

# Considerations for long-term anticoagulant therapy in patients with venous thromboembolism in the novel oral anticoagulant era

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**Background:** Patients who have had a venous thromboembolic event are generally advised to receive anticoagulant treatment for 3 months or longer to prevent a recurrent episode. Current guidelines recommend initial heparin and an oral vitamin K antagonist (VKA) for long-term anticoagulation. However, because of the well-described disadvantages of VKAs, including extensive food and drug interactions and the need for regular anticoagulation monitoring, novel oral anticoagulants (NOACs) have become an attractive option in recent years. These agents are given at fixed doses and do not require routine coagulation-time monitoring. The NOACs are discussed in this review with regard to the needs of patients on long-term anticoagulation.

**Methods:** Current guidelines from Europe and North America that refer to the treatment of deep vein thrombosis and/or pulmonary embolism are included, as well as published randomized Phase III clinical trials of NOACs. PubMed searches were used for sourcing case studies of long-term anticoagulant treatment, and results were filtered for human application and screened for relevance.

**Conclusion:** NOAC-based therapy showed a similar efficacy and safety profile to heparins/VKAs but without the need for regular anticoagulation monitoring or dietary adjustments, and can be taken as a fixed-dose regimen once or twice daily. This represents a significant step forward in facilitating the management of long-term anticoagulation therapy. Furthermore, in the EINSTEIN studies, improved patient satisfaction was documented with the NOAC rivaroxaban, which may result in better adherence to therapy and an overall reduction in the incidence of recurrent venous thromboembolism.

**Keywords:** anticoagulation, patient needs, vitamin K antagonist, direct thrombin inhibitor, direct Factor Xa inhibitor, deep vein thrombosis, pulmonary embolism

## Introduction

Patients who have had a venous thromboembolic event, that is, proximal deep vein thrombosis (DVT) or pulmonary embolism (PE), are generally advised to receive anticoagulant treatment for a minimum of 3 months.<sup>1,2</sup> The treatment period may be further extended, or even continued indefinitely, based on assessment of the individual's risks of recurrent venous thromboembolism (VTE) and bleeding. The risk of secondary complications, such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension, may also have an impact on the prospective treatment duration. The periods of VTE treatment described by the American College of Chest Physicians (ACCP) are initial (the first ~7 days), long-term (~7 days to

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~3 months), and extended (~3 months onward),<sup>2</sup> but many similar guidelines, such as those from the European Society of Cardiology (ESC),<sup>1</sup> simply categorize treatment as initial and long-term.

At present, there is no clear guidance on the optimal length of anticoagulant therapy for the prevention of recurrent VTE, except that the duration should be individualized based on the balance between the risks of a secondary event in patients who stop receiving anticoagulation and the risk of bleeding with continued therapy. Guidelines generally recommend initial treatment with parenteral unfractionated heparin, low-molecular-weight heparin (LMWH) or fondaparinux, overlapping with and transitioning to an oral vitamin K antagonist (VKA), such as warfarin, for long-term anticoagulation.<sup>1,2</sup> This dual-drug approach is required because VKAs take several days to reach therapeutic levels of anticoagulation, as determined by the international normalized ratio (INR).<sup>3</sup> Regular coagulation-time monitoring and dose adjustments to maintain the INR in the therapeutic range of 2.0–3.0 are required for the duration of therapy, because the pharmacodynamic effects of VKAs are highly variable and affected by diet, medications, genetic polymorphisms, and other factors. In recent years, the novel oral anticoagulants (NOACs) dabigatran (a direct thrombin inhibitor) and rivaroxaban, apixaban, and edoxaban (direct Factor Xa inhibitors) have been developed as treatment alternatives to VKAs. They offer a more predictable pharmacological profile and can be given at fixed doses without the need for routine coagulation monitoring.<sup>4</sup> These agents have all undergone successful clinical trials for VTE treatment, given either as single-drug therapies (rivaroxaban, apixaban) or after initial parenteral anticoagulation (dabigatran, edoxaban). Dabigatran, rivaroxaban, apixaban, and, most recently, edoxaban are approved for the treatment of acute DVT and PE and prevention of recurrent VTE in the USA and European Union.

This review discusses the risk factors for VTE recurrence and treatment-associated bleeding, current guidelines, and clinical trial data on the use of NOACs for the treatment of acute DVT and PE and prevention of recurrent VTE, as well as the needs of patients on long-term anticoagulation. Case studies are included to illustrate situations in which patients may require long-term anticoagulation and how this can be managed.

## Methods

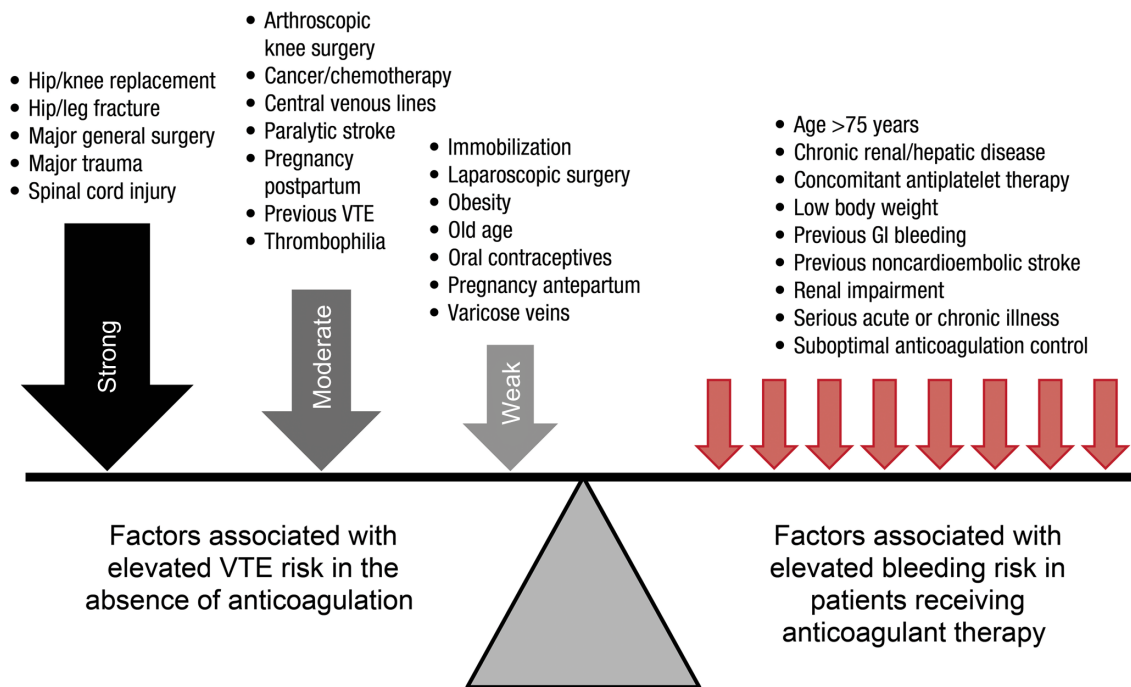
Current European and North American guidelines for the treatment of DVT and/or PE were reviewed, along with

published randomized Phase III clinical studies of NOACs. Case studies of long-term anticoagulant treatment were sourced via PubMed searches using the search strings [case AND warfarin AND cancer], [case AND PCC OR aPCC OR FVIIa AND reversal], and [case AND long-term anticoagulation AND X] in which X was replaced by cancer, antiphospholipid, antithrombin, Factor V Leiden, or protein C deficiency. Results were filtered to ensure that they were case reports and applied to humans and were further refined by a review of each abstract for relevance.

## Balancing the risks of recurrent VTE and bleeding

The risk of recurrent VTE increases when anticoagulation therapy is stopped, particularly if a patient has certain predisposing risk factors (Figure 1).<sup>1,2</sup> Risk factors for recurrent VTE include recent surgery and/or trauma, active cancer, advanced age, male sex, obesity, immobility, and thrombophilia. Some of these risk factors, such as surgery and immobility, may be reversible or transient, and it is unlikely that anticoagulation would be continued beyond the point at which the influence on VTE risk ceases. However, patients with a first unprovoked proximal DVT and/or PE, a second unprovoked VTE, or with ongoing comorbidities such as cancer may require long-term anticoagulation. The presence of residual vein thrombosis after initial anticoagulant treatment may be associated with an increased risk of recurrent DVT, although this is not clear.<sup>5</sup> In patients with a previous unprovoked VTE, the estimated risk of VTE recurrence was more than double for patients with elevated D-dimer levels compared with those with normal D-dimer levels, and recurrence may be particularly likely in men with high D-dimer levels.<sup>6</sup> However, the use of D-dimer testing to predict VTE recurrence is controversial. Genetic thrombophilia (eg, protein C, protein S, or antithrombin deficiency; prothrombin G20210A mutation; Factor V Leiden) can increase the risk of VTE recurrence, and patients with these mutations are therefore often recommended to receive lifelong anticoagulation (Table 1).<sup>1,2</sup>

Several prediction models have been developed to attempt to quantify the most important risk factors for DVT recurrence. Rodger et al identified hyperpigmentation, edema/redness of the leg, D-dimer  $\geq 250$   $\mu\text{g/L}$  while receiving anticoagulation, body mass index  $\geq 30$   $\text{kg/m}^2$ , and age  $\geq 65$  years as important factors for women with previous VTE and found that patients with two or more of these factors had a high risk of VTE recurrence.<sup>7</sup> The authors of the Vienna prediction model found that age, sex, location of VTE, body mass index, Factor V Leiden, prothrombin G20210A mutation,



**Figure 1** The balance between the risk of recurrent venous thromboembolism and bleeding events.

**Notes:** Data from Konstantinides et al<sup>1</sup> and Kearon et al.<sup>2</sup>

**Abbreviations:** GI, gastrointestinal; VTE, venous thromboembolism.

D-dimer concentration, and in vitro thrombin generation affected VTE recurrence rates, and they formulated a risk score accordingly.<sup>8</sup> The simple D-dimer, Age, Sex, Hormonal therapy (DASH) score assigns one point to each of the following: elevated D-dimer after stopping anticoagulation, age <50 years, male sex, and VTE not associated with hormonal therapy (for women). Patients with a score of 0 or 1 are at low risk of recurrence (3.1%/year), those with a score of 2 are at moderate risk (6.4%/year), and those with a score of 3 or above are at high risk (12.3%/year).<sup>9</sup> However, this scoring system requires further validation.

All anticoagulants carry a risk of bleeding owing to their mode of action. In addition, there are certain patient groups that are predisposed to an increased risk of bleeding when receiving anticoagulant treatment (Figure 1).<sup>2</sup> These include elderly patients, those with renal impairment, patients with low body weight, and those with a history of gastrointestinal bleeding. Previous noncardioembolic stroke, chronic renal or hepatic disease, serious acute or chronic illness, and concomitant antiplatelet therapy are all also implicated as factors that increase the risk of bleeding. Patients who have poor anticoagulant control when receiving VKAs, which may be a result of suboptimal coagulation monitoring,<sup>3</sup> are also at elevated risk if their INR is persistently above the recommended upper boundary of 3.0.<sup>2</sup>

## Current guidelines on the duration of antithrombotic therapy

Current guidelines on the anticoagulant treatment of VTE are summarized in Table 2.<sup>1,2,10</sup> The ACCP recommends that patients with unprovoked DVT of the leg (isolated distal or proximal) or unprovoked but hemodynamically stable PE receive at least 3 months of anticoagulant treatment.<sup>2</sup> After 3 months, these patients should be evaluated for the risk and benefit of continued therapy. In patients with unprovoked VTE, extending anticoagulant therapy beyond 3 months is recommended only if the associated risk of bleeding remains low. In patients who experience DVT or PE and do not have cancer, VKAs are preferred to LMWH for long-term therapy, with LMWH as a second choice over NOACs (at the time the ACCP guidelines were issued, there was a considerably smaller body of published clinical data on NOACs than is now the case). In patients with DVT and cancer, LMWH is preferred, with VKAs as a second choice over NOACs.<sup>2</sup> LMWH is also indicated in pregnant women because it does not cross the placenta.<sup>10</sup>

Although the ESC guidelines deal primarily with PE, the recommendations are similar to those of the ACCP (Table 2).<sup>1</sup> In patients with a first unprovoked event and a low risk of bleeding, an indefinite duration of anticoagulant therapy is recommended provided that this is consistent with the patient's preference. Most patients with a second

**Table I** Thrombophilia and development of thromboembolism

Reference	Presentation	Underlying risk factor for recurrent thrombosis	Treatment	Outcome
Citro et al <sup>40</sup>	A 69-year-old woman who was a heterozygote carrier of Factor V Leiden mutation presented to the emergency room with the clinical scenario of massive pulmonary embolism	Factor V Leiden heterozygosity	<ul style="list-style-type: none"> <li>• Unfractionated heparin</li> <li>• Surgical treatment consisting of complete excision of the thrombus</li> <li>• Long-term anticoagulation treatment (not specified)</li> </ul>	At 1-year follow-up, the patient was on long-term anticoagulation treatment and free of thromboembolic events
Cook et al <sup>41</sup>	A 30-year-old, previously healthy woman diagnosed with acute, spontaneous, left-ovarian vein thrombosis with proximal extension into the renal vein	Factor V Leiden homozygosity	<ul style="list-style-type: none"> <li>• Initial catheter-directed thrombolysis with tissue plasminogen activator, angioplasty of the left renal vein, heparinoid treatment</li> <li>• Long-term anticoagulation with rivaroxaban</li> </ul>	Complete resolution of thrombosis at 3 months; no adverse effects or bleeding reported
Jukic et al <sup>42</sup>	A case of cerebral sinus thrombosis as a recurrent thrombotic event in a patient with heterozygous prothrombin G20210A genotype after discontinuation of oral anticoagulation therapy	Heterozygous prothrombin G20210A genotype	<ul style="list-style-type: none"> <li>• Heparin and symptomatic therapy were started. On the fifth day, warfarin was included in the treatment (maintained at the international normalized ratio range of 2–3), and heparin was excluded after 8 days</li> </ul>	Constantly improving condition of the patient and discharged after 6 weeks with recommendation for long-term use of warfarin
Kim et al <sup>43</sup>	A 35-year-old man who developed superior mesenteric venous thrombosis and portal vein thrombosis showed markedly decreased protein C and S levels	Protein C and S deficiency	<ul style="list-style-type: none"> <li>• Heparin and total parenteral nutrition was given</li> <li>• 3 weeks after hospitalization, the patient was fed orally and heparin was replaced by warfarin</li> </ul>	The patient was discharged 27 days after admission and had returned to work by the 9 month follow-up. Recent protein C level was 60% of control
Kshatriya et al <sup>44</sup>	A 55-year-old Caucasian man with history of hypertension, diabetes mellitus, protein C deficiency, and deep vein thrombosis presented with typical angina	Protein C deficiency	<ul style="list-style-type: none"> <li>• Tomography and echocardiography presented a mobile mass in the left atrium</li> <li>• Cardiac catheterization and angiography indicated the presence of a myxoma rather than a thrombus</li> <li>• Cardiothoracic surgery was conducted for excision of the left atrial mass</li> </ul>	Full recovery with outpatient cardiology follow-up. Angina symptoms were completely relieved, and the patient was started on anticoagulation with warfarin for the history of deep vein thrombosis

unprovoked VTE are also recommended to receive indefinite anticoagulation.<sup>1</sup>

## Prevention of recurrent VTE with NOACs: evidence from Phase III clinical trials

Randomized, controlled Phase III clinical trials have been conducted to investigate the NOACs rivaroxaban, apixaban, edoxaban, and dabigatran for the treatment of acute VTE for periods of up to 12 months<sup>11–16</sup> and in extension studies for prevention of VTE recurrence for up to 3 years (Figure 2).<sup>11,17,18</sup> A meta-analysis of the six acute treatment trials found a similar overall efficacy for the NOACs compared with standard therapy (relative risk =0.89; 95% confidence interval [CI] =0.75–1.05), whereas in the three studies of extended

treatment, NOACs were superior to placebo for the prevention of recurrent VTE (relative risk =0.17; 95% CI =0.12–0.24).<sup>19</sup> In the EINSTEIN DVT and EINSTEIN PE studies, rivaroxaban 15 mg twice daily given for 21 days, followed by 20 mg once daily for 3 months, 6 months, or 12 months (depending on physician evaluation of risk factors), was noninferior to standard parenteral anticoagulation/VKA for the prevention of recurrent VTE ( $P<0.001$  for noninferiority in both studies and a pooled analysis).<sup>11,12,20</sup> The EINSTEIN EXT study evaluated the efficacy and safety of rivaroxaban for extended treatment of DVT (beyond the currently recommended treatment duration). Patients who had completed either the EINSTEIN DVT or EINSTEIN PE study or who had received VKA therapy outside of these trials for 6 months–12 months, and for whom the decision to stop or continue anticoagulation was

**Table 2** The US and European guidelines on the duration of anticoagulant treatment for venous thromboembolism

Patient and disease type	Recommendations for duration of anticoagulant treatment	
	ACCP 2012 <sup>2</sup>	ESC 2014 <sup>1</sup>
Patient with proximal DVT or hemodynamically stable PE associated with transient risk factors	VKA preferred over LMWH or NOAC Treat for 3 months	Anticoagulant treatment for 3 months
Patient with unprovoked proximal DVT or hemodynamically stable PE	VKA preferred over LMWH or NOAC First or subsequent unprovoked VTE with low/moderate bleeding risk: >3 months' treatment	First or subsequent unprovoked PE with a low bleeding risk: >3 months to indefinite anticoagulant treatment
Patient with isolated distal DVT	Consider serial imaging rather than anticoagulation to monitor for any clot extension if symptoms are not severe or clot extension is considered unlikely. Provide anticoagulant treatment if symptoms are severe or clot extends (recommended therapy and durations as above)	Recommendations not provided
VTE in a patient with active cancer	LMWH preferred over VKA: >3 months	LMWH for 3–6 months, then consider indefinite anticoagulation or until cancer is in remission
VTE in a pregnant woman	LMWH preferred over UFH: continue for a minimum of 3 months and for at least 6 weeks postpartum	LMWH preferred over UFH Anticoagulation (VKA permitted after birth) to continue for at least 6 weeks postpartum for a minimum overall treatment duration of 3 months
VTE in a patient with severe renal impairment (CrCl <30 mL/min)	UFH preferred over LMWH, rivaroxaban, or dabigatran owing to lack of renal clearance	UFH preferred to LMWH owing to short half-life and rapid reversal by protamine
Patient with PTS secondary to DVT	Use of mechanical compression (stockings, venous foot pump)	Recommendations not provided
Patient with CTEPH secondary to PE	Extended anticoagulation; pulmonary thromboendarterectomy if expertise available	Pulmonary thromboendarterectomy if operable, or targeted medical therapy (riociguat) if not All patients should receive lifelong anticoagulation
Patient with inherited thrombophilia	Recommendations not provided	Consider indefinite anticoagulant treatment after a first unprovoked VTE

**Note:** Data from previous studies.<sup>1,2,10</sup>

**Abbreviations:** ACCP, American College of Chest Physicians; CrCl, creatinine clearance; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ESC, European Society of Cardiology; LMWH, low-molecular-weight heparin; NOAC, novel oral anticoagulant; PE, pulmonary embolism; PTS, post-thrombotic syndrome; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

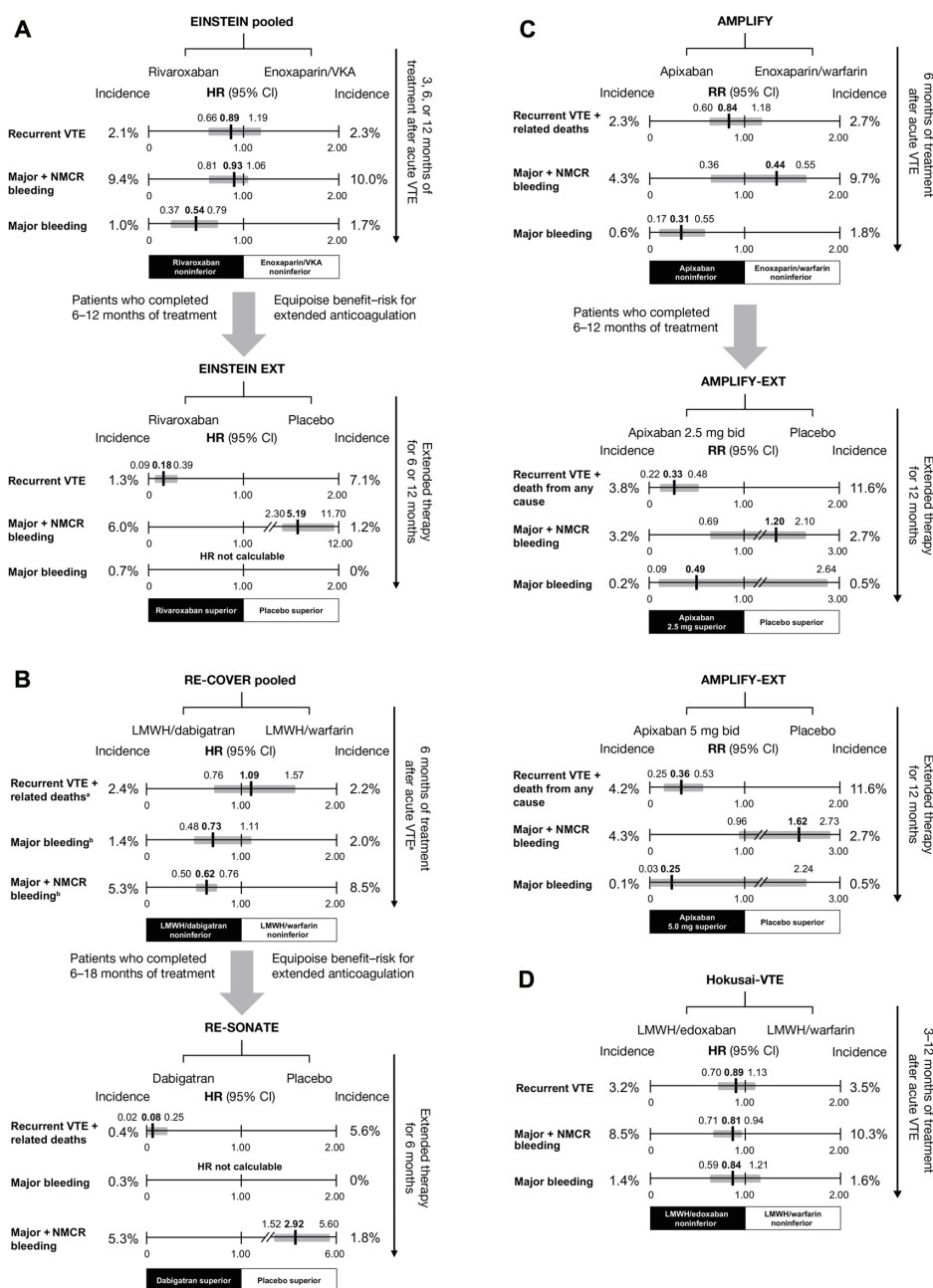
at equipoise, were randomized to receive rivaroxaban 20 mg once daily or placebo for a further 6 months or 12 months.<sup>11</sup> Patients who received rivaroxaban had an 82% relative risk reduction for recurrent VTE compared with those in the placebo arm ( $P<0.001$ ).

Similar to rivaroxaban, apixaban was also studied as a single drug for the treatment of VTE compared with standard dual-drug therapy. In the AMPLIFY study, patients with VTE received 6 months of treatment with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) or heparin/VKA; apixaban was noninferior to standard therapy for the prevention of recurrent VTE and VTE-related death ( $P<0.001$  for noninferiority).<sup>13</sup> In AMPLIFY-EXT, patients

who had completed AMPLIFY or had otherwise received 6 months–12 months of anticoagulant treatment, and for whom the decision to stop or continue anticoagulation was at equipoise, were randomized to apixaban 2.5 mg or 5 mg twice daily or placebo for a further 12 months. The lower and higher apixaban doses provided a respective 67% and 64% relative risk reduction for recurrent VTE plus all-cause mortality compared with placebo.<sup>17</sup>

Unlike rivaroxaban and apixaban, edoxaban was evaluated against warfarin for the treatment of acute VTE after all patients had received initial heparin. In the Hokusai-VTE study, patients received 3 months–12 months of therapy according to physician assessment and local guidelines.<sup>14</sup> The edoxaban





**Figure 2** Principal efficacy and safety results of Phase III clinical trials of novel oral anticoagulants for the acute treatment of venous thromboembolism and long-term prevention of recurrence.

**Notes:** Data from the acute treatment of VTE are presented for the (A) pooled EINSTEIN DVT and EINSTEIN PE,<sup>11,12,20</sup> (B) pooled RE-COVER I and RE-COVER II,<sup>15,16</sup> (C) AMPLIFY,<sup>13</sup> and (D) Hokusai-VTE<sup>14</sup> studies. Data from studies of extended treatment are also presented for the (A) EINSTEIN EXT,<sup>11</sup> (B) RE-SONATE,<sup>18</sup> and (C) AMPLIFY-EXT<sup>17</sup> studies. Patients in the extension studies did not necessarily complete the equivalent acute treatment study first. \*Efficacy data were derived during the 6-month study period; †safety data were obtained from the start of any study drug.

**Abbreviations:** bid, twice daily; CI, confidence interval; HR, hazard ratio; LMWH, low-molecular-weight heparin; NMCR, nonmajor clinically relevant; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism.

arm (60 mg once daily, or 30 mg once daily in patients with creatinine clearance [CrCl] 30 mL/min–50 mL/min, body weight ≤60 kg or receiving concomitant treatment with potent P-glycoprotein [P-gp] inhibitors) was noninferior to standard heparin/warfarin for the incidence of recurrent symptomatic VTE ( $P < 0.001$  for noninferiority). No extension study for edoxaban has yet been reported.

Dabigatran was evaluated in two studies for the treatment of acute VTE – RE-COVER and RE-COVER II – during which patients were randomized to receive dabigatran or VKA for 6 months.<sup>15,16</sup> As in Hokusai-VTE, all patients received initial parenteral anticoagulation. Dabigatran 150 mg twice daily was noninferior to VKA for the prevention of recurrent VTE and VTE-related death in a pooled analysis of the two

studies (hazard ratio [HR]=1.09; 95% CI=0.76–1.57).<sup>16</sup> The RE-SONATE extension study with dabigatran had a similar design to EINSTEIN EXT and AMPLIFY-EXT: patients who had received 6 months–18 months of anticoagulation received a further 6 months of dabigatran 150 mg twice daily or placebo.<sup>18</sup> Dabigatran treatment led to a 92% relative risk reduction over placebo for the prevention of VTE or unexplained death ( $P<0.001$ ). In a separate extension study, RE-MEDY, long-term dabigatran was compared with long-term warfarin and was noninferior for the incidence of recurrent or fatal VTE ( $P=0.01$  for noninferiority).<sup>18</sup>

As a result of these studies, the ESC now recommends apixaban (2.5 mg twice daily), rivaroxaban (20 mg once daily), and dabigatran (150 mg twice daily, or 110 mg twice daily for patients aged  $\geq 80$  years or those receiving concomitant verapamil treatment) as alternatives to VKA therapy (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary (Class IIa B level of recommendation).<sup>1</sup>

## Managing the risk of bleeding complications with long-term or extended NOAC treatment

### Bleeding risk and outcomes in clinical trials of NOACS

In general, results from the Phase III trials of NOACs suggest that the rate of clinically relevant bleeding is approximately 10% with 6 months–12 months of VKA therapy and is somewhat lower with NOACs (~4%–9%) (Figure 2).<sup>11–16</sup> In a meta-analysis of the acute treatment studies, the risk of major bleeding was significantly lower with the NOACs than standard therapy (relative risk =0.63; 95% CI=0.51–0.77) and was not significantly increased versus placebo in studies of extended therapy.<sup>19</sup> In the EINSTEIN DVT and EINSTEIN PE studies, major bleeding was defined as clinically overt and associated with a drop in hemoglobin levels of  $\geq 2.0$  g/dL, bleeding leading to the transfusion of  $\geq 2$  units of red cells, or bleeding occurring in a critical site (eg, intracranial or retroperitoneal) or contributing to death. Nonmajor clinically relevant bleeding did not meet the criteria outlined for major bleeding but was overt and associated with medical intervention, interruption or discontinuation of a study drug, unscheduled contact with a physician, or general discomfort or impairment in daily life.<sup>11,12</sup> In the EINSTEIN pooled analysis, there was a similar incidence of major plus nonmajor clinically relevant bleeding with rivaroxaban compared with standard therapy ( $P=0.27$ ); however, rivaroxaban was associated with a significant 46% relative reduction in the risk of major bleeding (HR =0.54;

95% CI =0.37–0.79;  $P=0.002$ ).<sup>20</sup> In this pooled analysis, major bleeding was also relatively infrequent with rivaroxaban compared with standard therapy in some patient subgroups at high risk, including those defined as fragile (age  $>75$  years, CrCl  $\leq 50$  mL/min, or weight  $\leq 60$  kg; HR =0.27, 95% CI=0.13–0.54,  $P=0.011$ ), and patients with an extensive clot burden (HR=0.36, 95% CI=0.18–0.73),<sup>20</sup> suggesting a broader benefit of treatment with rivaroxaban in high-risk subgroups. In the EINSTEIN EXT study, four of the 598 patients receiving rivaroxaban who were evaluated for safety had major bleeding (versus none with placebo;  $P=0.11$ ).<sup>11</sup> In AMPLIFY, the rates of major bleeding (0.6% vs 1.8%,  $P<0.001$ ) and major plus nonmajor clinically relevant bleeding (4.3% vs 9.7%,  $P<0.001$ ) were significantly lower with apixaban than with standard therapy,<sup>13</sup> whereas in AMPLIFY-EXT the rates of both these outcomes were low and similar to placebo.<sup>17</sup>

In Hokusai-VTE, major bleeding occurred at a similar frequency in the edoxaban and standard therapy arms ( $P=0.35$ ), whereas major plus nonmajor clinically relevant bleeding was significantly lower with edoxaban ( $P=0.004$ ).<sup>14</sup> Broadly the same definitions for major and nonmajor clinically relevant bleeding as for the EINSTEIN studies applied to AMPLIFY and Hokusai-VTE.<sup>13,14</sup> In the pooled RE-COVER and RE-COVER II analysis, major bleeding occurred with a similar incidence in the dabigatran and standard therapy arms (HR =0.73, 95% CI =0.48–1.11), whereas the incidence of major plus nonmajor clinically relevant bleeding was significantly reduced with dabigatran (HR =0.62, 95% CI =0.50–0.76).<sup>16</sup> In the pooled RE-COVER population, the risk of major bleeding with dabigatran compared with warfarin appeared to increase with advancing age ( $P=0.010$  for interaction); overall, however, subgroup analyses showed that dabigatran had a consistent profile regardless of variations in patient demographics and risk factors.<sup>16</sup> In the extension studies, there were two major bleeding events with dabigatran in RE-SONATE, and although the incidence of major plus nonmajor clinically relevant bleeding was significantly higher than that with placebo ( $P=0.001$ ), both major bleeding ( $P=0.06$ ) and major plus nonmajor clinically relevant bleeding ( $P<0.001$ ) were significantly lower with dabigatran than with warfarin in RE-MEDY.<sup>18</sup> In RE-COVER and the extension studies, the same definition was applied for major bleeding, whereas for nonmajor clinically relevant bleeding a slightly different list of criteria applied.<sup>15,18</sup>

## Bleeding management and contraindications with NOACs

Suggested algorithms for the management of bleeding in patients receiving NOACs are available, and these are largely similar to the well-established protocols for conventional

**Table 3** Summary of pharmacological properties of novel oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mode of action	Direct thrombin inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
Approved for VTE treatment in Europe and the US?	Yes	Yes	Yes	Yes
VTE treatment regimen	Parenteral anticoagulant for 5–10 days, then 150 mg bid	15 mg bid for 21 days, then 20 mg od	10 mg bid for 7 days, then 5 mg bid	Parenteral anticoagulant, then 60 mg od
Dose adjustments for VTE treatment	None tested	None mandated <sup>a</sup>	None tested	30 mg od tested in patients who were expected to have an increased bleeding risk <sup>b</sup>
Food	Take with or without food	VTE treatment doses to be taken with food	Take with or without food	Take with or without food
Time to maximum concentration/anticoagulant effect (hours)	0.5–2	2–4	3–4	1–2
Half-life in healthy individuals (hours)	12–14	5–13	~12	8–10
Proportion of drug subject to renal clearance <sup>c</sup> (%)	85	33 <sup>d</sup>	27	35
Co-medications contraindicated/not recommended	Strong P-gp inhibitors and inducers	Strong CYP3A4 and P-gp inhibitors	Strong CYP3A4 and P-gp inhibitors	Strong P-gp inhibitors

**Notes:** <sup>a</sup>A reduced dose of rivaroxaban 15 mg od after the initial period of 15 mg bid dosing (ie, after 21 days) may be considered based on individual patient benefit–risk analysis (Europe only, not tested in Phase III treatment studies); <sup>b</sup>creatinine clearance 30 mL/min–50 mL/min, body weight ≤60 kg, taking co-medications that are potent P-gp inhibitors; <sup>c</sup>unchanged drug; <sup>d</sup>33% of the dose also undergoes renal excretion as inactive metabolites. Data from previous studies.<sup>4,14,23–26</sup>

**Abbreviations:** bid, twice daily; CYP3A4, cytochrome P450 3A4; od, once daily; P-gp, P-glycoprotein; VTE, venous thromboembolism.

anticoagulants.<sup>21,22</sup> However, the pharmacological characteristics of NOACs (summarized in Table 3) provide particular advantages as well as challenges.<sup>4,14,23–26</sup> Their short half-lives, for example (typically in the range of 5 hours–17 hours), are in contrast with the half-life of warfarin (mean =40 hours), meaning that temporary discontinuation may be sufficient to manage nonsevere bleeding. The plasma concentration of a NOAC may need to be measured in an emergency, for example, in cases of suspected overdose or serious bleeding, or when an urgent surgical procedure is required. Prolongation of a dilute thrombin time or ecarin clotting time assay may indicate clinically relevant dabigatran concentrations; an activated thromboplastin time assay may also provide a qualitative indication of dabigatran activity.<sup>27</sup> Specific and quantitative anti-Factor Xa assays exist for apixaban and rivaroxaban, but if these are unavailable, prolongation of a suitably sensitive prothrombin time test can qualitatively indicate the presence of rivaroxaban. (This assay is not suitable for apixaban).<sup>27</sup> Guidance for measuring edoxaban concentrations is currently lacking, but an anti-Factor Xa assay may be appropriate.

Clearance of a NOAC in a patient with renal impairment will take longer, particularly with dabigatran, which

is largely dependent on renal elimination mechanisms. Dabigatran has a renal clearance of ~85%, whereas the values for apixaban and rivaroxaban range between 27% and 33%.<sup>24–26</sup> Renal clearance of VKAs, by contrast, is minimal. For more severe bleeding, usual interventions such as mechanical compression (eg, in cases of epistaxis), fluid replacement, and use of blood products are suggested.<sup>24–26,28–30</sup> Dabigatran can be dialyzed, but the other NOACs, because of their high protein binding, cannot. There is currently no specific reversal agent for any NOAC, although several are in development.<sup>31,32</sup> Idarucizumab, a Fab fragment directed against dabigatran, is in Phase III trials and is likely to be the first such reversal agent approved for use.<sup>33</sup> Currently, if bleeding is considered life-threatening, nonspecific prohemostatic agents, such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant Factor VIIa, may be used based on limited evidence, to be combined with emergency hemodynamic support (Table 4).<sup>24–26,28–30</sup>

The likelihood of bleeding in relation to NOACs can be minimized by assessing each patient's risk of bleeding and avoiding use in patients at known high risk of bleeding. These include patients with CrCl <15 mL/min



**Table 4** Reversal strategies for patients experiencing severe bleeding while receiving a novel oral anticoagulant

Reference	Presentation	Cause of hemorrhage	NOAC and treatment	Outcome
Dunkow et al <sup>15</sup>	An 85-year-old man diagnosed with acute liver failure, acute kidney injury, and anemia	Hemorrhagic shock secondary to bleeding in his upper gastrointestinal tract	<ul style="list-style-type: none"> <li>• Drug: dabigatran</li> <li>• Treatment: PCC, FFP</li> </ul>	The patient's hemoglobin concentration stabilized, and there were no further signs of overt bleeding
Javedani et al <sup>16</sup>	A 54-year-old man who experienced a new-onset stroke with a score of 9 on the National Institutes of Health stroke scale	Potential intracranial hemorrhage	<ul style="list-style-type: none"> <li>• Drug: dabigatran</li> <li>• Treatment: PCC, rFVIIa</li> </ul>	No evidence of intracranial hemorrhage was apparent on repeated computed tomography scans of the brain. The patient was discharged with ASA and warfarin and a stroke score of 8
Molina et al <sup>17</sup>	An 84-year-old woman with dementia, hypertension, diabetes, and chronic obstructive pulmonary disease who fell down some steps	Subarachnoid and intraventricular hemorrhage	<ul style="list-style-type: none"> <li>• Drug: rivaroxaban</li> <li>• Treatment: FFP, vitamin K</li> </ul>	Patient recovered previous neurological function, and warfarin was started 2 weeks–3 weeks later. The authors acknowledge that vitamin K was not appropriate for rivaroxaban reversal
Lakatos et al <sup>18</sup>	A 52-year-old Caucasian man with HIV receiving darunavir/ritonavir therapy	Gastrointestinal hemorrhage indicated by blood in stools; diarrhea, dehydration, and fever	<ul style="list-style-type: none"> <li>• Drug: rivaroxaban</li> <li>• Treatment: interruption of anticoagulant; intravenous hydration and ciprofloxacin 500 mg twice daily</li> </ul>	Resolution of bleeding shortly after interrupting rivaroxaban. Rivaroxaban should not be given concomitantly with HIV protease inhibitors because of a documented drug–drug interaction potential that can lead to elevated rivaroxaban concentrations
Gonzva et al <sup>19</sup>	A 67-year-old man with acute abdominal pain	Splenic rupture	<ul style="list-style-type: none"> <li>• Drug: rivaroxaban</li> <li>• Treatment: packed red blood cells, FFP, and PCC</li> </ul>	Hemorrhagic shock persisted for 12 hours until splenectomy. The patient developed multiorgan dysfunction 2 days later because of colic ischemia and required a colectomy

**Abbreviations:** ASA, acetylsalicylic acid; FFP, fresh frozen plasma; HIV, human immunodeficiency virus; NOAC, novel oral anticoagulant; PCC, prothrombin complex concentrate; rFVIIa, recombinant Factor VIIa.

(recommendations for patients with severe renal impairment [CrCl 15 mL/min–29 mL/min] vary by drug and region, but caution should be exercised even if it is permitted) or severe hepatic impairment (including cirrhotic patients with Child–Pugh score B or C).<sup>24–26,28–30</sup> The presence of a lesion or condition causing a clinically significant risk of major bleeding, such as a current or recent gastrointestinal ulcer, malignant neoplasm, recent brain/spinal injury or surgery, ophthalmic surgery, or recent intracranial hemorrhage, is a contraindication to NOAC treatment.<sup>24–26,28–30</sup> Additionally, NOACs should not be given in combination with other anticoagulants (except when switching between drugs), and concomitant use of antiplatelet agents or nonsteroidal anti-inflammatory drugs increases the risk of bleeding. For rivaroxaban and apixaban, coadministration with strong inhibitors of both P-gp and cytochrome P450 3A4 is not recommended because these agents (mostly azole antimycotics and human immunodeficiency virus protease inhibitors) share the same major elimination pathways, which could lead to increased drug exposure and bleeding risk.<sup>24,25,28,29</sup> Although not a cytochrome P450 3A4 substrate, dabigatran and its prodrug are P-gp substrates, meaning that concomitant administration with strong P-gp inhibitors can lead to clinically relevant increases in dabigatran concentrations.<sup>26,30</sup> Edoxaban clearance is also affected by concomitant strong P-gp inhibitors.<sup>34</sup>

In all cases, the balance between the risk of bleeding and risk of VTE should be the primary factor for deciding whether to give an anticoagulant and for determining the duration of treatment.

## Patient needs in long-term or extended anticoagulation

Patients requiring long-term or extended anticoagulation may find some of the limitations associated with VKA therapy, particularly regular coagulation monitoring and dietary restrictions, inconvenient in their daily lives.<sup>4</sup> In addition to benefits in terms of reduced risk of major bleeding, the NOACs are not subject to these limitations and, therefore, simplify long-term treatment. With rivaroxaban, this has been shown to correlate with a 27% reduction in hospital admissions compared with standard LMWH/VKA treatment for patients with DVT,<sup>35</sup> and a US model has shown that NOACs are cost saving for VTE treatment compared with standard therapy.<sup>36</sup> Patient-reported outcomes including treatment satisfaction were assessed in the EINSTEIN DVT and EINSTEIN PE studies, by using the newly developed and validated Anti-Clot Treatment Scale (ACTS). A greater treatment satisfaction was reported in the rivaroxaban groups of both studies. In EINSTEIN DVT, the mean ACTS Burdens scores were found to be 55.2 versus 52.6 ( $P<0.0001$ ), and overall mean ACTS Benefits scores 11.7 versus 11.5 ( $P=0.006$ ), for rivaroxaban versus enoxaparin/VKA, respectively.<sup>37</sup> A similar trend was seen in the PE population: mean ACTS Burdens scores were found to be 55.4 versus 51.9 ( $P<0.0001$ ), and mean ACTS Benefits scores were 11.9 versus 11.4 ( $P<0.001$ ).<sup>38</sup> The improved patient satisfaction with rivaroxaban reported in these studies<sup>37,38</sup> is likely to have a positive impact on adherence to therapy.<sup>37,38</sup> The use of once-daily regimens for long-term therapy also appears to encourage adherence compared with more frequent dosing.<sup>39</sup> This,

**Table 5** Warfarin drug interaction in cancer therapy

Reference	Presentation	Underlying risk factor for recurrent thrombosis	Treatment	Outcome
Onoda et al <sup>50</sup>	A 74-year-old female patient diagnosed with stage IV bronchioloalveolar carcinoma of the lung. The patient was on long-term warfarin therapy because of persistent atrial fibrillation	Cancer	<ul style="list-style-type: none"> <li>Gefitinib therapy was started</li> <li>The daily warfarin dose was decreased from 4 mg to 3 mg, but the INR increased from 2.0 to 2.4</li> <li>Daily warfarin dose was decreased to 2.5 mg, which returned the INR to the therapeutic range</li> </ul>	The patient's dyspnea was promptly improved, and a chest X-ray taken 6 months after initiation of treatment revealed a considerable improvement of the disease
Saif et al <sup>51</sup>	A 70-year-old female patient newly diagnosed with pancreatic adenocarcinoma was started on anti-cancer treatment until an elevation of the INR was observed	Cancer	<ul style="list-style-type: none"> <li>Immediate cessation of capecitabine and cessation of docetaxel after cycle 9</li> <li>Gemcitabine was continued every 2 weeks with close monitoring of PT/INR</li> <li>Second-line treatment was offered because of deterioration but was not administered</li> </ul>	Elevated INR, progressive disease, and clinical deterioration

**Abbreviations:** INR, international normalized ratio; PT, prothrombin time.

in turn, could reduce not only the risk of recurrent VTE but also the likelihood of long-term complications that can have a significant impact on a patient's quality of life (Table 5).

## Conclusion

To reduce the risk of recurrent VTE and its associated complications, many patients will require long-term or even extended anticoagulation therapy. The limitations of traditional heparin and VKA treatment can be a burden for patients and physicians, but the development of NOACs that are both effective and potentially reduce bleeding risk substantially reduces the impact of long-term anticoagulation. The extension studies for the NOACs showed that a significant residual risk of VTE remained after 6 months–12 months of VKA therapy. Patients who received rivaroxaban or apixaban showed a significant risk reduction for recurrent VTE compared with those receiving placebo. Study outcomes suggest that current recommendations for 3 months or >3 months of therapy could be revised to address the high residual risk of VTE that remains after 6 months–12 months of therapy with VKAs.

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