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Brief review

# The potential of target-specific oral anticoagulants for the acute and long-term treatment of venous thromboembolism

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## Abstract

**Background:**
Venous thromboembolism (VTE) comprises both deep vein thrombosis and pulmonary embolism. VTE is a leading cause of morbidity and mortality worldwide and its increasing incidence and prevalence are a major health concern. The primary medical objective during the acute phase of VTE treatment is to prevent thrombus extension and embolization. Extended treatment aims to prevent or minimize long-term complications, such as recurrent VTE, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.

**Scope:**
Anticoagulant therapy has been the mainstay of treatment for VTE and traditionally involves initial therapy with heparin, overlapping with and followed by a vitamin K antagonist. Although effective, standard heparin/ vitamin K antagonist therapy has several limitations that can be overcome by more recently developed target-specific oral anticoagulants (TSOACs). These agents have predictable pharmacokinetics, a rapid onset of action and few drug–drug or drug–food interactions. Furthermore, TSOACs offer convenient anticoagulation without the need for routine coagulation monitoring and dose adjustment.

**Findings:**
The efficacy and safety data from phase III clinical trials support the use of TSOACs for VTE treatment, including in special patient populations. Risk-stratification tools and strategies have been developed to assist physicians in managing anticoagulation treatment.

**Conclusions:**
Rivaroxaban is the first TSOAC to gain widespread approval for the treatment of acute deep vein thrombosis and pulmonary embolism and the long-term prevention of recurrent VTE as monotherapy. Dabigatran has also been approved for this indication recently. TSOACs, especially as monotherapy, represent a paradigm shift in clinical practice for the management of patients with VTE.

## Introduction

Venous thromboembolism (VTE) is a common and potentially fatal vascular disease[1]. VTE comprises deep vein thrombosis (DVT) and pulmonary embolism (PE)[2] and frequently results in long-term complications, including recurrent VTE, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension[2,3]. The focus of the acute treatment period of VTE management is to prevent thrombus extension and any acute hemodynamic or vascular complications[2]. Such complications lead to high rates of morbidity and mortality and represent substantial costs for healthcare systems[4,5]. The second phase of

 

treatment involves extended thromboprophylaxis as maintenance therapy, which aims to prevent long-term complications[2].

DVT and PE are frequently seen as related conditions[6], because DVT often precedes or coexists with PE[7]. However, these two conditions have also been reported as being unrelated because PE can occur without a detectable DVT, for example during trauma, reflecting *de novo* formation of a thrombus in the lungs[8]. Symptoms of DVT include pain, swelling, tenderness along the affected vessels and erythema or cyanosis[9]. After a first DVT episode, patients may develop swelling of the affected extremity and pain as a result of damaged venous valves, venous hypertension, skin ulceration and restricted mobility, and are at increased risk of experiencing recurrent DVT[10]. Obstruction of pulmonary arteries in PE can be potentially fatal, but PE can also be particularly difficult to diagnose because presenting symptoms can be non-specific[10,11], including shortness of breath, chest discomfort, anxiety, light-headedness or fainting[12].

Treatment of VTE in the acute setting can vary depending on the burden of disease at presentation; however, the second phase of long-term thromboprophylaxis as maintenance treatment is similar irrespective of initial treatment[13,14]. Compared with patients with DVT, those with PE are at a higher risk of recurrence, increased morbidity and risk of sudden death, and are more likely to present with hemodynamic instability. The need for safe and effective anticoagulation in the context of PE is, therefore, crucial[15]. The current standard anticoagulant therapy in the acute treatment phase of DVT and PE is a parenteral agent (intravenous unfractionated heparin [UFH], low molecular weight heparin [LMWH], or fondaparinux) for at least 5 days, with concurrent initiation of an oral vitamin K antagonist (VKA) until the international normalized ratio reaches the therapeutic range of 2.0–3.0[13,14]. Long-term therapy beyond 3 months is recommended for patients with unprovoked proximal DVT of the leg or an unprovoked PE, and who have a low or moderate risk of bleeding; those with recurrent VTE and a low risk of bleeding; and those with VTE in the setting of active cancer, if the risk of bleeding is not high[13]. For all non-cancer patients who require extended therapy, a VKA is the recommended agent; LMWH is the preferred treatment option for patients with cancer[12,13,16]. Patients with massive or high-risk PE and hemodynamic instability may be treated with thrombolytic therapy or undergo an embolectomy[13,14].

Anticoagulation, the cornerstone of the treatment and secondary prevention of VTE, has undergone an impressive evolution over the past 20 years. Historically, hospitalized patients were treated with intravenous UFH, which is effective but requires monitoring and weight-based dosage adjustments[17,18]. This approach has been superseded by either inpatient short-term therapy with subcutaneous, weight-based LMWH followed by prolonged outpatient treatment with oral VKAs or complete outpatient management using a weight-based LMWH bridging/VKA approach, and these two approaches are now considered the standard of care for treating VTE[13,14]. The introduction of LMWHs represented an improvement over UFH because of the ease of administration and the absence of frequent laboratory monitoring. However, LMWHs are not without limitations, such as the inconvenience of daily subcutaneous injections[19]. Oral VKA therapy, despite being effective and suitable for long-term treatment, also has several limitations, including a slow onset of action; dose–response variability caused by variations in metabolism due to genetic polymorphisms and extensive drug–drug and drug–food interactions; a narrow therapeutic window; and the need for frequent coagulation monitoring and dose adjustment[20]. Here, we review the literature on risk stratification in patients with VTE, the use of target-specific oral anticoagulants (TSOACs) for the management of VTE as either a monotherapy or a heparin lead-in strategy, and considerations in special patient populations with the use of these agents.

## Diagnosis and risk stratification

Several specific transient and persistent risk factors for provoked VTE are now recognized[5,14,21], including major general or orthopedic surgery, multiple trauma, hip or pelvis fracture, spinal cord injury, malignancy, congestive heart or respiratory failure, and advanced age[6,21]. Risk-predictive rules, such as the Wells Clinical Prediction Rule for Pulmonary Embolism and Deep Venous Thrombosis, aim to determine whether a patient has a high, moderate or low probability of DVT or PE, and are used in conjunction with imaging techniques and D-dimer measurement to assist in the evaluation of patients with suspected VTE[22,23]. The simplified version of the validated revised Geneva score assesses the clinical probability of PE on the basis of the combination of either a low-intermediate clinical probability (using a three-level scheme) or a 'PE unlikely' assessment (using a dichotomized rule) with a normal result on a highly sensitive D-dimer test[24]. This has been shown to have similar diagnostic accuracy and clinical utility to the original score[24].

After diagnosis, risk stratification of patients with DVT and PE helps to determine the required type and duration of treatment, depending on, for example, whether the index event was provoked or unprovoked[13,14]. Further risk stratification can be used to determine the safety of initiating treatment in the outpatient or inpatient setting (Table 1)[25].

For patients with PE, the presence of risk markers can be used to stratify the severity of PE according to the risk of

 

Table 1. Exclusionary risk factors and risk-stratification criteria for outpatient-based treatment of deep vein thrombosis[25].

| Exclusionary risk factors for outpatient treatment of DVT |
|---|
| Absolute exclusionary risk factors |
| Platelet count <100,000 |
| Active hemorrhage |
| Gastrointestinal bleeding event within 6 months |
| Heparin sensitivity |
| Underlying liver disorder |
| Familial bleeding disorder |
| Hypertensive: SBP >220 mmHg and DBP >120 mmHg |
| Catheter-associated DVT |
| Recent surgery |
| Morbid obesity >30% ideal body weight |
| Congenital/acquired hypercoagulable state |
| Iliofemoral thrombosis |
| Comorbid illness |
| Relative exclusionary risk factors |
| Age >75 years |
| Pregnancy |
| PE (clinically unstable or massive PE is absolute exclusionary criterion) |
| Renal insufficiency (CrCl <30 ml/min or dialysis-dependent patient is absolute exclusionary criterion) |
| Other factors increasing risk of home treatment (e.g., comorbidity, insurance compliance) |
| History of non-compliance with medicines |
| History of substance abuse |
| Language barrier |
| Inability to pay for LMWH |
| Inaccessibility to clinic or telephone |
| Unstable home environment |
| Incompetence to assume responsibility of self-care or inability of family/friend/nurse to administer care |
| Risk-stratification criteria |
| High risk |
| One absolute or two or more relative exclusionary risk factors (inpatient i.v. UFH) |
| Moderate risk |
| One relative exclusionary risk factor ± home health issues ± third-party payer issues |
| Treated in hospital short term with LMWH then restratified. If risk stratified as high, converted to i.v. UFH; if low, discharged to outpatient care with LMWH |
| Low risk |
| No exclusionary risk factors (outpatient LMWH; no hospitalization) |

CrCl, creatinine clearance; DBP, diastolic blood pressure; DVT, deep vein thrombosis; i.v., intravenous; LMWH, low molecular weight heparin; PE, pulmonary embolism; SBP, systolic blood pressure; UFH, unfractionated heparin.

premature death[14]. The simplified Pulmonary Embolism Severity Index (PESI) score estimates the 30 day mortality risk in PE patients based on the variables age, cancer, chronic cardiopulmonary disease, heart rate, systolic blood pressure and oxyhemoglobin saturation levels[26]; it does not differ from the original PESI score in terms of prognostic accuracy and is more practical to use[26]. In high-risk patients with PE (i.e., those who present with shock or persistent arterial hypotension), either thrombolytic therapy or pulmonary embolectomy may be the most appropriate therapeutic option[13,14]. In patients with PE at moderate or low risk of death (i.e., those without shock or hypotension), TSOACs may be an option because anticoagulant therapy is the most commonly recommended treatment[13,14].

Although patient populations stratified to receive standard anticoagulation or TSOACs may be similar, physicians should be aware of the disadvantages and advantages of each agent after risk stratification based on individual patient characteristics.

## Target-specific oral anticoagulants

Several TSOACs that act as either direct thrombin inhibitors, such as dabigatran etexilate, or direct Factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban, have been developed in an attempt to overcome some of the limitations of VKAs and LMWHs. Direct thrombin inhibitors such as dabigatran inactivate both fibrin-bound thrombin and free thrombin and thus have a higher ability to suppress thrombus expansion, in contrast with indirect inhibitors, such as heparin or LMWH, which have reduced capacity to inhibit fibrin-bound thrombin[19]. Direct Factor Xa inhibitors inhibit free Factor Xa just like indirect inhibitors (e.g., fondaparinux), but offer the additional advantage of inhibiting Factor Xa in the prothrombinase complex[19]. The TSOACs are administered orally, in contrast with parenteral LMWHs, and have shown predictable pharmacokinetics, with a rapid onset of action, low potential for drug interactions (Table 2) and food-independent metabolism compared with VKAs[15,32].

Table 2. Pharmacological profiles of target-specific oral anticoagulants in clinical use[27–31].

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| Target | Thrombin (IIa) | Factor Xa | Factor Xa | Factor Xa |
| Prodrug | Yes | No | No | No |
| Half-life (hours) | 12–14 | 5–9 young individuals, 11–13 elderly individuals | ~12 | 6–11 |
| $T_{max}$ (hours) | 2–4 | 2–4 | 3–4 | 1–2 |
| Bioavailability (%) | ~6.5 | 80–100* | ~50 | ~62 |
| Protein binding (%) | 34–35 | 92–95 | ~87 | 40–59 |
| Renal excretion (%) | 80† | 33 as unchanged drug‡ | ~27‡ | ~35–39‡ |
| Drug interactions | Potent P-gp inducers/ inhibitors | CYP3A4 and P-gp inducers/ inhibitors | CYP3A4 and P-gp inducers/ inhibitors | Potent P-gp inhibitors |

*Irrespective of food for the 10 mg dose and equal to 66% for the 20 mg dose under fasting conditions and increasing with food intake.
†Of absorbed drug.
‡Of ingested drug.
CYP3A4, cytochrome P450 3A4; P-gp, P-glycoprotein; $T_{max}$, time to reach the peak plasma concentration after administration.



These drugs are given at fixed doses and, unlike VKAs, do not require routine coagulation monitoring or dose adjustment[15,32]. Study results suggest that TSOACs may reduce the length of hospital stay, improve patient satisfaction and potentially improve adherence, in addition to being cost-effective[33–35]. Another potential advantage of the TSOACs is their use in cases of heparin-induced thrombocytopenia, where parenteral anticoagulation has been the mainstay of treatment.

TSOACs have been evaluated extensively in phase III studies and have shown potential to replace VKAs for long-term treatment[36–41]; furthermore, effective initial treatment without heparin bridging is possible[36,38,39]. There are two different therapeutic strategies for the use of TSOACs in VTE treatment: dabigatran and edoxaban treatment is based on a heparin-led regimen, whereas apixaban and rivaroxaban employ a monotherapy regimen using an intensified initial phase (apixaban: 10 mg twice daily for 7 days followed by 5 mg twice daily; rivaroxaban: 15 mg twice daily for 21 days followed by 20 mg once daily) to replace the use of bridging with heparins and thus simplify the anticoagulation treatment strategy[36–41]. Rapid initial anticoagulation treatment aims to prevent thrombus extension or development of a recurrent thrombus that could result in fatal PE (the risk of developing PE is highest during the first weeks after the initial event)[2,42–44]. Other chronic complications can develop, such as post-thrombotic syndrome[45].

The approval of rivaroxaban (the first TSOAC for the treatment of acute VTE and the long-term prevention of recurrent VTE) and the recent approval of dabigatran in Europe and the US for treatment of VTE, signifies a paradigm shift in the management of this disease.

## Direct thrombin inhibitor: dabigatran etexilate

The RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE phase III clinical trials studied the efficacy and safety of dabigatran etexilate for the treatment and secondary prevention of VTE[40,41,46] (Tables 3 and 4). The randomized, double-blind RE-COVER trial showed that dabigatran (150 mg twice daily for 6 months, after initial bridging with LMWH for a median of 9 days) demonstrated non-inferior efficacy compared with warfarin for the treatment of acute VTE (2.4% vs. 2.1%; hazard ratio [HR] 1.10; 95% confidence interval [CI] 0.65–1.84), with a similar safety profile (Table 3)[40]. The efficacy and safety of dabigatran for acute VTE treatment were confirmed by the RE-COVER II study[41].

The RE-MEDY study also evaluated the efficacy and safety of extended prophylaxis for VTE recurrence with dabigatran compared with warfarin for 6–36 months after an initial 3–6 months of anticoagulant treatment (Table 4)[46]. The incidence of recurrent or fatal VTE (1.8% vs. 1.3%; HR 1.44; 95% CI 0.78–2.64; $p = 0.01$ for non-inferiority) was higher with dabigatran etexilate 150 mg twice daily than with warfarin, although major bleeding (0.9% vs. 1.8%; HR 0.52; 95% CI 0.27–1.01; $p = 0.06$), major or clinically relevant bleeding (5.6% vs. 10.2%; HR 0.54; 95% CI 0.41–0.71; $p = 0.001$) and occurrence of any bleeding (19.4% vs. 26.2%; HR 0.71; 95% CI 0.61–0.83; $p < 0.001$) were lower with dabigatran compared with warfarin[46]. The rate of acute coronary events during treatment was noted to be higher with dabigatran than with warfarin (0.9% vs. 0.2%; $p = 0.02$)[46]. The RE-SONATE study investigated extended therapy with dabigatran after at least 3 months' treatment (with an approved anticoagulant or with dabigatran in either of the RE-COVER studies) and showed that dabigatran (150 mg twice daily) given for an additional 6 months reduced the relative risk of the composite of recurrent or fatal VTE or unexplained death by 92% compared with placebo (0.4% vs. 5.6%; HR 0.08; CI 0.02–0.25; $p < 0.001$ for superiority) (Table 4)[46]. This was at the expense of an increase in clinically relevant bleeding (5.3% vs. 1.8%;

Table 3. Summary of target-specific oral anticoagulants in studies of venous thromboembolism treatment[36–41].

| | Dabigatran | | Rivaroxaban | | Apixaban | Edoxaban |
|---|---|---|---|---|---|---|
| | RE-COVER | RE-COVER II | EINSTEIN DVT | EINSTEIN PE | AMPLIFY | Hokusai-VTE |
| Design | Double blind | Double blind | Open label | Open label | Double blind | Double blind |
| Initial treatment with LMWH/ fondaparinux | Yes | Yes | No | No | No | Yes |
| Treatment duration (months) | 6 | 6 | 3, 6 or 12 | 3, 6 or 12 | 6 | 3 to 12 |
| TSOAC treatment regimen | 150 mg bid | 150 mg bid | 15 mg bid for 21 days followed by 20 mg od | 15 mg bid for 21 days followed by 20 mg od | 10 mg bid for 7 days followed by 5 mg bid | 60 mg od* |
| Long-term treatment | bid | bid | od | od | bid | od |
| Comparator | Heparin/warfarin or LMWH/warfarin | Heparin/warfarin or LMWH/warfarin | Enoxaparin/VKA | Enoxaparin/VKA | Enoxaparin/warfarin | Heparin/warfarin |
| Number of patients randomized | 2564 | 2568 | 3449 | 4832 | 5395 | 8292 |
| Primary efficacy outcome definition | Symptomatic recurrent VTE (composite of fatal or non-fatal PE or DVT) | | | | | |
| Primary efficacy outcome TSOAC vs. comparator (%) | 2.4 vs. 2.1 | 2.4 vs. 2.2 | 2.1 vs. 3.0 | 2.1 vs. 1.8 | 2.3 vs. 2.7 | 3.2 vs. 3.5 |
| HR | 1.10 | 1.08 | 0.68 | 1.12 | 0.84* | 0.89 |
| 95% CI | 0.65–1.84 | 0.64–1.80 | 0.44–1.04 | 0.75–1.68 | 0.60–1.18 | 0.70–1.13 |
| *p*-value | <0.001 | <0.0001 | <0.001 | 0.003 | <0.001 | <0.001 |
| Primary safety outcome definition | (Not defined) Safety outcomes included major bleeding | (Not defined) Safety outcomes included major bleeding | Clinically relevant bleeding (composite of major or clinically relevant non-major bleeding) | | Major bleeding | Clinically relevant bleeding (composite of major or clinically relevant non-major bleeding) |
| Primary safety outcome TSOAC vs. comparator (%) | NR | NR | 8.1 vs. 8.1 | 10.3 vs. 11.4 | 0.6 vs. 1.8 | 8.5 vs. 10.3 |
| HR | NR | NR | 0.97 | 0.90 | 0.31† | 0.81 |
| 95% CI | NR | NR | 0.76–1.22 | 0.76–1.07 | 0.17–0.55 | 0.71–0.94 |
| *p*-value | NR | NR | 0.77 | 0.23 | <0.001 | 0.004 |
| Major bleeding TSOAC vs. comparator (%) | 1.6 vs. 1.9 | 1.2 vs. 1.7 | 0.8 vs. 1.2 | 1.1 vs. 2.2 | 0.6 vs. 1.8 | 1.4 vs. 1.6 |
| HR | 0.82 | 0.69 | 0.65 | 0.49 | 0.31† | 0.84 |
| 95% CI | 0.45–1.48 | 0.36–1.32 | 0.33–1.30 | 0.31–10.79 | 0.17–0.55 | 0.59–1.21 |
| *p*-value | NR | NR | 0.21 | 0.003 | <0.001 | 0.35 |

*Edoxaban 30 mg od for patients with moderate renal impairment (creatinine clearance of 30–50 ml/min), body weight of ≤60 kg or who are receiving strong P-glycoprotein inhibitors.
†Relative risk.
bid, twice daily; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; LMWH, low molecular weight heparin; NR, not reported; od, once daily; PE, pulmonary embolism; TSOAC, target-specific oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 4. Summary of target-specific oral anticoagulants in studies of extended treatment of venous thromboembolism[38,46,47].

| | Dabigatran | | Rivaroxaban | Apixaban | |
|---|---|---|---|---|---|
| | RE-MEDY | RE-SONATE | EINSTEIN EXT | AMPLIFY-EXT | |
| Design | Double blind | Double blind | Double blind | Double blind | |
| Treatment duration (months) | 6–36 | 6 | 6 or 12 | 12 | |
| TSOAC treatment regimen | 150 mg bid | 150 mg bid | 20 mg od | 2.5 mg bid | 5 mg bid |
| Comparator | Warfarin | Placebo | Placebo | Placebo | |
| Number of patients randomized | 2866 | 1353 | 1197 | 2486 | |
| Primary efficacy outcome definition | Symptomatic recurrent VTE (composite of fatal or non-fatal PE or DVT) | Symptomatic recurrent VTE (composite of fatal or non-fatal PE or DVT) or unexplained death | Symptomatic recurrent VTE (composite of fatal or non-fatal PE or DVT) | Composite of symptomatic recurrent VTE or death from any cause | |
| Primary efficacy outcome TSOAC vs. comparator (%) | 1.8 vs. 1.3 | 0.4 vs. 5.6 | 1.3 vs. 7.1 | 3.8 vs. 11.6 | 4.2 vs. 11.6 |
| HR | 1.44 | 0.08 | 0.18 | 0.33* | 0.36* |
| 95% CI | 0.78–2.64 | 0.02–0.25 | 0.09–0.39 | 0.22–0.48 | 0.25–0.53 |
| *p*-value | 0.01 | <0.001 | <0.001 | <0.001 | <0.001 |
| Primary safety outcome definition | (Not defined) Safety outcomes included major bleeding | (Not defined) Safety outcomes included major bleeding | Major bleeding | Major bleeding | |
| Primary safety outcome/major bleeding TSOAC vs. comparator (%) | 0.9 vs. 1.8 | 0.3 vs. 0 | 0.7 vs. 0 | 0.2 vs. 0.5 | 0.1 vs. 0.5 |
| HR | 0.52 | NR | NR | 0.49* | 0.25* |
| 95% CI | 0.27–1.02 | NR | NR | 0.09–2.64 | 0.03–2.24 |
| *p*-value | 0.06 | 1.0 | 0.11 | NR | NR |

*Relative risk.
bid, twice daily; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; LMWH, low molecular weight heparin; NR, not reported; od, once daily; PE, pulmonary embolism; TSOAC, target-specific oral anticoagulant; VTE, venous thromboembolism.

HR 2.9; 95% CI 1.5–5.6; $p = 0.001$) but without an increase in major bleeding[46].

## Direct Factor X inhibitors

### Rivaroxaban

The efficacy and safety of rivaroxaban for the treatment and secondary prevention of DVT and PE was evaluated in the phase III EINSTEIN program (Tables 3 and 4)[38,39]. In patients with an acute symptomatic DVT without PE, the EINSTEIN DVT study (Table 3) showed the rivaroxaban regimen (15 mg twice daily for 3 weeks followed by 20 mg once daily for 3, 6 or 12 months) to be non-inferior to standard therapy (1 mg/kg subcutaneous enoxaparin twice daily overlapping and followed by a dose-adjusted VKA) in preventing the recurrence of VTE (2.1% vs. 3.0%; HR 0.68; 95% CI 0.44–1.04; $p < 0.001$ for non-inferiority)[38]. The principal safety outcome, defined as a major or clinically relevant non-major bleeding event, occurred in the same proportion of patients receiving rivaroxaban or standard of care therapy (8.1% vs. 8.1%; HR 0.97; 95% CI 0.76–1.22; $p = 0.77$)[38]. Overall, the outcome of net clinical benefit (symptomatic recurrent VTE plus major bleeding) was significantly better in the rivaroxaban group than in the standard therapy group (2.9% vs. 4.2%; HR 0.67; 95% CI 0.47–0.95; $p = 0.03$)[38]. In patients with acute symptomatic PE with or without DVT, the EINSTEIN PE study (Table 3), using the same design and outcome measures as EINSTEIN DVT, showed non-inferior efficacy of rivaroxaban compared with standard of care in preventing the primary efficacy outcome of recurrent symptomatic VTE (2.1% vs. 1.8%; HR 1.12; 95% CI 0.75–1.68; $p = 0.003$ for non-inferiority)[39]. The principal safety outcome was not significantly different between treatments (10.3% for rivaroxaban vs. 11.4% for standard of care; HR 0.90; 95% CI 0.76–1.07; $p = 0.23$); however, rivaroxaban may have an improved benefit–risk profile, because it significantly reduced major bleeding compared with standard therapy (1.1% vs. 2.2%; HR 0.49; 95% CI 0.31–0.79; $p = 0.003$)[39]. The lower incidence of major bleeding with rivaroxaban was related to critical-site bleeding including retroperitoneal, intracranial, pericardial and intra-articular bleeding[39].

In the EINSTEIN EXT study (Table 4), rivaroxaban (20 mg once daily) demonstrated superior efficacy compared with placebo in the extended treatment (6 or 12 months) of patients who had already completed 6–12 months of anticoagulant therapy for VTE (1.3% vs. 7.1%; HR 0.18; 95% CI 0.09–0.39; $p < 0.001$)[38]. No significant differences between the rates of major bleeding associated with rivaroxaban and placebo were observed (0.7% vs. 0%; $p = 0.11$)[38]. In light of the data from the phase III EINSTEIN program, rivaroxaban has been widely approved for the treatment of DVT and PE and the prevention of recurrent VTE[27].

### Apixaban

The randomized, double-blind, phase III AMPLIFY study compared the efficacy and safety of apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) with that of subcutaneous enoxaparin followed by warfarin for treatment of acute VTE (Table 3)[36]. Apixaban was non-inferior to standard therapy for the primary efficacy outcome of recurrent symptomatic VTE or VTE-related death (2.3% vs. 2.7%; relative risk [RR] 0.84; 95% CI 0.60–1.18; $p < 0.001$). Apixaban treatment was associated with lower rates of major bleeding (0.6% vs. 1.8%; RR 0.31; 95% CI 0.17–0.55; $p < 0.001$ for superiority), the composite of major bleeding and clinically relevant non-major bleeding (4.3% vs. 9.7%; RR 0.44; 95% CI 0.36–0.55; $p < 0.001$ for superiority), non-fatal major bleeding at a critical site (0.1% vs. 0.5%) and non-fatal major intracranial bleeding (0.1% vs. 0.2%)[36].

The randomized, double-blind AMPLIFY-EXT phase III clinical study investigated the efficacy and safety of apixaban (2.5 mg and 5 mg twice daily) compared with placebo for extended secondary prevention of VTE (i.e., for 12 months) after an initial 6–12 months of anticoagulation treatment (Table 4)[47]. The primary efficacy outcome, defined as the composite of symptomatic recurrent VTE or death from any cause, was significantly lower with apixaban: 3.8% for apixaban 2.5 mg twice daily (RR 0.33; 95% CI 0.22–0.48; $p < 0.001$) and 4.2% for apixaban 5 mg twice daily (RR 0.36; 95% CI 0.25–0.53; $p < 0.001$) versus 11.6% with placebo. Recurrent VTE or VTE-related death also occurred significantly less frequently with apixaban 2.5 mg twice daily (1.7%; 7.2% difference with placebo; 95% CI 5.0–9.3; $p < 0.001$) and apixaban 5 mg twice daily (1.7%; 7.0% difference with placebo; 95% CI 4.9–9.1; $p < 0.001$) than with placebo (8.8%). There was a trend for lower rates of major bleeding in the groups receiving anticoagulation therapy (0.2% and 0.1% for apixaban 2.5 mg and 5 mg, respectively) than in the placebo group (0.5%), although the same result was not seen for non-major clinically relevant bleeding (3.0% and 4.2% for apixaban 2.5 mg and 5 mg, respectively, vs. 2.3% with placebo)[47].

### Edoxaban

The randomized, double-blind, Hokusai-VTE phase III clinical study compared the efficacy (non-inferiority) and safety of edoxaban 60 mg once daily after initial treatment with LMWH with a therapeutic regimen of LMWH/warfarin in the acute VTE setting (Table 3)[37]. The study design was intended to reflect clinical practice by using an initial standard heparin treatment and flexible treatment duration of between 3 and 12 months. Edoxaban showed

non-inferiority compared with standard therapy regarding the primary efficacy outcome of first recurrent VTE or VTE-related death (3.2% vs. 3.5%; HR 0.89; 95% CI 0.70–1.13; $p<0.001$). The occurrence of major or non-major clinically relevant bleeding within the 3 days after the end of study treatment (principal safety outcome) was significantly lower with edoxaban than with LMWH/warfarin (8.5% vs. 10.3%; HR 0.81; 95% CI 0.71–0.94; $p=0.004$ for superiority). There was a lower incidence of major bleeding with edoxaban than with standard therapy; however, this was not significantly different (1.4% vs. 1.6%; HR 0.84; 95% CI 0.59–1.21; $p=0.35$ for superiority)[37].

## Specific patient populations

### Patients with cancer

Patients with cancer have an increased risk of VTE related to hypercoagulability of malignancy, as well as immobility, surgical procedures, indwelling catheters, and chemotherapeutic and anti-angiogenic therapy[48]. VTE is associated with a poor prognosis and is a significant predictor of death in patients with cancer[49,50]. There are limited efficacy and safety data available regarding the treatment of VTE with TSOACs in patients with cancer because of the low general number of cancer patients in these studies (EINSTEIN DVT, EINSTEIN PE and Hokusai-VTE)[37–39], or because these patients were excluded from the studies (e.g., AMPLIFY)[36]. Patients with cancer for whom long-term treatment with LMWH was planned were excluded from the AMPLIFY study[36].

Approximately 5% of the total study population investigated in the phase III EINSTEIN trials presented with active cancer[38,39]. A pooled analysis of data from patients with cancer in EINSTEIN DVT and EINSTEIN PE confirmed lower recurrence of VTE and major bleeding with rivaroxaban compared with enoxaparin/VKA therapy (5.1% vs. 7.1%; HR 0.69; 95% CI 0.36–1.33 and 2.8% vs. 5.0%; HR 0.53; 95% CI 0.23–1.23, respectively)[51]. The tolerability of apixaban in patients with cancer was investigated in a small phase II, double-blind pilot study, in which patients receiving chemotherapy for a diverse array of cancer types for 12 weeks had a rate of major bleeding of 2.2% (95% CI 0.26–7.5) and no fatal bleeding events[52]. In the AMPLIFY study of apixaban, patients with cancer who were to receive long-term treatment with LMWH were excluded, which has limited the applicability for this subgroup of patients[36]. In the Hokusai-VTE study, in which the prevalence of patients with cancer was approximately 9%, there was a non-statistically significant trend favoring edoxaban treatment compared with warfarin in cancer patients regarding the outcome of major and clinically relevant non-major bleeding (18.3% vs. 25.3%; $p=0.6544$)[37].

The paucity of data regarding the use of TSOACs in patients with cancer has led recent international clinical practice guidelines to emphasize that the use of these agents is not recommended for cancer patients with VTE[53,54]. Moreover, the potential exists for drug–drug interactions between the TSOACs and certain agents used in cancer therapy that affect the cytochrome P450 (rivaroxaban and apixaban) or P-glycoprotein (dabigatran, rivaroxaban and apixaban) systems[55]. However, the potential lower risk of major bleeding seen with rivaroxaban compared with enoxaparin/VKA in patients with cancer in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies encourages additional investigation[51]. Further studies are also required to define the bleeding complications of the TSOACs in these patients, who may be predisposed to hemorrhage because of malignancy-related causes and decreased clearance associated with concomitant liver or kidney dysfunction. LMWHs are the current standard for treatment and prevention of VTE in patients with underlying malignancy[13]. Studies such as CLOT[56], LITE[57] and CANTHANOX[58] provided the basis for such a recommendation after showing that LMWHs were at least as effective and safe as VKA therapy in preventing recurrent VTE in adult cancer patients with acute symptomatic VTE.

### Pregnant patients

Pregnancy, both antepartum and postpartum, is associated with an increased incidence of VTE, particularly in women with previous episodes of VTE and/or thrombophilia[59]. DVT accounts for 80% of VTE cases, and PE for 20% of cases[59]. Heparin thromboprophylaxis is considered for VTE prevention in pregnant women with a history of idiopathic thrombosis or symptomatic thrombophilia[60], because these agents do not cross the placenta[59]. In contrast, the TSOACs, which have the potential to cross the placenta owing to their small size, are contraindicated during pregnancy because these agents have not been evaluated in pregnant women[27,28], or because only limited data exist[29]. So far, evidence from animal studies suggests that rivaroxaban may cross the placenta[27], and animal reproduction studies have shown reproductive toxicity for dabigatran[29] but not for apixaban[28].

### Patients with antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilic state characterized by the association of antiphospholipid antibodies with thrombosis and/or pregnancy morbidity and mortality, and is able to affect any vascular bed[61]. The prevalence of APS is

estimated to be 2–4% in the general population[62]. The mainstay of treatment of thrombotic APS is long-term anticoagulation with VKAs, although the optimal intensity of anticoagulation remains controversial[63]. However, no published studies exist addressing the safety and efficacy of TSOACs in patients with APS. An ongoing prospective, randomized, controlled, phase II/III clinical trial comparing rivaroxaban with warfarin in patients with APS will help to clarify the potential role of TSOACs in the management and prevention of thrombosis in APS[64].

### Elderly patients or patients with renal impairment

The incidences of VTE and of both idiopathic and secondary PE increase with age. Approximately two-thirds of patients with acute PE are aged ≥60 years, with a mean age of 62 years. The rate of PE is increased eightfold when comparing patients >80 years old with patients <50 years of age[14]. Age ≥75 years is recognized as an independent risk factor for VTE, but anticoagulation is frequently under-used in elderly patients because of fear of bleeding[65]. Patients with creatinine clearance (CrCl) <30 ml/min were excluded from the clinical trials discussed previously, which may indirectly have reduced the proportion of elderly patients included, making it difficult to extrapolate the results to geriatric patients in daily practice. Some accumulation of dabigatran has been observed in patients with mild and moderate renal impairment[66]. A pooled analysis of the EINSTEIN data showed a lower rate of VTE recurrence with rivaroxaban compared with standard therapy (2.7% vs. 3.8%; HR 0.68; 95% CI 0.39–1.18) in fragile patients, defined as being elderly (>75 years), with renal failure (CrCl <50 ml/min) and/or low body weight (<50 kg)[51]. Rivaroxaban was also associated with a significant reduction in the incidence of major bleeding compared with standard therapy (1.3% vs. 4.5%; HR 0.27; 95% CI 0.13–0.54)[51]. In the AMPLIFY and AMPLIFY-EXT study, patients with CrCl <25 ml/min or serum creatinine >2.5 mg/dl were excluded. No significant difference was seen between apixaban- and enoxaparin/warfarin-treated patients regarding the rates of VTE, irrespective of their level of renal impairment. However, patients with normal renal function, as well as those with either mild or moderate or severe renal impairment, showed reductions in major bleeding when treated with apixaban compared with standard therapy[36]. In the Hokusai-VTE study, patients with CrCl 30–50 ml/min or body weight ≤60 kg accounted for 20% of the overall population. A dose reduction of edoxaban from 60 mg once daily to 30 mg once daily was permitted for these patients because of the increased risk of bleeding[37]. This dose reduction was also considered for patients receiving concomitant treatment with potent P-glycoprotein inhibitors[37]. Edoxaban 30 mg once daily showed similar efficacy and significantly lower rates of bleeding compared with the warfarin group[37].

## Managing complications

With the approval of the TSOACs for the management of VTE, and their inclusion in treatment guidelines, it is of the utmost importance that physicians become familiar with the management of complications associated not only with treatment failure but also with situations such as emergency surgery, anticoagulant overdose and bleeding complications[67]. Well established reversal strategies exist for standard therapy with VKAs: the anticoagulant effect of VKAs is reversed by administering vitamin K (although this effect takes time), plasma concentrates or prothrombin complex concentrates, whereas protamine sulfate is used to counteract UFH-based anticoagulation and, partially, the effect of LMWHs. Management of bleeding in patients taking TSOACs should be individualized according to the severity and site of the hemorrhage. Strategies for managing bleeding events in patients receiving TSOACs may include delaying or discontinuing anticoagulant therapy; symptomatic treatment, such as mechanical compression, surgical hemostasis with bleeding control procedures, fluid replacement and hemodynamic support; or transfusion of blood products (packed red cells and/or fresh frozen plasma) (Figure 1)[28,29,68]. Although no validated specific antidotes for the TSOACs exist, some agents have shown promise[30], and prothrombin complex concentrate, activated prothrombin complex concentrate or recombinant Factor VIIa may be used to manage severe or life-threatening bleeding[27–29,68,69]. Activated charcoal has been suggested as a treatment option to decrease the absorption of rivaroxaban and apixaban in situations of overdose[27,28]; however, this will only yield results if administered very soon (within 1–3 hours) after the intake of these oral anticoagulants, before they are absorbed.

There are encouraging preclinical data on the use of a monoclonal antibody fragment as an antidote against dabigatran[70]. In addition, a recombinant modified form of Factor Xa (PRT064445), which is catalytically inactive but able to bind direct Factor Xa inhibitors, has been shown to restore hemostasis in a rabbit liver laceration model upon treatment with rivaroxaban[71]. PRT064445, but not recombinant Factor VIIa, also reversed rivaroxaban-induced anticoagulation as measured by a reduction in blood loss in a rabbit model[72].

Management strategies for the failure of LMWH treatment include increasing the dose, changing the LMWH preparation, or switching to a VKA. The strategies to manage failure of VKA treatment are more challenging and include targeting a higher international normalized ratio value with increasing anticoagulation, switching to UFH/LMWH or adding acetylsalicylic acid[67]. A strategy

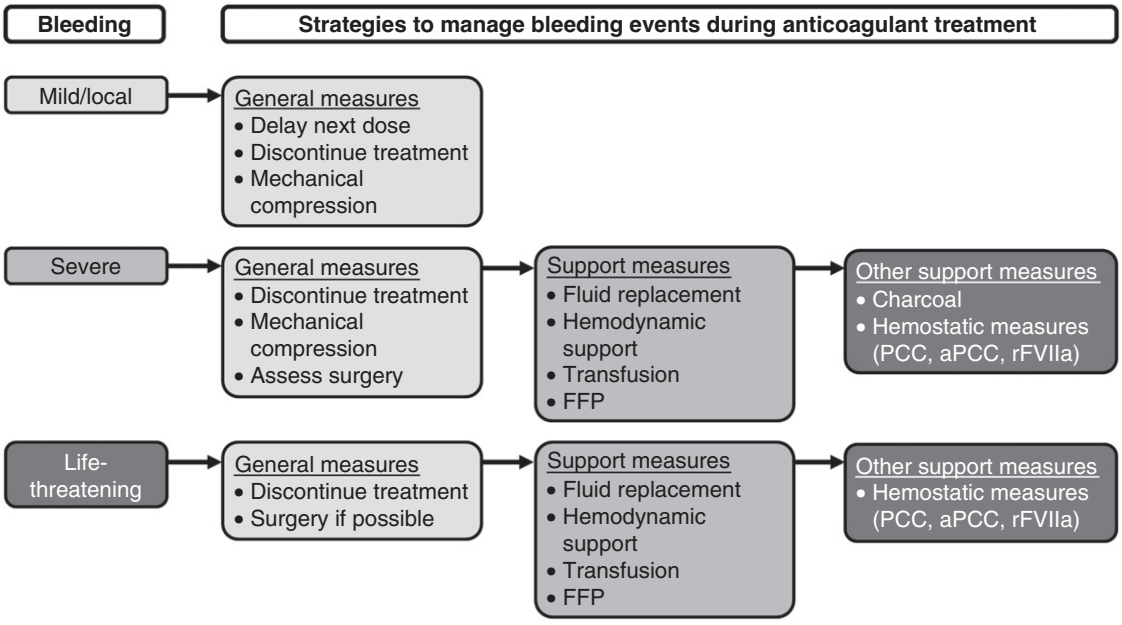


Figure 1. Bleeding management strategies devised for patients receiving target-specific oral anticoagulants. aPCC, activated prothrombin complex concentrate; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; rFVIIa, recombinant Factor VIIa.



to manage failure of treatment with the TSOACs is still to be defined. The benefit of switching from one TSOAC to another has not yet been verified by head-to-head trials, and dose escalation is not recommended by the approved labeling of TSOACs[27–29]. Recommendations to assist clinicians in converting patients from a TSOAC to conventional agents, however, do exist[27–29,68].

Emergency surgery in patients receiving anticoagulation is another situation for which management strategies need to be in place and similar strategies are to be applied to the TSOACs[27–29,68]. The time frame between the last anticoagulant dose and the surgical intervention must be established according to the pharmacokinetic profile of the anticoagulant, in order to reduce the risk of bleeding. Anticoagulation therapy should be restarted after surgery as soon as possible, provided that hemostasis has been achieved[27–29,68].

## Conclusion

Rivaroxaban was the first oral anticoagulant since the VKAs to be widely approved for the treatment of DVT and PE and the prevention of recurrent VTE. Dabigatran has recently received a positive opinion from the Committee for Medicinal Products for Human Use for this indication in Europe, and has also been approved for the treatment of DVT and PE and the prevention of recurrent VTE in the US (April 2014); the approval of apixaban and edoxaban for the same indication is widely anticipated. In contrast to warfarin, the rapid onset of action of the TSOACs, similar to that of subcutaneous enoxaparin, makes heparin bridging unnecessary. However, only rivaroxaban and apixaban offer a simplified monotherapy approach by including an initial intensified phase of treatment, thus replacing the use of heparin during the period in which patients are at the highest risk of developing recurrent VTE. Irrespective of their monotherapy or heparin lead-in therapeutic regimens, the approval of TSOACs represents a paradigm shift in the treatment of VTE as these agents become incorporated into routine clinical practice and included in guidelines for the management of VTE. TSOACs are likely to provide benefits over conventional oral anticoagulants such as warfarin, including increased adherence, because of simplified non-monitored therapy, particularly in the long term, which will decrease the number of patients receiving suboptimal anticoagulation. TSOACs also have the potential for improved clinical outcomes, especially reduced overall bleeding and intracranial bleeding, in addition to expected decreased overall healthcare costs. The predictable pharmacokinetic and pharmacodynamic profiles of these agents, together with risk-stratification strategies, will allow anticoagulant therapy to be tailored to the needs of individual patients.

## Transparency

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