EXPERT REVIEWS

Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-Extension study)

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Over recent years, research on anticoagulant drugs has been guided by the requirement for convenient administration and a wide therapeutic window to allow fixed dosing without the need for coagulation monitoring. Rivaroxaban is the first of a new class of anticoagulant drugs, the direct, selective inhibitors of Factor Xa. The EINSTEIN-Extension study compared rivaroxaban with placebo in patients who completed their standard treatment course after venous thromboembolism (VTE), in whom there was equipoise with respect to the need for continued anticoagulation. After 6–12 months of treatment, rivaroxaban significantly reduced the risk of recurrent VTE at the cost of a moderate increase in bleeding complications. Overall, these results suggest that rivaroxaban can be a valid alternative to warfarin for patients requiring long-term secondary prevention of VTE. However, additional data are needed for special populations including the elderly, patients with cancer, renally impaired patients and morbidly obese patients, all of whom were scarcely represented in this trial.

Keywords: oral anticoagulants • pulmonary embolism • recurrence • rivaroxaban • venous thromboembolism

Until recently, the only available anticoagulant drugs for the treatment of venous thromboembolism (VTE) were represented by either unfractionated or low-molecular-weight heparins, and vitamin K antagonists (VKAs). More recently, the new synthetic, selective Factor Xa (FXa) inhibitor fondaparinux was approved for clinical use. All these drugs have been proven to be highly effective for the acute and long-term treatment of VTE, but they also have a number of drawbacks. Both heparins and fondaparinux are administered parenterally and are therefore not optimal for long-term use, while VKA presents unpredictable pharmacokinetic (PK) and pharmacodynamic (PD) features with several food and drug interactions and a narrow therapeutic window that requires frequent laboratory monitoring. Thus, the management of patients on VKA treatment is cumbersome, and also in specialized settings only approxmately half of international normalized ratio values are within the therapeutic range [1]. The quality of the international normalized ratio control is clinically relevant, since the time spent within the therapeutic range is inversely correlated with the incidence of thromboembolic or hemorrhagic events [2].

Because patients with VTE have a considerable long-term risk of recurrence, secondary prevention with VKA is usually prescribed for a minimum of 3 months and, in some cases, life-long. The results of a long-term, prospective cohort study of patients with VTE showed a cumulative incidence of recurrent events of 11% within 1 year after stopping VKA, 29.1% within 5 years and 39.9% within 10 years [3]. This risk of recurrence greatly varies across different subgroups of patients, mainly depending on the presence or absence of major identifiable risk factors for VTE at the time of the index event. Clinical studies have shown that within 1 year of stopping anticoagulant therapy, the cumulative incidence of recurrent VTE events is approximately 3% when VTE occurs in association with

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a major, removable risk factor (usually defined as recent major surgery, major trauma or fracture, pregnancy or puerperium or hormonal therapy) [4], 15% in the absence of identifiable risk factors, thus when the event is apparently unprovoked [3], and up to 27% when VTE is associated with active cancer [5]. Based on this simple stratification of VTE patients, current clinical practice guidelines recommend different durations of secondary prevention with VKA: 3 months for patients with VTE associated with a transient risk factor; indefinitely in presence of a permanent risk factor (e.g., cancer, antiphospholipid syndrome); and at least 3 months, but possibly indefinitely based on the individual risk–benefit profile in patients with unprovoked VTE [6]. According to these recommendations, a substantial proportion of patients with VTE should receive extended treatment with VKA, given that up to 50% of VTE events remain classified as unprovoked [3], and 10–20% are associated with cancer [7] or, less frequently, with severe thrombophilia.

In recent years, research on anticoagulant drugs has been guided by the requirement for convenient administration with predictable PK, PD and a wide therapeutic window that would permit fixed dosing without the need for coagulation monitoring. This research has, in particular, focused on selectively targeting thrombin (Factor IIa) and FXa, which are common to both the intrinsic and extrinsic coagulation pathways [8]. Rivaroxaban is the first of the new class of oral FXa inhibitors.

Rivaroxaban (BAY 59–7939) is a potent and selective FXa inhibitor with oral route of administration and a high bioavailability [9,10]. The drug inhibits not only free FXa, but also prothrombinase activity and clot-associated FXa activity, which prevents clot-associated FXa from activating prothrombin and thereby contributing to the propagation of thrombosis [11]. Rivaroxaban is well tolerated, has a rapid onset of action with a predictable dose proportional PD and PK [12]; its half-life is approximately 5–9 h in healthy subjects and it is mainly excreted via the kidneys, although it is also expelled via the fecal/biliar route [13]. Coadministration with food intake only slightly increases peak plasma concentrations of rivaroxaban [14], and only low potential interactions with other drugs have been shown [14]. Phase I studies demonstrated that gender and bodyweight did not have a clinically relevant influence on the PK and PD of rivaroxaban in healthy subjects, suggesting that this drug could be administered at a fixed dose in any patient [15,16]. Phase II clinical trials evaluated rivaroxaban for the treatment of deep venous thrombosis (DVT) with total daily doses ranging from 20 to 60 mg [17,18], and on the basis of the positive results of these studies, rivaroxaban was further investigated for the treatment of VTE in Phase III studies, the EINSTEIN studies.

EINSTEIN program

The role of rivaroxaban for the treatment of VTE was investigated in three large randomized trials in the EINSTEIN program: the EINSTEIN-DVT study was planned to probe the role of rivaroxaban as a standalone drug for the treatment of acute DVT [19]; the ongoing EINSTEIN-PE study is evaluating the role of rivaroxaban for the treatment of acute pulmonary embolism (PE); and the EINSTEIN-Extension study was designed to evaluate extended anticoagulant treatment with rivaroxaban in patients who have been treated for acute VTE [19].

Design of the EINSTEIN-Extension study

The EINSTEIN-Extension study was planned to assess the benefit to risk ratio of prolonged treatment with rivaroxaban after an initial course of anticoagulant treatment in patients with VTE.

This was a randomized, double-blind, placebo-controlled superiority study in which patients who completed the first 6–12 months of oral anticoagulant treatment with VKA or with rivaroxaban (if previously enrolled in the EINSTEIN-DVT or EINSTEIN-PE studies) after symptomatic DVT or PE were randomly assigned to receive prolonged treatment with rivaroxaban 20 mg once daily or with placebo for an additional 6 or 12 months.

The primary efficacy outcome of the study was the incidence of symptomatic recurrent VTE, defined as the composite of objectively diagnosed DVT and/or nonfatal or fatal PE. Secondary outcomes included all-cause mortality and cardiovascular events (i.e., acute coronary syndrome, ischemic stroke, transient ischemic attack or systemic embolism). Principal safety outcome was major bleeding, defined as overt bleeding associated with a fall in the hemoglobin level at least of 20 g per liter or if it led to transfusion of two or more units of red cells or if it occurred in a critical site or contributed to death. Finally, the net clinical benefit of treatment with rivaroxaban, derived from the composite of the primary efficacy outcome and major bleeding, was calculated for all patients.

Study population

The EINSTEIN-Extension study selected patients with objectively confirmed symptomatic DVT or PE after the completion of the initial treatment period if the investigators believed there was equipoise with respect to the need for continued anticoagulation.

Patients with another indication for a VKA, with severe renal insufficiency or clinically significant liver disease, bacterial endocarditis, active bleeding or high risk of bleeding, uncontrolled arterial hypertension, concomitant pregnancy or breast feeding, and coexistent use of strong cytochrome P450 3A4 inhibitors or inducers were not included in the study.

Results

A total of 1197 patients were enrolled in the study, of whom 34.1% had completed the EINSTEIN-DVT study, 19.1% had completed the EINSTEIN-PE study, and 47.5% came from routine care. Baseline characteristics were well balanced between groups. The mean age of the patients was 58 years; 38% of patients had PE; approximately 73% of patients had an unprovoked event and 4–5% had active cancer; approximately 18% of patients in the rivaroxaban group and 14% in the placebo group had a previous VTE event.

The primary efficacy outcome occurred in eight out of 602 patients (1.3%) in the rivaroxaban group and in 42 out of 594 patients (7.1%) in the placebo group, for a hazard ratio (HR) of 0.18 (95% CI: 0.09–0.39). The principal safety outcome, represented by major bleeding, occurred in four patients (0.7%) in the

rivaroxaban group and in no patients in the placebo group (p = 0.11). Clinically relevant nonmajor bleeding occurred in 32 patients (5.4%) in the rivaroxaban group and in seven patients (1.2%) in the placebo group. The net clinical benefit, defined as the composite of the primary efficacy outcome and major bleeding, occurred in 12 patients (2.0%) receiving rivaroxaban and in 42 patients (7.1%) receiving placebo, for a HR of 0.28 (95% CI: 0.15–0.53). With regard to secondary outcomes, there were few cases of death (one in the rivaroxaban group and two in the placebo group) and cardiovascular events (three in the rivaroxban group and four in the placebo group), without any statistically significant difference between the two study groups. Finally, there were no concerns with the use of rivaroxaban regarding liver dysfunction.

Study conclusion

The results of the EINSTEIN-Extension study show that rivaroxaban is an effective anticoagulant agent for the long-term secondary prevention of VTE in moderate to high-risk patients, without safety concerns in terms of nonbleeding adverse events. With regard to bleeding complications, it should be noted that major bleeding events were uncommon, although, as expected, the composite of major bleeding and clinically relevant nonmajor bleeding was significantly higher than in the placebo group. The authors calculated that, overall, prolonged treatment with rivaroxaban prevented 34 recurrent events at the cost of four major bleeding events.

Reported subgroup analyses, which are based on a limited number of patients, suggested that rivaroxaban does not require dose adjustments according to age, sex, weight or renal function, and there was no suggestion of drug-induced liver toxicity.

Expert commentary

The EINSTEIN-Extension study substantially demonstrates that rivaroxaban can reduce the rate of long-term recurrent VTE in patients with a previous episode at the cost of a moderate increase in bleeding complications. Since international guidelines on the treatment of VTE now recommend that a substantial proportion of patients with VTE should receive indefinite treatment with VKA [6], this study may contribute to improve long-term secondary prevention strategies. In fact, the availability of new anticoagulant drugs (besides rivaroxaban, novel anticoagulants dabigatran, apixaban and edoxaban are under Phase III investigatons) with a convenient route of administration, and a single, fixed daily dose that applies to all patients irrespectively of bodyweight or age and do not require routine laboratory monitoring, undoubtedly will offer several advantages to both patients and physicians. In particular, the availability of such drugs may reduce, in patients for whom there is equipoise with respect to the need for continued anticoagulation, the possibility of premature discontinuations induced by the difficult management of the treatment with VKA. On the other hand, given that the optimal duration of secondary prevention in particular in patients with unprovoked VTE is poorly defined, the availability of simpler, alternative treatments should not induce physicians to trivialize long-term preventive strategies by prescribing these new compounds long-term indiscriminately. Previous studies with warfarin have clearly shown that extending treatment duration for 1–2 years after the first 3 months is effective in reducing the risk for recurrences, but this benefit is maintained only while patients are on treatment, and is subsequently lost after treatment discontinuation, regardless of the duration [20,21]. Before concluding that the new oral anticoagulants are appropriate for life-long therapy for most patients thanks to their practical advantages, we believe that additional data are necessary, in particular with regard to long-term safety and, last, but certainly not least, cost-related issues.

With regard to safety, the reported incidence of bleeding in the EINSTEIN-Extension study was lower than that reported with VKAs in previous observational studies. This finding is interesting and potentially promising; however, it could also be attributed to patient selection. Future studies should in particular assess the safety of rivaroxaban in special populations such as patients with cancer, elderly patients, obese and renally impaired patients. All these groups were scarcely represented in the EINSTEIN-Extension study.

Finally, more data are required on the optimal management of major bleeding events and on the management of patients requiring urgent invasive procedures. Ongoing studies are assessing different reversal strategies as well as laboratory tests to monitor, when needed, the anticoagulant activity of rivaroxaban and other anti-FXa agents.

Five-year view

In the near future, the clinical scenario of the long-term management of VTE is likely to change considerably. First of all, individual assessment of the risk of recurrence is getting more accurate thanks to the identification of independent predictors of recurrence among baseline characteristics and post-baseline variables (e.g. D-dimer and residual venous obstruction). Moreover, in recent years, research has also focused on combining several variables in clinical prediction rules that have been derived and validated, thus allowing a further stratification of long-term prognosis in patients who experience a VTE event. Therefore, in the near future, patients are likely to receive a tailored long-term therapy, based on their risk profile. In the perspective of an individualized treatment, the availability of new oral anticoagulant drugs will surely play a key role, offering an important alternative to VKA or low-molecular-weight heparin. This will be particularly important for the long-term treatment of cancer patients with VTE, for whom low-molecular-weight heparin is currently recommendend for the first 3–6 months of treatment, for the treatment of patients with superficial vein thrombosis, for whom a 6-week treatment course with another parenteral drug, fondaparinux, was recently proposed, and for the treatment of patients requiring long-term secondary prevention. The progressively increasing use of these new drugs, which in particular will not need routine laboratory monitoring, will also change the way anticoagulation clinics currently work. These centers will likely need to reorganize their activities in order to continue to provide periodic clinical visits, perhaps the measurement of alternative blood tests such as D-dimer, ultrasound testing and immediate availability in case of signs and symptoms of recurrence, bleeding or other clinical problems.

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Key issues

- In this study, rivaroxaban proved to be effective and safe for the long-term secondary prevention of venous thromboembolism (VTE).
- Rivaroxaban does not require routine laboratory testing, thus greatly simplifying the management of patients with VTE.
- The increasing use of rivaroxaban and other new anticoagulant drugs may change the long-term management of patients with VTE, and anticoagulation clinics will need to reorganize in order to provide high-quality clinical monitoring.
- Along with the risk of recurrent VTE, bleeding risk also needs to be carefully considered for every patient when administering any anticoagulant drug, including rivaroxaban, for long-term treatment.
- More information is needed on the efficacy to safety profile of rivaroxaban in special populations, such as patients with cancer, elderly patients, renally impaired patients and morbidly obese patients.

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