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Review Article

Extended non-vitamin K antagonist oral anticoagulation therapy for prevention of recurrent venous thromboembolism

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ABSTRACT

Evidence from the use of traditional therapy (low-molecular-weight heparin/vitamin K antagonists) for venous thromboembolism (VTE) treatment and prevention suggests that extending treatment beyond the acute phase reduces recurrence. More recently, several non-vitamin K antagonist oral anticoagulants (NOACs) have been approved in the acute setting; accumulating evidence suggests continuing treatment with these agents beyond 12 months offers additional benefits to patients with VTE.

This review examines the evidence for NOAC use in longer-duration anticoagulation treatment, and discusses guidelines from major societies. Clinical data from the phase III extension studies for apixaban, dabigatran and rivaroxaban are presented, and the clinical and economic costs and benefits are examined. Evidence from other therapy areas utilising extended treatment regimens highlights the possible impact of factors relevant to extended anticoagulation therapy. Phase IV studies of NOACs are presented.

US and European guidelines advise long-term therapy in certain instances, taking into account evidence on NOAC use in VTE accumulated recently. They support NOAC use where they have been selected as the initial therapy choice and therapy needs to be extended beyond 3 months. The phase III extension studies demonstrate the benefits of extended NOAC use versus treatment cessation, with reduced recurrence rates versus placebo, although associated with a potential moderate increase in bleeding risk. Phase IV data are also emerging, with the recent XALIA study showing that a broad range of patients with VTE can benefit from continued rivaroxaban treatment; ongoing research will yield data on long-term use of the other NOACs in routine clinical practice.

Contents

Abbreviations: ACCP, American College of Chest Physicians; Bid, twice daily; CI, confidence interval; DVT, deep-vein thrombosis; ESC, European Society of Cardiology; LMWH, low-molecular-weight heparin; NICE, National Institute for Health and Care Excellence; NOAC, non-vitamin K antagonist oral anticoagulants; od, once daily; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

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1. Introduction

Venous thromboembolism (VTE), comprising deep-vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease [1]. The incidence rate among the general population is 1–2 cases per 1000 people, and the risk of VTE recurrence increases with advancing age [2,3]. Standard therapy for treatment and prevention of VTE has historically involved heparin/fondaparinux followed by and overlapping with a vitamin K antagonist (VKA) [4]. Recently, several non-VKA oral anticoagulants (NOACs; apixaban, dabigatran, edoxaban and rivaroxaban) have been approved in this setting, after the respective phase III and extension trials demonstrated the efficacy and safety of these agents in VTE treatment and prevention of recurrent events [5–11].

2. Rationale for extended treatment

Duration of anticoagulation can be categorised into initial treatment, lasting 3–6 months, and long-term treatment lasting beyond 3–6 months (although there is variation between authors on these terms, e.g. some describe therapy beyond 3 months with no scheduled stop date as extended therapy) [4,12]. There is a strong rationale for anticoagulation treatment beyond the acute phase in many patients with VTE, because the risk of recurrent VTE after stopping anticoagulation treatment is high, particularly for unprovoked DVT (~40% at 10 years) (Fig. 1) [13]. Extended warfarin treatment for 12 months versus 3 months after unprovoked proximal DVT was associated with a reduced rate of VTE recurrence; furthermore, this clinical benefit was not maintained after cessation of anticoagulation treatment at 12 months [14]. Similar outcomes have been seen for patients with PE receiving warfarin versus placebo for 18 months after completing 6 months of VKA treatment. Again, the clinical benefit did not persist after cessation of treatment at 18 months [15]. Long-term low-intensity warfarin (target international normalised ratio of 1.5–2.0) for treatment of unprovoked VTE also reduced rates of the composite endpoint of recurrent VTE, major haemorrhage and death versus placebo; the randomised trial was terminated early by an independent safety monitoring board because the benefits were so pronounced in the absence of any obvious harms [16]. However, there are currently no studies supporting the safety and efficacy of extended anticoagulant treatment beyond 2 years, although the risk of recurrence has been shown to decrease after 5 years (Fig. 1) [13]. This suggests that the net clinical benefit of extended anticoagulation may be different for the first 5 years compared with the period thereafter. Physicians should be aware of this possibility when considering whether to treat patients for an indefinite period.

The relative effectiveness of standard treatments has also been compared, with some studies showing a similar impact between low-molecular-weight heparin (LMWH) and VKAs on recurrent VTE rates [17]. However, patient demographics and clinical characteristics may also influence treatment effectiveness in extended or long-term anticoagulation. In patients with VTE and cancer, which is a major risk factor for recurrent VTE, extended treatment with LMWH reduced rates of recurrent VTE (although not mortality) versus VKAs [18]. Other agents have also been tested for extended anticoagulation. The Van Gogh Extension study compared 6 months of treatment with the Factor Xa inhibitor idraparinux with placebo in patients who had previously completed 6 months of anticoagulation therapy [19]. Rates of recurrent VTE were lower in the idraparinux group; however, there was a higher rate of major bleeding with idraparinux than with placebo.

These findings highlight that there is a good basis for extended or long-term anticoagulation treatment in VTE. Given the clear benefits shown with standard therapeutic options, looking at the potential role for the NOACs in these settings is of interest. This review will discuss the current guidelines, phase III data, risks and benefits, and evidence from routine clinical practice relating to anticoagulation beyond the acute phase with the NOACs.

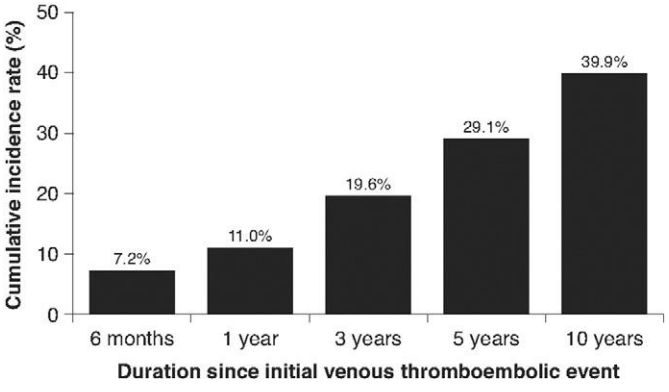

Fig. 1. VTE recurrence risk in patients with unprovoked DVT. DVT, deep-vein thrombosis; VTE, venous thromboembolism [Single column].

3. Evidence for non-vitamin K antagonist oral anticoagulants for long-term anticoagulation

Most evidence regarding the rationale for extended treatment has been derived from studies using VKAs [13,14,16]; however, of the four NOAC extension studies reported to date, only one has compared a NOAC with a VKA [11]. The American College of Chest Physicians (ACCP) guidelines recommend extended anticoagulation in certain patients [4,20]. The decision depends on whether the DVT is proximal or distal, whether the patient has active cancer and whether VTE was provoked (e.g. as a result of surgery or a non-surgical transient risk factor). For example, extended or longer-term treatment is advised for a first unprovoked proximal VTE provided the patient's bleeding risk is low or moderate; in patients with a higher bleeding risk, anticoagulation is only recommended for 3 months. The strength of these recommendations also varies: the former advice is given an evidence rating of 2B, meaning that it is only a weak recommendation based on moderate-quality evidence; however, the latter is graded as 1B, meaning that although the evidence quality is moderate, the strength of the recommendation is high.

The ACCP makes specific therapy recommendations for extended anticoagulation. The 2012 guidelines generally favoured the use of a VKA over LMWH for patients without cancer, and LMWH over VKAs for patients with cancer; VKAs were recommended over dabigatran or rivaroxaban (apixaban and edoxaban were not approved for VTE treatment and prevention at the time of publication of these ACCP guidelines) in patients with or without cancer, owing to the paucity of post-authorisation data. The recent 2016 update accounts for the interim accumulation of evidence on the NOACs in this setting [20]. The update advises that NOACs are preferred to VKAs for the first 3 months of treatment in patients with DVT of the leg or PE with no cancer. For patients with cancer-associated thrombosis, LMWH is advised over VKAs or the NOACs. For extended or long-term therapy beyond 3 months, it is recommended to continue with the initial therapy choice. In most cases, anticoagulation for 3 months is advised over long-term treatment (no scheduled stop date). The exceptions to this are patients with: a first unprovoked proximal DVT of the leg or PE and a low or moderate bleeding risk, a second unprovoked VTE and a low or moderate bleeding risk and patients with cancer-associated thrombosis. Owing to the lack of head-to-head comparisons between the NOACs and an insufficient amount of indirect evidence, the guidelines do not state a preference for a specific NOAC; instead, they advise that drug-specific adverse events, local cost/coverage issues and patient preference should be considered as factors influencing NOAC choice.

In Europe, the European Society of Cardiology (ESC) published guidelines in 2014 for the acute management of PE [21]. These also

include recommendations on longer-duration anticoagulation, because the authors acknowledge that some patients will benefit from treatment beyond the 3-month initial phase and may require extended or long-term anticoagulation treatment. In both situations, weighing of the benefits versus potential bleeding risk is necessary. Candidates identified as being likely to need indefinite treatment are cancer patients and those who have experienced an unprovoked proximal DVT or PE and who are at a low risk of bleeding. It is important to note that indefinite treatment is not synonymous with lifetime treatment, but instead means that the duration of therapy cannot be predetermined; however, lifetime treatment is advised for most patients with a second unprovoked event. The ESC guidelines also address extended/long-term treatment with the NOACs, concluding that it is effective and safe (and probably safer than standard VKA regimens). The authors recommend considering apixaban, dabigatran or rivaroxaban as options instead of VKAs when anticoagulation is required (Class IIa, Evidence Level B; meaning that the weight of evidence or opinion is in favour of the therapy's efficacy, and the data are derived from a single randomised trial or large non-randomised studies).

The National Institute for Health and Care Excellence (NICE) in the UK has also published guidelines with recommendations for extended/long-term treatment of VTE [22]. VKA treatment may be offered beyond 3 months for patients experiencing unprovoked PE and considered for unprovoked proximal DVT. In both cases, the risks of bleeding and recurrent VTE should be taken into consideration, and the benefits and risks discussed with the patient.

Several prospective and retrospective bleeding risk assessment tools are available, with each based upon individual risk factors from dissimilar patient populations with varying primary events, ages, and co-morbidities, and derived from clinical trial or real-life data. Although these tools can provide insight into the potential risks of therapy, selecting the most appropriate bleeding risk stratification model to use for each patient can be a challenge for physicians. This is especially the case when the risk assessment tools are being used to determine the risks of extended/long-term treatment of VTE. A previous study noted that out of six different bleeding risk stratification models evaluating elderly patients (≥80 years) with VTE for low/medium/high risk of bleeding, none were accurate in predicting the observed bleeding risk [23].

4. Benefits of non-vitamin K antagonist oral anticoagulants for long-term anticoagulation

The NOACs offer a range of potential benefits for long-term anticoagulation (Table 1). The lack of requirement for regular coagulation monitoring reduces the burden on both patients and healthcare systems. Oral routes of administration are also generally preferred to injections by most patients [24–26], and oral administration is more suitable than frequent injections for long-term use (in the initial phase of acute treatment, parenteral injections [e.g. heparin or fondaparinux] are required for a short lead-in period of ≥5 days before commencing dabigatran or edoxaban, but apixaban and rivaroxaban can be initiated without prior treatment with other agents). Food–drug and drug–drug interactions with the NOACs also appear to be limited compared with VKAs (although oral bioavailability of rivaroxaban is reduced in fasting conditions at doses of 15 and 20 mg), meaning that dietary adjustments are not required and NOACs are generally suitable for patients being treated for co-morbidities.

Table 1
Potential benefits and risks of long-term anticoagulation treatment.

Benefits	Risks
Oral route of administration	Increased bleeding rates
Limited food–drug and drug–drug interactions	Adherence/persistence issues
Reduced economic/healthcare burden	Over- or under-prescribing
Reduced VTE recurrence risk	
Anticoagulation monitoring not required	

VTE, venous thromboembolism.

A second consideration involves the economic benefits that extended treatment with NOACs may provide. Both DVT and PE are associated with substantial costs, and recurrent episodes increase costs further. Most of these costs are attributable to hospitalisation, the treatment facility and staff and outpatient management [27,28]. Rivaroxaban reduces the frequency and duration of hospitalisations versus standard anticoagulation in the acute treatment of patients with DVT and PE [29,30], whereas acute apixaban treatment for VTE reduces hospitalisations and time to first hospitalisation [31]. The lack of routine coagulation monitoring needed with use of NOACs may also simplify patient management, thereby further reducing the burden on healthcare providers and patients.

Data are accumulating that demonstrate the clinical benefit of the NOACs in long-term treatment. Recently, apixaban, dabigatran and rivaroxaban have been studied in this setting in a series of extension studies (AMPLIFY-EXT, RE-MEDY and RE-SONATE, and EINSTEIN EXT, respectively) involving continued treatment of patients who had already been receiving anticoagulation treatment (Table 2) [9–11].

AMPLIFY-EXT evaluated patients who had completed 6–12 months of anticoagulation treatment with apixaban, and for whom either continuation or cessation of treatment was an option [10]. Patients received either a further 12 months of apixaban at a dose of 2.5 mg or 5 mg twice daily, or placebo. Rates for the primary endpoint of recurrent VTE or mortality from any cause were 3.8%, 4.2% and 11.6%, respectively (relative risk [95% confidence interval (CI)] vs placebo: 0.33 [0.22–0.48] and 0.66 [0.25–0.53], respectively); for major bleeding, rates were 0.2%, 0.1% and 0.5%, respectively (relative risk [95% CI] vs placebo: 0.49 [0.09–2.64] and 0.25 [0.03–2.24], respectively).

In RE-MEDY, an active control study of dabigatran, patients received either dabigatran (150 mg twice daily) or warfarin for 6–36 months after at least 3 months of prior anticoagulation treatment [11]. Recurrent or fatal VTE occurred in 1.8% of patients treated with dabigatran versus 1.3% of warfarin-treated patients ($P = 0.01$ for non-inferiority); major bleeding rates were numerically lower with dabigatran (0.9% vs 1.8%) but this difference was not statistically significant.

In the placebo-controlled RE-SONATE study, dabigatran (150 mg twice daily) or placebo was administered for up to 12 months [11]. Rates of recurrent or fatal VTE were significantly lower with dabigatran (0.4% vs 5.6%; $P < 0.001$). Rates of major bleeding were low in both groups (0.3% with dabigatran; no major bleeding episodes occurred in the placebo group); however, for the composite of major or non-major clinically relevant bleeding, the rate was significantly greater with dabigatran (5.3% vs 1.8%; $P = 0.001$).

In EINSTEIN EXT, patients who had completed 6–12 months of rivaroxaban or VKA anticoagulation treatment were randomised to receive either rivaroxaban or placebo for 6 or 12 months [9]. Extended rivaroxaban treatment was associated with a significantly lower rate of recurrent VTE (1.3% vs 7.1%, respectively; $P < 0.001$), although there was a moderate, but non-significant, increase in the rate of major bleeding complications (0.7% of patients in the rivaroxaban group vs none in the placebo group; $P = 0.11$) [9].

For each of the extension studies, special patient groups (e.g. those with co-morbidities or cancer, or the elderly) were only lightly represented, and patients with severe renal dysfunction were excluded; therefore, further investigation is needed in these patients. Some authors have attempted to draw comparisons between the individual NOACs based on the phase III acute-phase study results, despite differences in study designs, eligibility criteria, patient baseline demographics and clinical characteristics [32,33]. For the same reasons, attempts to conclude superiority of an individual NOAC versus the others for long-term treatment of VTE based on comparisons of their respective extension study results must be treated with a high degree of caution. Despite this, the general conclusion that can be drawn from the extension studies is that NOACs are associated with low rates of recurrent VTE and

Table 2
Comparison of key details of the NOAC extension studies.

	AMPLIFY-EXT	RE-MEDY	RE-SONATE	EINSTEIN EXT
Therapy	Apixaban	Dabigatran	Dabigatran	Rivaroxaban
Dosing regimen	2.5 mg bid 5 mg bid	150 mg bid	150 mg bid	20 mg od
Comparator	Placebo	Warfarin	Placebo	Placebo
Duration	12 months	6–36 months	Up to 12 months	6 or 12 months
Inclusion criteria	Patients with VTE aged ≥18 years who received 6–12 months of anticoagulation treatment	Patients with symptomatic VTE aged ≥18 years who had received 3–12 months of anticoagulation treatment	Patients with symptomatic VTE aged ≥18 years who had received 6–18 months of anticoagulation treatment	Patients with symptomatic VTE who were of the legal age for consent and had received 6–12 months of anticoagulation treatment
Mean age (years)[a]	Apixaban 2.5 mg: 56.6 ± 15.3 Apixaban 5 mg: 56.4 ± 15.6	55.4 ± 15.0	56.1 ± 15.5	58.2 ± 15.6
Unprovoked VTE, n (%)	Apixaban 2.5 mg: 783 (93.2) Apixaban 5 mg: 737 (90.7) Placebo: 755 (91.1)	NR	NR	Rivaroxaban: 440 (73.1) Placebo: 441 (74.2)
Design	Randomised, double-blind, superiority	Randomised, double-blind, non-inferiority	Randomised, double-blind, superiority	Randomised, double-blind, superiority
Primary endpoint(s)	Recurrent VTE or death from any cause, major bleeding	Recurrent VTE or VTE-related death	Recurrent VTE or VTE-related death	Recurrent VTE, major bleeding
Primary endpoint met, n (%)	Recurrent VTE or death from any cause Apixaban 2.5 mg: 32 (3.8) Apixaban 5 mg: 34 (4.2) Placebo: 96 (11.6) Major bleeding events Apixaban 2.5 mg: 2 (0.2) Apixaban 5 mg: 1 (0.1) Placebo: 4 (0.5)	Recurrent or fatal VTE: Dabigatran: 26 (1.8) Warfarin: 18 (1.3)	Recurrent or fatal VTE, or unexplained death: Dabigatran: 3 (0.4) Placebo: 37 (5.6)	Symptomatic, recurrent VTE: Rivaroxaban: 8 (1.3) Placebo: 42 (7.1) Major bleeding events Rivaroxaban 20 mg: 4 (0.7) Placebo: 0 (0.0)

Bid, twice daily; NOAC, non-vitamin K antagonist oral anticoagulant; NR, not reported; od, once daily; VTE, venous thromboembolism.
[a] NOAC arm only.

major bleeding. In addition, based on outcomes in patients given placebo, it is clear that for all patients with VTE (not only those in special patient groups) not prescribing anticoagulation treatment is not a viable approach. This is particularly the case in high-risk patients; for example, patients with impaired renal function (creatinine clearance <80 ml/min) receiving placebo had much higher rates of VTE recurrence compared with patients receiving NOACs (range 6.5–10.9% vs 0.5–2.2%, respectively) but lower rates of bleeding events (range 1.2–4.3% vs 5.3–15.4%, respectively) [9–11].

Venous thromboembolic events are either unprovoked (idiopathic) or provoked (due to risk factors, e.g. hospitalisation, surgery, or pregnancy). Patients with an unprovoked index event have a higher risk of recurrent VTE, especially during the first year after the initial anticoagulation treatment has been stopped [34]. For example, the cumulative risks of recurrence at 1, 5, and 10 years after an unprovoked versus provoked VTE were 15% versus 7%, 41% versus 16%, and 53% versus 23%, respectively [13]. When selecting a treatment strategy, the risk of VTE recurrence must be balanced against the risk of bleeding for each patient. In addition, a lack of consensus on the duration of anticoagulation treatment to prevent recurrent VTE, and differing treatment burden for each patient, means that the most appropriate treatment strategy may not always be clear. For those patients with unprovoked VTE at high risk of a recurrent venous thromboembolic event and at low or moderate risk of bleeding, the improved benefit–risk profile of NOACs may enable long-term anticoagulation treatment, with regular assessments to monitor the benefit–risk ratio. Although treatment duration is usually limited to 3 months for provoked VTE, if the index event was life-threatening or extensive, extended anticoagulation is recommended, and once again, the improved benefit–risk profile of NOACs may be preferred over VKAs.

5. Potential issues with long-term anticoagulation

Clinicians need to balance the long-term risk of VTE recurrence if anticoagulation treatment is stopped versus the burden and risks of ongoing treatment, because, in addition to the established benefits, there are also potential issues with long-term use of anticoagulation.

One issue with anticoagulation therapy is the process of reliably identifying patients who would benefit from long-term treatment. VTE recurrence risk can be assessed via laboratory methods, including assays for D-dimer. D-dimer levels are significantly associated with VTE recurrence risk after adjustment for confounders [35]; however, there is wide inter-laboratory variation in D-dimer assessments [36]. This could result in over- or under-statement of the risk of VTE recurrence. In the former instance, this could result in unnecessary prescribing, putting patients at risk of bleeding without discernible benefit. Similarly, under-prescribing on the basis of inaccurate D-dimer testing results could mean that patients who stand to benefit from long-term anticoagulation do not receive it. There are three available algorithms (the HERDOO2 model, the Vienna prediction model and the DASH score) that can help identify those patients with a high risk of VTE recurrence who might need long-term treatment [37]. Male sex and elevated D-dimer levels have been identified in all three models as being important risk factors for recurrence, although the models differ subtly. The HERDOO2 model measures D-dimer levels during anticoagulation (not after its withdrawal) and suggests that age > 65 years is a risk factor for recurrence, unlike the DASH score, which attributes age < 50 years to a higher risk of recurrence. The complexity of the Vienna model means that it may not be the most suitable algorithm for routine use [37].

Adherence is also a concern for patients with chronic illnesses requiring long-term treatment. In many such diseases (e.g. diabetes, hypertension) adherence is often poor, impacting on treatment outcomes and increasing healthcare costs [38–40]. Although the lack of requirement for routine coagulation monitoring offers advantages for simplified patient management and reduced healthcare resource use, the downside is that lack of regular monitoring may make it difficult to ensure that patients take medication as prescribed. Poor adherence is likely to increase the chance of recurrent VTE and the associated costs. Despite this concern, NOACs have qualities that lend themselves to improving adherence, such as relatively simple dosing regimens and an oral route of administration. Well-developed outpatient management programmes, strategies aimed at enhancing adherence and protocols for identifying patients most at risk of poor

adherence can all play a part in ensuring good compliance with NOAC treatment regimens.

As noted above, another potential issue regarding long-term anticoagulation with NOACs is the possibility of an increased risk of bleeding episodes, although the evidence for this is mixed. In AMPLIFY-EXT, rates of major and non-major clinically relevant bleeding were not significantly different between either the 2.5 mg or 5 mg dose of apixaban and placebo. In RE-MEDY, extended dabigatran use carried a numerically lower risk of major bleeding versus warfarin (the risk was significantly lower for the composite of major bleeding plus non-major clinically relevant bleeding than with warfarin). In comparison with placebo in RE-SONATE, however, numerically more major bleeding incidents occurred with dabigatran (although this was not statistically significant), and the risk of major or non-major clinically relevant bleeding was significantly greater with dabigatran. In EINSTEIN EXT, major bleeding rates were similar between rivaroxaban and standard anticoagulation; however, rates of non-major clinically relevant bleeding were higher with rivaroxaban (5.4% vs 1.2%), although this latter finding may be explained in part by the open-label study design. These points also highlight that estimating benefit–risk is needed for extended/long-term anticoagulation, although it is not often done.

6. Phase IV and ongoing studies of long-term anticoagulation

Data from routine clinical practice on NOAC use for VTE treatment and prevention are limited. In addition to clinical trials of extended anticoagulation, assessment of this therapy in routine clinical practice is essential. This is to confirm whether the results of clinical trials apply to a broad range of patients beyond the highly controlled setting of a clinical study. This is essential, because patients receiving co-medications or with certain co-morbidities are often excluded from clinical trials, but patients with these characteristics can pose difficulties for extended anticoagulation in the daily care setting. Recent data are available from the Dresden NOAC Registry (a multicentre, single-region registry in Germany) [41]. In this registry, follow-up data were available for 1775 (100%) enrolled patients who were treated with rivaroxaban. Almost one-third (32.4%) of these patients received rivaroxaban for the prevention of recurrent VTE; the median treatment duration was 9 months, with an annual major bleeding rate of 4.1% (95% CI 2.5–6.4) [41]. Compared with EINSTEIN EXT, patients in the Dresden NOAC Registry were older and had higher rates of renal insufficiency (creatinine clearance or glomerular filtration rate < 50 ml/min); these characteristics may explain the relatively high rates of major bleeding observed in the Dresden NOAC Registry.

The international, multicentre, non-interventional XALIA study, comparing rivaroxaban with standard anticoagulation, was completed recently [42]. Patients with DVT alone or with concomitant PE were enrolled (patients with isolated PE were not eligible); the observation period ended 12 months after final enrolment, meaning that each patient had at least 12 months of follow-up. The enrolment period for XALIA was ~21 months (June 2012–March 2014); therefore, patients could potentially be followed up for as long as 33 months. The median follow-up was 239 days (interquartile range 154–388 days) and the median duration of treatment was 181 days (interquartile range 94–310 days) in patients receiving rivaroxaban. XALIA demonstrated that the single-drug approach with rivaroxaban was associated with low rates of recurrent VTE and major bleeding, and was a safe and effective alternative to standard anticoagulation in a broad patient population. The rate of recurrent VTE for rivaroxaban compared with standard anticoagulation therapy was 1.4% versus 2.3% (propensity score-adjusted hazard ratio 0.91; 95% CI 0.54–154]; P = 0.72), and the frequency of major bleeding was 0·8% and 2·1%, respectively (propensity score-adjusted hazard ratio 0.0.77; 95% CI 0.40–1.50; P = 0.44) [42]. These findings were consistent with those of the phase III EINSTEIN DVT study, and suggest that longer-duration anticoagulation treatment with rivaroxaban may, therefore, be of benefit to patients with DVT. Phase IV data on extended apixaban, dabigatran or edoxaban use are currently lacking, and what data are available are focused on prevention of stroke in patients with atrial fibrillation rather than treatment of VTE [43,44].

EINSTEIN CHOICE will also provide information on extended anticoagulation [45]. The study is a randomised, double-blind, multicentre trial of two doses of rivaroxaban (20 mg once daily and 10 mg once daily) versus acetylsalicylic acid. All treatments will be administered for 12 months after completion of 6–12 months of anticoagulation treatment for the index acute venous thromboembolic event. The aim is to establish whether the lower dose of rivaroxaban has the potential to maintain high efficacy while further improving the safety profile and to determine the efficacy of rivaroxaban versus acetylsalicylic acid for the prevention of recurrent VTE. This study aims to further expand understanding of the long-term treatment of VTE, thereby allowing physicians to tailor treatment based on a patient's individual profile. The estimated completion date of the study is October 2016.

7. Conclusions

Many patients will gain from longer-term anticoagulation treatment for recurrent VTE. Studies involving standard therapies show clear benefits versus placebo or stopping treatment, and the phase III NOAC extension studies confirm the safety and efficacy of prolonged use of apixaban, dabigatran and rivaroxaban. When deciding on long-term anticoagulation, physicians and patients may opt for NOACs, because their characteristics may be considered preferable to standard treatment options, as well as offering possible economic benefits.

Resources should be directed at developing strategies to improve treatment adherence in order to enhance the likelihood of patients receiving the full benefits of long-term anticoagulation treatment. Concerted efforts should also be made to ensure better accuracy and compliance with standard operating procedures for laboratory risk assessment methods, because these play an important role in the identification of patients who are most likely to benefit from extended treatment. It is also essential to identify factors that may limit the adoption of long-term anticoagulation in clinical practice, such as the complexity of assessing bleeding risk in patients with VTE. The development of simplified risk assessment tools in order to accurately assess the risks of long-term anticoagulation treatment could help to address this issue.

Finally, future studies involving broader patient populations in routine clinical practice to complement the findings from phase III extension studies will be valuable in determining the safety and effectiveness of long-term NOAC use in patients with VTE.

Disclosures

Both authors contributed to the development of this manuscript and are fully responsible for all contents. FP has participated in speaker's board and advisory board meetings for: Aspen, Bayer, Boehringer Ingelheim, Pfizer-Bristol-Myers Squibb and Portola. DII has no disclosures.

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