hokusai = Comparative Investigation of Low Molecular Weight (LMWH) Heparin/Edoxaban/Tosylate (DU176b) Versus (LMWH) Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; LMWH = low-molecular-weight heparin; NOAC = new oral anticoagulant agent; od = once daily; PE = pulmonary embolism; RE-COVER = Efficacy and Safety of dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; TTR = time in therapeutic range; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.
dose or at the reduced dose of 30 mg in patients with impaired renal function or low body weight (42). Dabigatran and apixaban were given twice daily, whereas rivaroxaban and edoxaban were given once daily (37,38,41). Rivaroxaban and apixaban were evaluated according to the “single-drug approach,” which means that the initial heparin treatment is used for no longer than 48 h (39–41). When the single-drug approach was followed, increased doses of rivaroxaban (50% of the maintenance dose for 3 weeks) and apixaban (100% of the maintenance dose for 1 week) were used because of the increased risk for early recurrences. This increase was observed in previous trials evaluating NOACs without initial heparin treatment (22–24). Initial heparin pre-treatment (5 to 9 days) was used with dabigatran and edoxaban (37,38,42).

**MAIN RESULTS OF THE STUDIES.** Concerning the primary efficacy outcomes, dabigatran (hazard ratio [HR]: 1.09; 95% CI: 0.76 to 1.57) (38), rivaroxaban (HR: 0.89; 95% CI: 0.66 to 1.19) (43), apixaban (relative risk [RR]: 0.84; 95% CI: 0.60 to 1.18) (41), and edoxaban (HR: 0.89; 95% CI: 0.70 to 1.13) (42) were all non-inferior to conventional treatment. Apixaban was associated with a significant reduction in major bleeding compared with conventional treatment (RR: 0.31; 95% CI: 0.17 to 0.55) (41). This outcome was also the case for rivaroxaban in the pulmonary embolism study but not in the DVT trial (40). Edoxaban was safer than conventional treatment in terms of clinically relevant bleeding (HR: 0.81; 95% CI: 0.71 to 0.94) (42), and this scenario was also the case for dabigatran (HR: 0.62; 95% CI: 0.50 to 0.76) (38). Similar rates of clinically relevant bleeding compared with conventional treatment were observed with rivaroxaban (HR: 0.93; 95% CI: 0.81 to 1.06) (43). A statistically nonsignificant reduction in intracranial hemorrhage was reported with all NOACs, but the studies were not sized to show a definitive effect on this safety outcome. Fatal bleeding was significantly reduced in the Hokusai study with edoxaban compared with warfarin (2 events vs. 10 events; odds ratio [OR]: 0.20; 95% CI: 0.04 to 0.91) (42). No definitive data are available concerning the incidence of gastrointestinal or mucosal bleeding with NOACs in patients with VTE. Twice-daily apixaban could be preferred for its safety profile, as shown by the 69% reduction in major bleeding (41).

No direct head-to-head comparisons are available for NOACs in VTE treatment. Dabigatran or edoxaban could be preferred in patients requiring heparin treatment in the acute phase (pretreatment with heparin was formally tested in Phase III clinical trials with these agents). Indeed, the use of heparin and NOACs in regimens different from those evaluated in clinical trials and approved for clinical use could expose patients to overtreatment or undertreatment. Whether the efficacy and safety profile of rivaroxaban and apixaban is preserved if the duration of the initial increased dose is shortened or skipped is unclear. It is conceivable that if pre-NOAC administration of LMWH lasted <7 days, the initial increased doses of apixaban and rivaroxaban should be given for 7 or 21 days, respectively. In case of LMWH treatment lasting >7 days, it may be reasonable to start apixaban with the maintenance dose (5 mg twice daily) or to continue LMWH up to 3 weeks, and then start with the maintenance dose of rivaroxaban (20 mg once daily). Edoxaban is the only agent for which efficacy results are provided in patients with pulmonary embolism with and without right ventricular dysfunction (42). Edoxaban is also the only agent for which dose reduction was tested in patients with creatinine clearance between 30 and 50 ml/min, weighing <60 kg, or receiving concomitant treatment with potent P-glycoprotein inhibitors.

Concerning patients with renal failure, those with creatinine clearance <30 ml/min (<25 ml/min for apixaban) were excluded from all Phase III trials. For patients with fluctuations in renal function (e.g., concomitant diuretic agents) or borderline stage III kidney disease (creatinine clearance near 30 ml/min), reduced doses of edoxaban could be considered. The efficacy and safety of reduced doses of rivaroxaban or apixaban in patients with VTE and moderate renal failure have not been evaluated in clinical trials (Table 2). When NOACs are used in these patients, renal function should be checked at least twice a year (Table 3) (36).

Several meta-analyses have been performed on studies with NOACs for the treatment of VTE. A meta-analysis including 10 trials and 35,029 patients found that the rates of recurrent VTE (4.1% patient-years vs. 4.4% patient-years) and the related case fatality rates (16% vs. 13%) were similar in patients receiving NOACs or conventional therapy (44). Major bleeding (1.8% per patient-year vs. 3.1% per patient-year), fatal bleeding (0.1% per patient-year vs. 0.3% per patient-year), and the related case fatality rates (6% vs. 10%; p = 0.18) were lower with NOACs than with conventional therapy. In a subsequent meta-analysis, NOACs were associated with a reduction in all-cause mortality (risk ratio: 0.51; 95% CI: 0.26 to 1.01) (45).

In a meta-analysis, the results in patients with pulmonary embolism were evaluated independently from those in patients with DVT (46). In patients with acute pulmonary embolism, recurrence of VTE...
occurred in similar proportions in patients randomized to receive NOACs or conventional treatment (2.4% vs. 2.6%; OR: 0.89; 95% CI: 0.70 to 1.12). Treatment with NOACs was associated with a reduced rate of major bleeding by approximately 50% (RR: 0.49; 95% CI: 0.26 to 0.95) (47). Similar rates of clinically relevant bleeding were observed with NOACs or conventional treatment (10.2% vs. 11.3%; OR: 0.89; 95% CI: 0.77 to 1.03) (46).

A network meta-analysis, on the basis of indirect comparison of NOACs for the treatment of VTE, revealed a relative risk for a major bleeding event of 0.42 (95% CI: 0.21 to 0.87; p = 0.02) for apixaban versus dabigatran; 0.57 (95% CI: 0.29 to 1.15; p = 0.12) for apixaban versus edoxaban; 0.37 (95% CI: 0.19 to 0.73; p < 0.001) for apixaban vs. edoxaban; 0.74 (95% CI: 0.42 to 1.30; p = 0.30) for rivaroxaban versus dabigatran; 0.64 (95% CI: 0.38 to 1.08; p = 0.10) for rivaroxaban versus edoxaban; and 1.15 (95% CI: 0.66 to 2.00; p = 0.62) for edoxaban versus dabigatran (48).

**RESULTS IN PARTICULAR PATIENTS**

In all of the studies, subgroup analyses were performed on the efficacy and safety of NOACs in specific populations of patients.

**ELDERLY PATIENTS.** A recent analysis of the dabigatran trials showed that the efficacy of dabigatran compared with warfarin was to some extent higher in elderly patients (p = 0.099 for interaction), with equal efficacy at approximately 60 years of age (38). The difference in efficacy was not statistically significant at any age. Concerning clinically relevant bleeding, the risk reduction in favor of dabigatran was influenced by age (p = 0.010 for interaction) and was greater in younger patients.

No age effect in efficacy and safety was observed in subgroup analyses in the rivaroxaban, apixaban, and edoxaban studies (Table 4) (41-43). However, only a minority of the patients included in Phase III studies (about 5%) were aged >80 years.

In a meta-analysis of Phase III studies, a significantly lower rate of recurrent VTE was observed with NOACs compared with conventional treatment in patients aged ≥75 years (RR: 0.56; 95% CI: 0.38 to 0.82) (49). In these patients, a significant reduction in major bleeding was associated with NOACs (RR: 0.49; 95% CI: 0.25 to 0.96).

**PATIENTS WITH RENAL INSUFFICIENCY.** In a recently published subgroup analysis of the rivaroxaban studies, increasing rates of recurrent VTE were observed in patients with deteriorated renal function (50). Similar HRs for recurrent VTE were observed across renal function categories in the rivaroxaban and conventional treatment groups (Table 4). Concerning major bleeding, in patients with deteriorating renal function, a trend in favor of rivaroxaban was observed compared with conventional treatment. No effect was observed with respect to efficacy and safety across the renal function impairment categories in subgroup

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Treatment of VTE in Particular Clinical Situations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV renal failure</td>
<td>Prefer conventional treatment*</td>
</tr>
<tr>
<td>Concomitant treatment with verapamil or dronedarone</td>
<td>Prefer conventional treatment or rivaroxaban</td>
</tr>
<tr>
<td>Concomitant treatment with carbamazepine, phenobarbital, phenytoin</td>
<td>Prefer conventional treatment</td>
</tr>
<tr>
<td>Active cancer</td>
<td>LMWH or conventional treatment or NOACs†</td>
</tr>
<tr>
<td>Isolated distal DVT</td>
<td>If to be treated, prefer conventional treatment or LMWH or NOACs†</td>
</tr>
<tr>
<td>Unsuspected VTE</td>
<td>If to be treated, treat as symptomatic VTE§</td>
</tr>
<tr>
<td>Upper arm</td>
<td>Treat as lower-limb VTE</td>
</tr>
<tr>
<td>Splanchnic or cerebral vein thrombosis</td>
<td>Prefer conventional treatment</td>
</tr>
<tr>
<td>APLA</td>
<td>Prefer conventional treatment</td>
</tr>
<tr>
<td>Patients with vena cava filter</td>
<td>Prefer conventional treatment</td>
</tr>
</tbody>
</table>

*Indications reported here are on the basis of the available evidence. A conservative approach is suggested in clinical situations in which NOAC data are limited. This scenario does not mean that the choice of NOACs cannot be made on the basis of clinical judgment. Patients should be informed about the lack of evidence for this particular situation. Positive D-dimer thrombosis that is extensive or close to the proximal veins (e.g., >5 cm in length, involves multiple veins, >7 mm maximum diameter), no reversible provoking factor for DVT, active cancer, history of VTE, and inpatient status are risk factors for proximal extension of distal DVT and could be used to identify patients to be treated with anticoagulant agents (20). Similarly, the presence of symptoms that are deemed to be due to distal DVT should lead to consideration of the patient for anticoagulant treatment. In this case, the accuracy of the diagnosis of distal DVT was indeed higher. bVTE is unsuspected or incidental if detected on results of imaging tests performed for other purposes. The need for anticoagulation for unsuspected VTE has never been assessed in clinical trials. In current clinical practice, anticoagulant treatment is given for unsuspected proximal DVT and at least segmental PE (20).

APLA = antiphospholipid antibodies; other abbreviations as in Table 1.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Practical Aspects of VTE Treatment With NOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>How to:</td>
<td></td>
</tr>
<tr>
<td>Follow-up patients on NOACs</td>
<td>Normal renal function: first visit + renal function and blood cell count at 1 mo, then every 6 mo Abnormal renal function: first visit + renal function and blood cell count at 1 mo, then at least twice a year</td>
</tr>
<tr>
<td>Switch from VKAs</td>
<td>INR &lt;2: NOACs can be initiated immediately INR 2.0-2.5: better to start NOACs the next day INR ≥2.5: take into account the actual INR value and the half-life of the VKA. A new INR can be scheduled before starting the NOAC</td>
</tr>
<tr>
<td>How to manage:</td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE on NOAC treatment</td>
<td>Verify compliance to NOAC treatment Reassess concomitant medications Consider change to a different NOAC or to conventional treatment</td>
</tr>
<tr>
<td>Overdosing</td>
<td>With active bleeding: Manage as patients with bleeding complications In the absence of bleeding: Consider activated charcoal if &lt;2 h Withhold the next dose</td>
</tr>
<tr>
<td>Missing dose</td>
<td>In bid regimens: take if &lt;6 h from scheduled intake In od regimens: take if &lt;12 h from scheduled intake</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; other abbreviations as in Table 1.
analyses in the dabigatran, apixaban, and edoxaban studies (38,41,42).

**Patients with extreme body weight.** An analysis was performed to determine the association between body weight and clinical outcomes in patients treated with rivaroxaban compared with conventional therapy (51). There was no association between body weight (≥50 kg, >50 to <100 kg, and ≥100 kg) and risk of recurrent VTE for patients taking rivaroxaban or receiving conventional therapy (Table 4). Major bleeding was not associated with body weight for patients taking rivaroxaban, whereas in patients

### Table 4: Efficacy and Safety of NOACs in Particular Populations: Results on Efficacy and Safety of NOACs as Reported in Papers or Substudies Published After the Main Publications of Phase III Studies

<table>
<thead>
<tr>
<th>Trial Name (Ref. #)</th>
<th>Context</th>
<th>Treatment</th>
<th>Definition</th>
<th>Recurrent VTE</th>
<th>Safety Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER studies (53)</td>
<td>Renal function</td>
<td>Dabigatran (150 mg bid) Warfarin</td>
<td>Creatinine clearance ≥80 ml/min</td>
<td>3.1% vs. 2.6%</td>
<td>CRB: 3.3% vs. 6.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Creatinine clearance 50 to &lt;80 ml/min</td>
<td>1.9% vs. 1.6%</td>
<td>CRB: 7.1% vs. 12.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Creatinine clearance 30 to &lt;50 ml/min</td>
<td>0% vs. 4.1%</td>
<td>CRB: 11.3% vs. 10.5%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td>Use of NSAIDs</td>
<td>2.8% dabigatran, 2.0% warfarin</td>
<td>MB: 1.1 dabigatran, 1.0% warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nonuse of NSAIDs</td>
<td>2.6% dabigatran, 2.5% warfarin</td>
<td>MB: 0.9% dabigatran, 1.8% warfarin</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td>Use of aspirin</td>
<td>3.1% dabigatran, 2.3% warfarin</td>
<td>MB: 1.0% dabigatran, 3.0% warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nonuse of aspirin</td>
<td>2.6% dabigatran, 2.4% warfarin</td>
<td>MB: 1.0% dabigatran, 1.5% warfarin</td>
</tr>
<tr>
<td>RE-MEDY study (54)</td>
<td>Thrombophilia</td>
<td>Dabigatran (150 mg bid) Warfarin</td>
<td>Thrombophilia present</td>
<td>1.5% dabigatran, 2.3% warfarin</td>
<td>MB: 0.5% dabigatran, 2.5% warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thrombophilia absent</td>
<td>2.3% dabigatran, 0.7% warfarin</td>
<td>MB: 0.4% dabigatran, 0.8% warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thrombophilia not tested</td>
<td>1.8% dabigatran, 1.3% warfarin</td>
<td>MB: 1.4% dabigatran, 1.7% warfarin</td>
</tr>
<tr>
<td>EINSTEIN-DVT and PE (43,50-52)</td>
<td>Fragile patients</td>
<td>Rivaroxaban (15 mg bid for 3 weeks, then 20 mg od) Enoxa/VKA</td>
<td>Age ≥75 yrs (n = 1,279), or creatinine clearance &lt;50 ml/min, or body weight ≤50 kg</td>
<td>2.7% rivaroxaban, 3.8% enoxa/warfarin</td>
<td>MB: 1.3% rivaroxaban, 4.5% enoxa/warfarin</td>
</tr>
<tr>
<td></td>
<td>Renal function</td>
<td></td>
<td>Creatinine clearance ≥80 ml/min</td>
<td>1.9% rivaroxaban, 1.9% enoxa/warfarin</td>
<td>MB: 0.9% rivaroxaban, 1.1% enoxa/warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Creatinine clearance 50 to &lt;80 ml/min</td>
<td>1.8% rivaroxaban, 1.9% enoxa/warfarin</td>
<td>MB: 0.8% rivaroxaban, 1.0% enoxa/warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Creatinine clearance 30 to &lt;50 ml/min</td>
<td>2.4% rivaroxaban, 3.1% enoxa/warfarin</td>
<td>MB: 1.4% rivaroxaban, 3.0% enoxa/warfarin</td>
</tr>
<tr>
<td></td>
<td>Body weight</td>
<td></td>
<td>≤50 kg</td>
<td>6.7% rivaroxaban, 2.2% enoxa/warfarin</td>
<td>MB: 1.3% rivaroxaban, 4.4% enoxa/warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;50 kg and &lt;100 kg</td>
<td>1.9% rivaroxaban, 2.4% enoxa/warfarin</td>
<td>MB: 1.0% rivaroxaban, 1.8% enoxa/warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥100 kg</td>
<td>2.3% rivaroxaban, 2.0% enoxa/warfarin</td>
<td>MB: 0.9% rivaroxaban, 1.2% enoxa/warfarin</td>
</tr>
<tr>
<td></td>
<td>NSAIDs*</td>
<td>Use of NSAIDs</td>
<td>NR</td>
<td>MB: 4.7% rivaroxaban, 8.4% enoxa/warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonuse of NSAIDs</td>
<td>NR</td>
<td>MB: 1.4% rivaroxaban, 2.7% enoxa/warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspirin*</td>
<td>Use of aspirin</td>
<td>NR</td>
<td>MB: 3.3% rivaroxaban, 6.9% enoxa/warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonuse of aspirin</td>
<td>NR</td>
<td>MB: 1.6% rivaroxaban, 2.9% enoxa/warfarin</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN PE (65)</td>
<td>PESI score</td>
<td>Rivaroxaban (15 mg bid for 3 weeks, then 20 mg od) Enoxa/VKA</td>
<td>Simplified PESI scores of 0,</td>
<td>0.8% rivaroxaban, 0.7% enoxa/VKA</td>
<td>MB: 0.5% rivaroxaban, 0.7% enoxa/warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simplified PESI scores of 1, or</td>
<td>1.0% rivaroxaban, 1.1% enoxa/warfarin</td>
<td>MB: 0.3% rivaroxaban, 1.1% enoxa/warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simplified PESI scores ≥2</td>
<td>1.6% rivaroxaban, 3.6% enoxa/warfarin</td>
<td>MB: 0.8% rivaroxaban, 3.2% enoxa/warfarin</td>
</tr>
</tbody>
</table>

*Percentages per patient-year.

CRB = clinically relevant bleeding; MB = major bleeding; NSAIDs = nonsteroidal anti-inflammatory drugs; NR = not reported; PESI = pulmonary embolism severity index; other abbreviations as in Table 1.
undergoing conventional treatment, major bleeding was more common in patients with low body weight. No effects on efficacy and safety were observed in subgroup analyses for body weight categories in the dabigatran, apixaban, and edoxaban studies. However, patients with body weight <50 kg were marginally represented in all trials.

In a meta-analysis of Phase III trials comparing NOACs with conventional treatment for acute symptomatic VTE, the efficacy of NOACs in patients with a body weight >100 kg was consistent with that of the general population (49).

The efficacy and safety of apixaban and dabigatran in the treatment of VTE were confirmed across different classes of body mass index. Caution is recommended with the use of NOACs in patients with body weight <50 kg and >150 kg.

Fragile patients. Among patients included in studies with rivaroxaban, 1,573 were categorized as fragile because of age >75 years (n = 1,279), moderate or severe renal impairment according to a creatinine clearance level <50 ml/min (n = 649), or body weight ≤50 kg (n = 107) (43). Recurrent VTE was more common in fragile than in nonfragile patients (Table 4), with no difference between treatment groups. In fragile patients, major bleeding was significantly lower with rivaroxaban compared with conventional therapy (HR: 0.27; 95% CI: 0.13 to 0.54). This difference was not seen in nonfragile patients.

A favorable efficacy profile was shown with edoxaban compared with warfarin in the subgroup analysis in fragile patients, without any safety concern.

Patients receiving nonsteroidal anti-inflammatory agents. An analysis was performed in the rivaroxaban trials on the efficacy and safety of concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) (52). According to this analysis, the incidence of clinically relevant bleeding (37.5% per patient-year vs. 16.6% per patient-year; HR: 1.77; 95% CI: 1.46 to 2.14) and that of major bleeding (6.5% per patient-year vs. 2.0% per patient-year; HR: 2.37; 95% CI: 1.51 to 3.75) were higher in patients concomitantly treated with NSAIDs and anticoagulant agents. Clinically relevant bleeding was more common in aspirin users than in nonusers (36.6% vs. 16.9% per patient-year; HR: 1.70; 95% CI: 1.38 to 2.11). Major bleeding occurred in 4.8% per patient-year in aspirin users compared with 2.2% per patient-year in nonusers (HR: 1.50; 95% CI: 0.86 to 2.62). Increases in risk for clinically relevant and major bleeding were similar for rivaroxaban and conventional treatment.

A similar analysis was reported on the efficacy and safety of concomitant treatment with NSAIDs and dabigatran (53). About 10% of patients included in the dabigatran studies received aspirin and about 20% received NSAIDs. No apparent difference in recurrent VTE was observed in patients with concomitant NSAIDs or low-dose aspirin versus those without (Table 4). Incidence of bleeding was similar or numerically lower for dabigatran versus warfarin. Treatment with concomitant NSAIDs/low-dose aspirin resulted in no statistically significant interactions for efficacy or safety.

Patients with molecular thrombophilia. In the dabigatran studies, thrombophilia did not affect the efficacy or safety profiles of dabigatran compared with warfarin (54). Dabigatran was noninferior to warfarin in preventing recurrent VTE or pulmonary embolism, with a similar or lower risk of bleeding events, regardless of thrombophilia status. There is no reason to hypothesize that there would be a different efficacy to safety profile of NOACs in patients with thrombophilia. The only exception could be for antiphospholipid syndrome or lupus anticoagulant agent (Table 2). Ad hoc studies are currently ongoing with rivaroxaban (NCT02116036 and NCT02157272) and apixaban (NCT02295475) in patients with these abnormalities.

LIMITS OF THE AVAILABLE TRIALS

LIMITED NUMBER OF PATIENTS WITH CANCER. A proportion ranging between 2.5% and 9.4% of patients included in the Phase III trials with NOACs had cancer (37–42). This finding contrasts sharply with data from clinical practice reporting that about 20% of patients with VTE have cancer. In addition, it has been claimed that patients with cancer included in the NOAC Phase III trials were not completely representative of the full spectrum of patients with cancer. Indeed, it is possible that patients with more extensive disease were not included in the studies. Furthermore, in these studies, the comparator was warfarin and not LMWH, which is considered the treatment of choice for cancer patients with VTE. Thus, there are some concerns about whether the results of these studies are applicable to patients with cancer-associated VTE.

The results of 6 studies comparing NOACs with conventional anticoagulation for treatment of VTE, including patients with cancer, were pooled in a meta-analysis (55). VTE recurred in 3.9% and 6.0% of patients with cancer treated with NOACs or with conventional treatment, respectively (OR: 0.63; 95% CI: 0.37 to 1.10). Major bleeding occurred in 3.2% and 4.2% of patients receiving NOACs and conventional treatment (OR: 0.77; 95% CI: 0.41 to 1.44). Several studies aimed at assessing the efficacy and
safety of NOACs in patients with cancer-associated VTE have started or are about to start. Until more data become available, caution is advised regarding the use of NOACs in patients with cancer, particularly in the case of cancer patients receiving chemotherapy. Patients should be informed of the advantages, in terms of practicality of these agents, but also on the lack of data in the cancer setting.

OPTIMAL RISK-TAILORED STRATEGIES FOR INITIAL TREATMENT OF PATIENTS WITH PULMONARY EMBOLISM. In-hospital mortality in hemodynamically unstable patients with acute pulmonary embolism may be as high as 58.3% (56). At the other extreme, clinical risk assessment models, including pulmonary embolism severity index (PESI) (or simplified PESI) scores, can identify patients with acute pulmonary embolism at risk of 1% or lower 30-day death (57). In hemodynamically stable patients with acute pulmonary embolism, right ventricular dilation, as seen with echocardiography (OR: 2.36; 95% CI: 1.3 to 4.3) or computed tomography angiography (OR: 1.64; 95% CI: 1.06 to 2.52), and increased serum troponin level (OR: 5.90; 95% CI: 2.68 to 12.95) were associated with increased short-term risk of death (58-60). Thrombolytic therapy is reserved for selected patients with pulmonary embolism and hemodynamic compromise (61,62) or for patients with DVT-associated phlegmasia of the lower limbs (20,31). Patients with acute pulmonary embolism requiring thrombolytic treatment in the acute phase were excluded from clinical trials. A case series on treatment with thrombolysis and rivaroxaban in 98 patients with acute pulmonary embolism reported no excess bleeding complications (63).

Whether the results obtained with NOACs in the treatment of acute pulmonary embolism apply to hemodynamically stable patients with right ventricular dysfunction and increased serum troponin levels is unclear. The combination of LMWH followed by edoxaban was more effective than conventional treatment in the prevention of recurrent VTE in patients with acute pulmonary embolism and increased B-type natriuretic peptide levels included in the Hokusai study (42). In this study, the combination of LMWH followed by edoxaban was non-inferior to conventional treatment in patients with acute pulmonary embolism and right ventricular dysfunction according to computed tomography scanning. Data on right ventricular dysfunction and/or injury were not available for patients included in the remaining Phase III trials.

Studies with antifactor Xa agents reported data on the anatomic extent of pulmonary embolism, as assessed by the thrombotic burden at computed tomography scan (40-42). About one-fourth of the patients included in the rivaroxaban pulmonary embolism study had extensive pulmonary embolism (involvement of >25% of the entire pulmonary vasculature), about 58% had intermediate pulmonary embolism, and about 12% had limited pulmonary embolism (≤25% of a single lobe) (40). In the apixaban study, about one-third of patients with pulmonary embolism had extensive pulmonary artery involvement (41). Efficacy and safety profiles of rivaroxaban and apixaban were confirmed in patients with different magnitudes of vascular involvement. However, a poor association has been shown between the burden of emboli at computed tomography scan and the clinical outcome in several studies, and risk stratification based on embolic burden has been discontinued (31,64).

In a post hoc analysis of the rivaroxaban for pulmonary embolism study, a simplified PESI score was calculated in almost all patients; 54%, 36%, and 10% had PESI scores of 0, 1, and 2, respectively (65). The simplified PESI score was significantly associated with fatal pulmonary embolism and all-cause mortality at 7 days (p = 0.014 and p < 0.0001, respectively), at 14 days (p = 0.035 and p < 0.0001), and at the end of the intended treatment period (p = 0.0001 and p < 0.0001). No treatment effect was observed with rivaroxaban or conventional treatment according to the simplified PESI score (Table 4). Adverse outcomes occurred more frequently in patients with simplified PESI scores ≥2.

SAFETY AND FEASIBILITY OF HOME TREATMENT OR SHORT HOSPITAL STAY. Home treatment is now common in clinical practice for patients with DVT, except those with severe renal failure or high bleeding risk; the evidence regarding the safety of home treatment for patients with acute pulmonary embolism is encouraging but still limited (66,67). Patients with acute pulmonary embolism at low risk of short-term mortality according to the simplified PESI score and the absence of right ventricular dysfunction are candidates for short hospitalization or even home treatment if adequate support for initiation of anticoagulation is available in the outpatient setting (31). In clinical practice, regardless of the anticoagulant agent, home treatment is made challenging by difficulties in the identification of low-risk patients and in the assessment of bleeding risk in patients starting anticoagulation. Indeed, the accuracy of available risk scores for bleeding risk assessment in patients with VTE (Outpatient Bleeding Risk Index and the Kuijer, RIETE, and Kearon scores)
was shown to be poor to moderate (68). Positive predictive values and positive likelihood ratios seem to be low and vary from 3.1% to 6.6% and from 0.72 to 1.59, respectively. The HAS-BLED score (hypertension [uncontrolled systolic blood pressure \(>160\) mm Hg], abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios, elderly, and concomitant drugs and/or alcohol excess) seems to have the best predictive value for bleeding complications during the first 3 months of treatment (area under the curve: 0.68; 95% CI: 0.59 to 0.78) (69). None of the existing bleeding scores seemed to predict major bleeding better than chance (70). If the reduction in bleeding risk observed with NOACs in Phase III trials is confirmed in real-world studies, the issue of bleeding risk scores could become less important.

NOACs have the potential to facilitate the home treatment of VTE. However, limited data are currently available on the use of NOACs for outpatient treatment. About 52% of patients included in the rivaroxaban DVT study and 90% of those included in the rivaroxaban pulmonary embolism study were admitted to the hospital (71). The proportion of patients with a length of hospital stay \(\leq5\) days was 54% and 31% in those receiving rivaroxaban or conventional treatment, respectively. For patients with pulmonary embolism, the corresponding values were 45% and 33%.

**MANAGEMENT OF ISOLATED DISTAL DVT.** DVT is defined as distal when it is limited to below the popliteal vein. Moderate diagnostic accuracy has been shown with lower-limb ultrasonography for the diagnosis of distal DVT, and there is no definitive evidence that the clinical course of patients with distal DVT is influenced by anticoagulant treatment (72,73). Thus, international guidelines currently accept 2 approaches: to treat distal DVT as proximal DVT or to observe the patients by using serial ultrasound imaging and initiate therapy with anticoagulant agents only in the case of extension to the proximal veins (Table 2) (20). A randomized trial has recently been presented in which patients with distal DVT were randomized to receive the LMWH nadroparin or placebo for 42 days (74). At day 42, symptomatic proximal extension of DVT or pulmonary embolism occurred in 7 patients in the placebo arm and in 4 patients in the nadroparin arm: 5.4% versus 3.3% \((p = 0.54)\). Five major or clinically relevant episodes of nonmajor bleeding occurred, all in the nadroparin arm. Although this study reported no significant advantage of anticoagulant treatment compared with placebo in patients with distal DVT, it also found that distal DVT extends to the proximal veins or causes pulmonary embolism in a nonnegligible proportion of patients.

Patients with isolated distal DVT were excluded from clinical trials with NOACs, and further evidence is needed to apply the results obtained in major VTE to these patients. It is implausible that patients with calf DVT would not benefit from NOACs and should be denied the advantage of NOACs (over conventional therapy). However, patients should be informed about the lack of evidence in this particular indication.

**MANAGEMENT OF BLEEDING COMPLICATIONS.** In patients experiencing major bleeding while undergoing treatment with vitamin K antagonists, current guidelines recommend the use of prothrombin complex concentrates to resupply coagulation factors (75,76). These concentrates rapidly normalize clotting times, although a clear benefit in terms of clinical outcome remains to be demonstrated (77). The administration of prothrombin complex concentrates in healthy volunteers treated with rivaroxaban was associated with a complete and rapid normalization of clotting times that was not observed in healthy volunteers treated with dabigatran (78). On the basis of this evidence, the use of prothrombin complex concentrates is recommended in patients experiencing major bleeding while undergoing treatment with antifactor Xa agents (Figure 1) (36).

Clinical data are available regarding the use of specific target antibodies created to reverse the anticoagulant effect of NOACs. Idarucizumab, an antibody fragment developed to reverse the anticoagulant effects of dabigatran, completely reversed the anticoagulant effect of this agent within minutes when given as a single intravenous bolus in 90 dabigatran-treated patients who had serious bleeding or required an urgent procedure (79–81). Idarucizumab is now licensed in the United States and Europe for dabigatran reversal. Andexanet alfa, a modified recombinant human factor Xa molecule that is catalytically inactive but retains the ability to bind direct and indirect factor Xa inhibitors, was able to correct the anticoagulant effect of apixaban in 34 volunteers (82,83). In a recent study, andexanet reversed the anticoagulant activity of therapeutic doses of apixaban and rivaroxaban in healthy elderly volunteers within minutes after its administration and for the duration of infusion, with no evidence of clinical toxic effects (84).

The clinical development of small molecules able to antagonize the effect of several parenteral and oral antifactor Xa agents has also started (85). However, given the short half-life of the NOACs, the clinical
value in real life of these antidotes remains to be
defined. Administration of activated charcoal should be considered when the last dose of NOACs occurred within 2 h (36).

A proposal regarding the management of surgery or invasive procedures while undergoing treatment with NOACs for VTE is reported in Figure 1 and in the Central Illustration.

**NOACs FOR EXTENDED TREATMENT OF VTE**

**DESIGN OF THE CLINICAL TRIALS.** In the extended treatment of VTE, clinical trials were conducted with dabigatran, rivaroxaban, and apixaban (Table 5). Dabigatran, rivaroxaban, and 2 doses of apixaban were compared with placebo in patients with uncertainty about the clinical benefit of continued anticoagulation (39,86,87). Dabigatran was also compared with warfarin in patients with indications for extended treatment of VTE (86). All of the trials of NOACs versus placebo were superiority studies, whereas the trial of dabigatran versus warfarin was a noninferiority study. The primary outcome was recurrent VTE and VTE-related death; the exception was the study with apixaban, which had recurrent VTE and overall mortality as the primary outcome. The primary safety outcome in all of the studies was major bleeding. Treatment duration was 12 months in the dabigatran and apixaban studies versus placebo, and 6 or 12 months in the rivaroxaban study. In the study of dabigatran versus warfarin, treatment was given for up to 36 months.

**MAIN RESULTS OF THE STUDIES.** Dabigatran (HR: 0.08; 95% CI: 0.02 to 0.25) (80), rivaroxaban (HR: 0.18; 95% CI: 0.09 to 0.39) (39), and both doses of apixaban (RR: 0.36; 95% CI: 0.25 to 0.53 for the 5-mg twice-daily dose; RR: 0.33; 95% CI: 0.22 to 0.48 for the 2.5-mg twice-daily dose) (87) were more effective than placebo for the extended treatment of VTE. The rate of major bleeding was low in all of the placebo-controlled studies. Dabigatran, rivaroxaban, and the higher dose
of apixaban were associated with an increased rate of clinically relevant bleeding, whereas this outcome did not occur with the lower dose of apixaban. Dabigatran was noninferior to warfarin for the extended treatment of VTE, with an improved safety profile (86). The lower dose of apixaban was as effective as and safer than the higher dose for the extended treatment of VTE in patients with clinical equipoise regarding the continuation or cessation of anticoagulation therapy (87). An ongoing clinical trial is aimed at assessing the clinical value of full-dose rivaroxaban compared with the prophylactic dose and aspirin in the extended treatment of VTE (88).

In a meta-analysis of Phase III placebo-controlled studies on extended treatment, both all-cause mortality and recurrent VTE were lower with NOACs than with placebo (0.6% per year vs. 1.1% per year [p = 0.01] and 1.9% per year vs. 10.9% per year [p < 0.0001], respectively) (45). No significant difference between treatments was observed in case
Table 5: Main Results of Phase III Studies With NOACs for Extended Treatment of VTE

<table>
<thead>
<tr>
<th>NOAC (Ref. #)</th>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>Duration (months)</th>
<th>Efficacy Outcome</th>
<th>Safety Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>RE-MEDY</td>
<td>2,856</td>
<td>Dabigatran 150 mg bid vs. warfarin (INR 2–3)</td>
<td>18–36</td>
<td>Recurrent VTE: 1.8% with dabigatran, 1.3% with warfarin</td>
<td>Major bleeding: 0.9% with dabigatran, 1.8% with warfarin</td>
</tr>
<tr>
<td></td>
<td>RESONATE</td>
<td>1,343</td>
<td>Dabigatran 150 mg bid vs. placebo</td>
<td>6</td>
<td>Recurrent VTE: 0.4% with dabigatran, 5.6% with warfarin</td>
<td>Major bleeding: 0.3% with dabigatran, 0% with placebo</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>(39)</td>
<td>602</td>
<td>Rivaroxaban 20 mg daily vs. placebo</td>
<td>6 or 12</td>
<td>Recurrent VTE: 1.3% with rivaroxaban, 7.1% with placebo</td>
<td>Major bleeding: 0.7% with rivaroxaban, 0% with placebo</td>
</tr>
<tr>
<td>Apixaban</td>
<td>AMPLIFY-extension</td>
<td>2,486</td>
<td>Apixaban 2.5 mg bid vs. placebo</td>
<td>12</td>
<td>Recurrent VTE and death: 1.7% with apixaban, 8.8% with placebo</td>
<td>Major bleeding: 0.2% with apixaban, 0.5% with placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apixaban 5 mg twice daily vs. placebo</td>
<td></td>
<td>Recurrent VTE and death: 1.7% with apixaban, 8.8% with placebo</td>
<td>Major bleeding: 0.1% with apixaban, 0.5% with placebo</td>
</tr>
</tbody>
</table>

RESONATE – Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE; other abbreviations as in Tables 1 and 3.

fatality rates of VTE recurrence ($p = 0.17$). No fatal bleeding events were reported with NOACs during extended treatment. A nonsignificant increase in major bleeding was reported in patients receiving NOACs (risk ratio: 1.41; 95% CI: 0.53 to 3.76).

The enhanced benefit-to-risk profile of the NOACs relative to the vitamin K antagonists could lead to a change in practice concerning extended treatment in patients with unprovoked VTE or in those with persistent risk factors. Indeed, the benefit of extending treatment with low doses could increase the proportion of patients prescribed extended treatment. However, when making decisions regarding extended treatment, the poor predictive value of commonly used bleeding risk scores should be taken into account. The extension studies also open the way for shifting patients from conventional treatment to NOACs.

**NOACs in Clinical Practice**

The real-world safety profile of NOACs remains to be defined. If the efficacy to safety profile reported in Phase III trials is confirmed, the reduction in medical costs estimated in economic analyses could also be translated to the real world (89).

The PREFER (PREvention of thromboembolic events) registry showed that in clinical practice, NOACs were more frequently used for treatment of VTE in younger patients (age <65 years, 26.8%; age 65 to 74 years, 19.8%; and age ≥75 years, 14.3%). NOACs were used less frequently in those with lower weight (≤60 kg vs. >60 kg 13.4% vs. 23.3%), renal insufficiency (22.7% vs. 11.1% in patients with creatinine clearance levels ≤60 ml/min), diabetes (22.9% vs. 13.5% in patients without and with diabetes), and those at risk of bleeding (according to HAS-BLED score [low 27.1%; medium 17.8%; and high 12.5%]) (90). Use in pulmonary embolism was as frequent as use in DVT.

Disease-based registry studies aimed at evaluating NOACs in real-life patients are underway (NCT02210819, NCT02155491, NCT02295475, and NCT02345343).

**NOACs for VTE Treatment in the Current Guidelines**

Because the results of clinical trials with NOACs were published in the past few years, these agents have been considered only in the most recent guidelines. In the 2014 European Society of Cardiology guidelines for the management of pulmonary embolism, dabigatran, rivaroxaban, apixaban, and edoxaban were all recommended as alternatives to conventional anticoagulation agents for the treatment of pulmonary embolism (31). Rivaroxaban and apixaban are indicated according to the single-drug approach, whereas dabigatran and edoxaban should be used after initial heparin treatment. Dabigatran, rivaroxaban, and apixaban are also indicated as alternatives to warfarin for extended treatment.

**The Responsible Use of NOACs for the Treatment of VTE**

Although >30,000 patients have been included in studies with NOACs for the treatment of VTE, these patients may not be completely representative of the real-life population of patients with this disease. As an example, the mean age of patients included in the trials is significantly lower than the mean age of patients with VTE included in disease registries; mortality rates reported in clinical trials were also
lower than that seen in registries. Thus, caution should be used whenever a NOAC is to be given in compromised patients or in complex clinical settings. Although the treatment is apparently easier, it requires a high level of clinical judgment to identify the patients to be treated and exclude those more likely to have complications.

Although associated with a reduced rate of bleeding complications, NOACs may still cause bleeding. To reduce these complications, emphasis should be given to clinical history and patient education. A follow-up program should also be formed with the purpose of providing the patients with clinical surveillance and optimizing treatment adherence.

A document has been released on how to manage NOACs in specific clinical situations in patients with atrial fibrillation (36). Although patients with VTE differ from those with atrial fibrillation, and although transfer of evidence from 1 clinical setting to another is not always appropriate, it is conceivable that the same indications can be applied to patients with VTE until specific data become available.

CONCLUSIONS

In the treatment of VTE, NOACs are at least as effective as warfarin but produce less bleeding and are more convenient to administer. The availability of NOACs for the treatment of VTE has the potential to be a landmark achievement and, likely, the most significant accomplishment in antithrombotic therapy since the introduction of LMWH approximately 30 years ago. The results obtained with these agents allow effective and simplified treatment in a large proportion of patients with VTE. Better definitions of efficacy and safety of NOACs in specific patient subgroups (including those with cancer or intermediate-to-high-risk pulmonary embolism), as well as in those affected by thrombosis at unusual sites, will be tasks for clinical research in the coming years.

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KEY WORDS anticoagulant agents, pulmonary embolism, venous thrombosis