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REVIEW

Rivaroxaban for the Treatment of Pulmonary Embolism

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ABSTRACT

With the advent of new oral anticoagulants (NOACs) for the treatment of deep-vein thrombosis (DVT) and/or pulmonary embolism (PE), a new era of oral anticoagulation for patients with venous thromboembolism (VTE) has begun. Rivaroxaban is the first NOAC to receive regulatory approval for the acute and continued treatment of DVT and PE, and for the secondary prevention of VTE. Here, the clinical trials of rivaroxaban in patients with VTE are reviewed, and the clinical use of rivaroxaban for patients with PE is discussed. Even though rivaroxaban will facilitate the therapeutic management of PE, its use in specific clinical situations needs further study.

Keywords: Anticoagulation; Cardiology; Deep-vein thrombosis; New oral anticoagulants; Rivaroxaban; Pulmonary embolism; Venous thromboembolism

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INTRODUCTION

Deep-vein thrombosis (DVT) and pulmonary embolism (PE) are two different clinical manifestations of venous thromboembolism (VTE) (incidence 1–1.5 per 1,000 person years) [1]. PE is the third most common cause of cardiovascular mortality, after acute coronary syndromes and stroke [2]. The reported all-cause mortality after acute PE is 5–15% [3], driven by the severity of the initial presentation, recurrent PE, and associated comorbidities.

In the treatment of VTE, three distinct phases can be identified: initial treatment, continued treatment, and long-term secondary prevention of recurrent VTE [4, 5]. Although the treatment of DVT and PE share the same principles, the potentially life-threatening

outcome of (recurrent) PE explains the differences in the practical therapeutic management of DVT and PE. Therapy for PE is more rigorously monitored, and the increased clinical vigilance in the initial treatment phase explains the reluctance for ambulatory treatment. Compared with DVT treatment, there is also a lower threshold for long-term secondary prevention after an unprovoked PE.

The perception that PE patients differ from DVT patients is also illustrated by the different time course in the implementation of therapeutic innovations. The use of low molecular weight heparins (LMWHs) was investigated and implemented in DVT patients before it became standard practice in PE patients [6–8]. Likewise, whereas the ambulatory treatment of patients with DVT has been widespread for over a decade [9, 10], outpatient treatment of patients with PE at low risk of an adverse outcome has only been validated in the past years [11]. Due to these differences in outcome and nuances in therapeutic approach, efficacy and safety outcomes may not be readily translatable from one group of VTE patients to another.

Conventional anticoagulant treatment has certain well-known drawbacks, both pharmacologically and practically. Nonetheless, these drugs have been used for decades, and physicians are well trained in the use of LMWHs and vitamin K antagonists (VKAs). Conversely, although new oral anticoagulants (NOACs) offer a promising potential to overcome these limitations through their oral availability and more predictable pharmacokinetics, it will require some time to optimally implement their use in clinical practice.

This manuscript aims to highlight the evidence as well as the areas of uncertainty for the use of rivaroxaban in the treatment of PE.

CLINICAL DEVELOPMENT OF RIVAROXABAN

Rivaroxaban was the first drug to receive regulatory approval for the treatment of VTE, but it is expected that dabigatran, apixaban, and edoxaban will also become available for this indication, as these drugs are in their final phases of their clinical development programmes or regulatory approval [12–15].

Prevention of VTE After Major Orthopaedic Surgery

All NOACs follow a similar pattern of clinical development. Clinical trials in the prevention of VTE after major orthopaedic surgery, using a venogram to assess their efficacy in preventing mostly asymptomatic venous thrombosis, are a well-established clinical development model to validate the efficacy and safety of NOACs. The approval of NOACs for the prevention of VTE in orthopaedic patients has preceded other indications: dabigatran, rivaroxaban, apixaban, and edoxaban all are approved in some parts of the world for preventing VTE after elective knee or hip replacement [16].

The RECORD programme (Regulation of Coagulation in major Orthopaedic surgery reducing the Risk of DVT and PE) investigated rivaroxaban for the prevention of VTE after major orthopaedic surgery. These trials demonstrated a superior efficacy of rivaroxaban 10 mg once-daily (od) as compared with subcutaneous enoxaparin 40 mg od or enoxaparin 30 mg twice-daily (bid) for thromboprophylaxis after knee and hip replacement surgery, without a clinically significant excess of bleeding events [17–20]. The efficacy and safety of rivaroxaban was further confirmed in post-marketing studies and phase 2 studies with rivaroxaban as the comparator drug [21, 22].

Treatment of DVT and PE

Once trials have established the efficacy and safety of NOACs in the prevention of VTE after major orthopaedic surgery, large-scale trials are initiated for the treatment and secondary prevention of VTE, and for stroke prevention in patients with atrial fibrillation. The EINSTEIN programme investigated the efficacy and safety of rivaroxaban for the treatment of acute DVT (EINSTEIN DVT), acute PE (with or without symptomatic DVT; EINSTEIN PE), and for the secondary prevention of recurrent symptomatic VTE (EINSTEIN-Extension) [23, 24]. An overview of the design of these trials is shown in Fig. 1 [23, 24].

The main efficacy and safety outcomes of the EINSTEIN studies are summarized in Table 1 [23, 24].

Rivaroxaban was consistently shown to be non-inferior to standard enoxaparin/VKA therapy for the reduction of recurrent VTE in EINSTEIN DVT and EINSTEIN PE. These trials collectively included over 8,000 patients and were statistically powered to investigate outcomes in patients with DVT and PE.

However, some differences between the results of the EINSTEIN DVT and EINSTEIN PE studies are worth mentioning. In the DVT study, there was a trend for a superior efficacy outcome with rivaroxaban compared with enoxaparin/VKA therapy [2.1 versus 3.0%, respectively; hazard ratio (HR) = 0.68; $P = 0.08$], which was not observed in the EINSTEIN PE study (2.1 versus 1.8%; HR = 1.12; $P = 0.57$) [23].

In EINSTEIN PE, a 50% reduction in major bleeding was observed in patients receiving

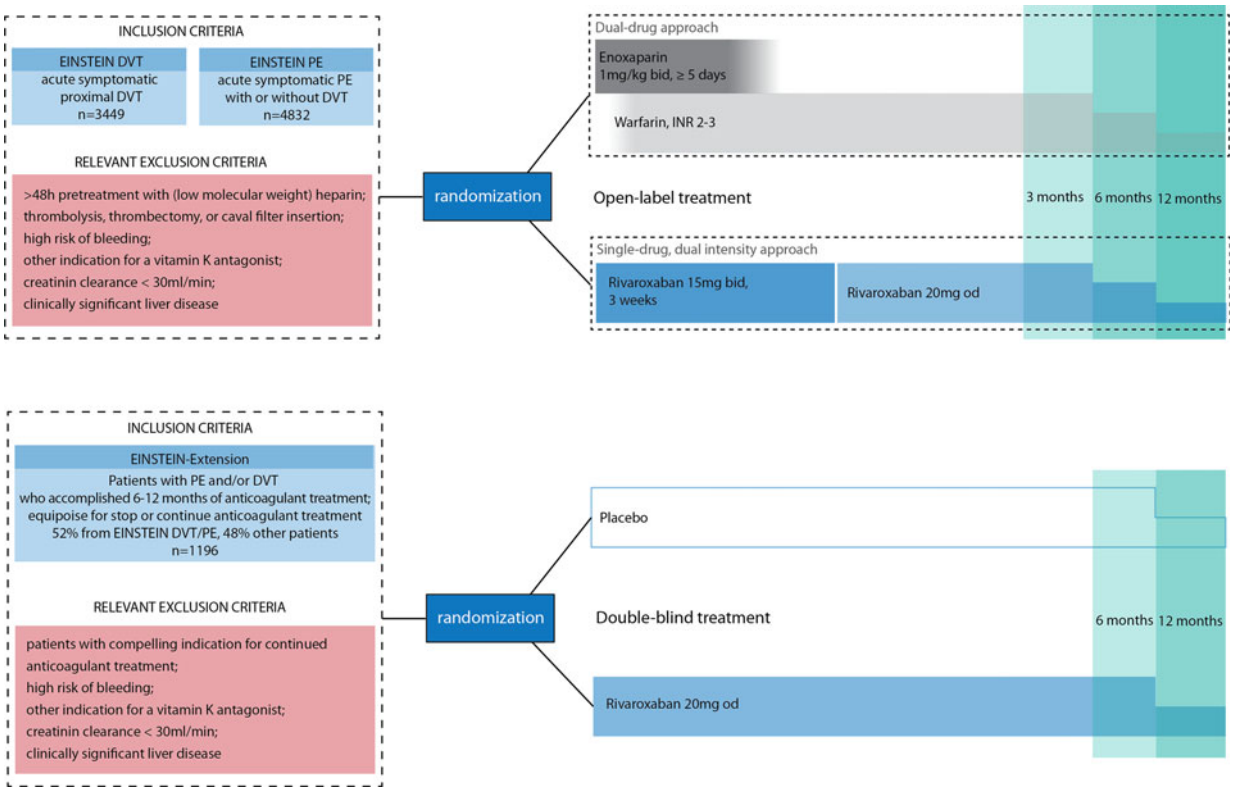

Fig. 1 Design of the EINSTEIN DVT, EINSTEIN PE, and EINSTEIN-Extension trial. *bid* twice-daily, *DVT* deep-vein thrombosis, *INR* international normalized ratio, *od* once-daily, *PE* pulmonary embolism

Table 1 Summary of the results of the clinical trials of rivaroxaban for the treatment of acute VTE and secondary prevention of VTE

	Efficacy			**Safety**[c]					
	Recurrent VTE			**First major or CRNM bleeding**			**Major bleeding**		
	Rivaroxaban	**LMWH + VKA**[a]	**HR (95% CI)**	**Rivaroxaban**	**LMWH + VKA**[a]	**HR (95% CI)**	**Rivaroxaban**	**LMWH + VKA**[a]	**HR (95% CI)**
EINSTEIN DVT ($n = 3,449$) [23][b]	2.1%	3.0%	0.68 (0.44, 1.04)	8.1%	8.1%	0.97 (0.76, 1.22)	0.8%	1.2%	0.65 (0.33, 1.30)
Conclusion	Non-inferior to standard therapy[d]			Comparable to standard therapy			Comparable to standard therapy		
EINSTEIN PE ($n = 4,832$) [24][b]	2.1%	1.8%	1.12 (0.75, 1.68)	10.3%	11.4%	0.90 (0.76, 1.07)	1.1%	2.2%	0.49 (0.31, 0.79)
Conclusion	Non-inferior to standard therapy[d]			Comparable to standard therapy			Less major bleeds compared to standard therapy		

	Efficacy			**Safety**[c]					
	Recurrent VTE			**First major or CRNM bleeding**			**Major bleeding**		
	Rivaroxaban	**Placebo**	**HR (95% CI)**	**Rivaroxaban**	**Placebo**	**HR (95% CI)**	**Rivaroxaban**	**Placebo**	**HR (95% CI)**
EINSTEIN Extension ($n = 1,196$) [23][b]	1.3%	7.1%	0.18 (0.09, 0.39)	6.0%	1.2%	5.19 (2.3, 11.7)	0.7%	0	n/a
Conclusion	Superior compared to placebo			More bleeds compared to placebo			More major bleeds compared to placebo		

CRNM clinically relevant non-major bleeding, *DVT* deep-vein thrombosis, *HR* hazard ratio, *INR* international normalized ratio, *LWMH* low molecular weight heparin, *n/a* not applicable, *PE* pulmonary embolism, *VTE* venous thromboembolism, *VKA* vitamin K antagonist, *95% CI* 95% confidence interval

[a] LMWH + VKA: standard treatment is initial treatment with LMWH for at least 5 days, overlapping with INR-adjusted warfarin treatment

[b] Efficacy analysis is based on the intention-to-treat analysis population

[c] Safety population may differ from the intention-to-treat analysis population

[d] Non-inferiority margin of 2.0

rivaroxaban as compared with those receiving enoxaparin/VKA therapy (1.1 versus 2.2%, respectively; HR = 0.49, $P = 0.003$). The reduction in major bleeding with rivaroxaban was only significant in EINSTEIN PE, whereas a trend in the reduction of major bleeding was observed in EINSTEIN DVT (0.8 versus 1.2%, respectively; HR = 0.65; $P = 0.21$) [24].

Thus, it seems that DVT and PE patient populations are slightly different, or are being managed differently by physicians. The somewhat better quality of anticoagulant management in the EINSTEIN PE study [time in therapeutic range (TTR): 63%] as compared with the EINSTEIN DVT study (TTR: 58%), and the longer anticoagulant treatment duration of patients with PE as compared with patients with DVT illustrate the more vigilant attitude of physicians towards patients with PE, which may, in part, explain the observed differences in efficacy and safety outcomes of the EINSTEIN studies.

INTERNAL VALIDITY OF THE EINSTEIN STUDIES

Design

The EINSTEIN DVT and EINSTEIN PE studies were open-label studies with a prospective, randomized, open-label, blinded-endpoint adjudication design (PROBE). The pros and cons of open-label versus double-blind studies with a VKA comparator have been discussed extensively [25]. Double-blind trials imply the use of a double dummy and a 'shammed' international normalized ratio (INR) when warfarin is the active comparator. Hence, trial logistics and feasibility are more challenging and the clinical management of experienced study centres may not reflect clinical reality. In contrast, open-label studies are prone to bias. This bias may go against the investigational drug, as was suggested in the EINSTEIN studies, with an increased diagnostic suspicion of recurrent events in the rivaroxaban groups, and an underreporting of bleeding outcomes in the comparator group [23, 24]. This underlines the need for a stringent reporting of suspected outcomes, and a blinded, independent adjudication committee.

Initial Treatment: Single-Drug, Dual-Intensity Versus Dual-Drug Approach

In contrast with the delayed onset of the anticoagulant effect of VKAs, NOACs have a rapid onset of anticoagulant activity, similar to LMWHs [26]. NOACs may, thus, provide timely therapeutic anticoagulation when administered as the initial treatment to patients with acute VTE, obviating the need for an initial treatment period with LMWHs.

Previous clinical development programmes have pointed to the importance of the initial treatment phase. The recurrent events in the first month of ximelagatran treatment (single drug/single intensity) when compared with standard LMHW/VKA treatment suggested a need for an intensified initial treatment [27]. This initial treatment phase may be especially relevant in patients with PE. Indeed, the long-acting factor Xa inhibitor, idraparinux, was less effective than standard therapy in the initial treatment of PE, whereas its efficacy was similar to standard antithrombotic therapy for DVT [28].

In the EINSTEIN studies, a single-drug approach has been investigated with an intensified regimen for 3 weeks [23, 24]. This duration of intensified treatment was modelled on dose-finding studies, which showed that a strategy of 15 mg bid (for 3 weeks) followed by 20 mg od (for continued treatment) was not

associated with an increased risk of bleeding when treating patients with acute symptomatic DVT, and that it was effective, as suggested by a reduction in thrombus burden, as a surrogate endpoint for efficacy in these phase 2 trials [29, 30].

The Apixaban after the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis with First-Line Therapy (AMPLIFY) study, investigating apixaban for the treatment of DVT and PE, also opted for a single-drug approach. In this trial, however, the intensified treatment was limited to 1 week of apixaban 10 mg bid, followed by apixaban 5 mg bid after the first week [12].

In contrast, in the clinical trials with dabigatran and edoxaban, the initial treatment was open-label therapeutic unfractionated heparin (UFH) or LMWH in both treatment arms, overlapping with either warfarin or sham warfarin [13, 15]. In these double-blind studies, therapy was then continued with warfarin or the NOAC under investigation upon discontinuation of the open-label UFH/LMWH, i.e. when the (sham) INR is in therapeutic range. This dual-drug approach raises the question of which duration of initial LMWH treatment prior to starting the NOAC is needed in clinical practice.

Since no phase 2 studies had been carried out with rivaroxaban in patients with PE, the EINSTEIN PE study included a repeat imaging scan after 3 weeks of treatment in the first 400 patients who were randomized in the EINSTEIN PE study. The clot resolution was similar in rivaroxaban and enoxaparin/VKA patients. Remarkably, 3 weeks of anticoagulant treatment resulted in a decrease of vascular obstruction of 71 and 62%, and a complete clot resolution in 44 and 31% when analysed with computed tomography (CT) scan and perfusion scanning, respectively [31].

Non-Inferiority Analysis

The primary efficacy analysis was a non-inferiority analysis, with a non-inferiority margin of 2.0 [24]. The non-inferiority margin of 2.0 may appear a generous margin of non-inferiority, as apparently, a non-inferiority claim could be granted despite twice as many recurrent events. However, the non-inferiority claim implied that the upper limit of the 95% confidence interval (CI) for the HR of the primary efficacy outcome was less than this pre-specified margin of 2.0. Since the upper limit of the 95% CI was indeed lower than 2.0 (HR = 1.12, 95% CI 0.75, 1.68), the trial demonstrated non-inferiority. The statistical concept of the non-inferiority margin in the EINSTEIN studies was based on preserving at least 75% of the treatment effect of the comparator arm.

For clinicians, this statistical concept is best translated into absolute rates or recurrences. The observed absolute difference for the patient population with PE included in the EINSTEIN PE study was 0.24% (95% CI −0.5, 1.0%); thus, excluding an absolute of 1% of the primary efficacy outcome recurrent VTE.

EXTERNAL VALIDITY OF THE EINSTEIN PE STUDY: IMPLICATIONS FOR PHYSICIANS AND PATIENTS

The patient management and the patient characteristics in clinical studies are different from daily clinical practice [32]. Even if an open-label clinical trial, such as the EINSTEIN PE study, more closely resembles clinical practice than a double-blind clinical study with a VKA, the patient selection and the meticulous follow-up of clinical trial patients are likely to lead to superior anticoagulant control.

This raises a number of questions: to which extent does the EINSTEIN PE study allow physicians to evaluate and implement this new treatment in a wide range of patients? Can we identify patients who are most likely to benefit? And which PE patients are not good candidates for oral rivaroxaban? Here, the authors discuss the clinical path of a patient with PE, from clinical suspicion to long-term secondary prevention, with a focus on the potential impact of this new therapy.

Impact on Diagnosis

The diagnostic algorithms, combining clinical probability (empirical or using prediction scores), D-dimer level and widely available imaging techniques (CT angiography having largely replaced ventilation–perfusion lung scintigraphy) have facilitated the diagnostic strategies [33, 34]. Nevertheless, in patients with a suspected diagnosis of PE, decisions about empirical treatment are often made prior to a definite diagnosis. In patients with a high clinical probability without an elevated bleeding risk, anticoagulant treatment with heparins can be initiated prior to objective diagnosing PE [33, 35, 36].

Whereas rivaroxaban may be an alternative for LMWH in case of suspected DVT, awaiting the ultrasound result to objectively confirm or refute the diagnosis, physicians are more reluctant to initiate oral rivaroxaban prior to the diagnostic investigations for suspected PE. Indeed, the alternative diagnoses and the potential interventions in patients who present with an acute chest syndrome and the absence of an antidote (should an invasive procedure be needed or in case of a bleeding) justify a more conservative approach for patients with a high clinical probability of PE, who are often hospitalized as opposed to the more ambulatory setting of patients with suspected DVT. Therefore, patients with a high clinical probability of PE for whom initiating anticoagulant treatment prior to the diagnostic exams is considered appropriate are better initiated on LMWH or UFH.

Impact on Initial Treatment of Patients with PE

High-Risk Patients

Patients with PE or with a high probability for PE should be stratified based on their risk profile. The PE-related early mortality of high-risk patients, i.e. patients who are hemodynamically unstable, is high (>15%) [33, 37]. Unstable patients presenting with shock or hypotension should be treated with thrombolytic therapy, or considered for embolectomy if thrombolysis is contra-indicated [38]. Patients with hemodynamic instability and patients who received thrombolytic therapy were not included in NOAC trials (Fig. 1). These patients can, therefore, not be considered appropriate candidates for initial treatment with rivaroxaban. However, upon favourable clinical evolution, rivaroxaban can be considered for the continued treatment and for long-term secondary prevention.

Intermediate-Risk Patients

Intermediate-risk patients can be identified based on the presence of right ventricular (RV) dysfunction (RV dilatation on echocardiography or CT scan, increased levels of natriuretic peptides) or markers of myocardial injury (cardiac troponins) [33]. Patients with so-called ‘submassive’ PE associated with RV dysfunction and/or increased cardiac biomarkers should be

monitored closely, and thrombolytic therapy should be considered upon unfavourable clinical evolution after the initiation of anticoagulant therapy [35]. It seems cautious to administer parenteral heparin to patients who might be candidates for thrombolytic therapy [35].

A limitation of the EINSTEIN PE study [24] is the absence of markers of PE severity or data on RV dysfunction or damage in the EINSTEIN PE study. However, the EINSTEIN PE study does include indirect markers of PE severity (i.e. the stay in intensive care units in 12% of included patients), or the demonstration of extensive disease based on the anatomical extent of the thrombus load, as assessed on CT scan or perfusion scintigraphy, to illustrate that a significant portion of the included patients had extensive disease [24].

Most physicians will delay the intake of an oral drug until the initial clinical evolution is favourable and the patient remains stable. For the majority of the patients, close monitoring of 1–2 days is adequate to confirm a reassuring clinical evolution, after which oral treatment can be initiated.

Low-Risk Patients

The majority of patients included in the EINSTEIN PE study were low-risk patients. Of note, 58 and 33% of patients who were randomized in the EINSTEIN PE study were pretreated with LMWH for 1 or 2 days prior to randomization, respectively [24]. This means that <10% of all study patients were treated with a strictly one-drug regimen. However, given the rapid onset of action of NOACs and the consistent finding of non-inferiority throughout the study, it seems fair to assume that an all-oral regimen from the start is suited for most patients in the absence of elevated risk.

Will NOACs Facilitate Outpatient Treatment of Low-Risk Patients?

For low-risk patients, outpatient treatment has recently been validated as a safe alternative for hospitalization [11]. The EINSTEIN PE study recruited mainly a lower-risk population, which is illustrated by the rather low overall mortality rate during the intended treatment period (2.5%) [24]. The EINSTEIN PE study reported that 89% of patients were hospitalized, suggesting that a fair minority of approximately 10% were not hospitalized, or observed for <24 h [24]. The single-drug approach, without the need for subcutaneous injections nor frequent INR measurements, will further facilitate ambulatory treatment in low-risk patients, but validation of the safety and efficacy of ambulatory treatment of low-risk PE patients with a NOAC would be welcomed. Several clinical prognostic scores for PE have been validated to help physicians identify low-risk patients with a PE who are potential candidates for outpatient care, such as the (simplified) Pulmonary Embolism Severity Index (PESI) [39–41]. Unfortunately, these scores were not determined in the EINSTEIN PE study.

Impact on Continued Treatment and Follow-Up of Patients

VKAs, with a target INR of 2–3, are the gold standard for continued treatment and long-term secondary prevention. In case of rivaroxaban treatment, the initial treatment phase encompasses an intensified treatment regimen (15 mg bid) for 3 weeks, followed by continued treatment of 20 mg od for at least 3 months (Fig. 2).

The stringent need for INR monitoring and dose adjustment of VKAs ensured a clinical follow-up of patients with acute PE. The absence

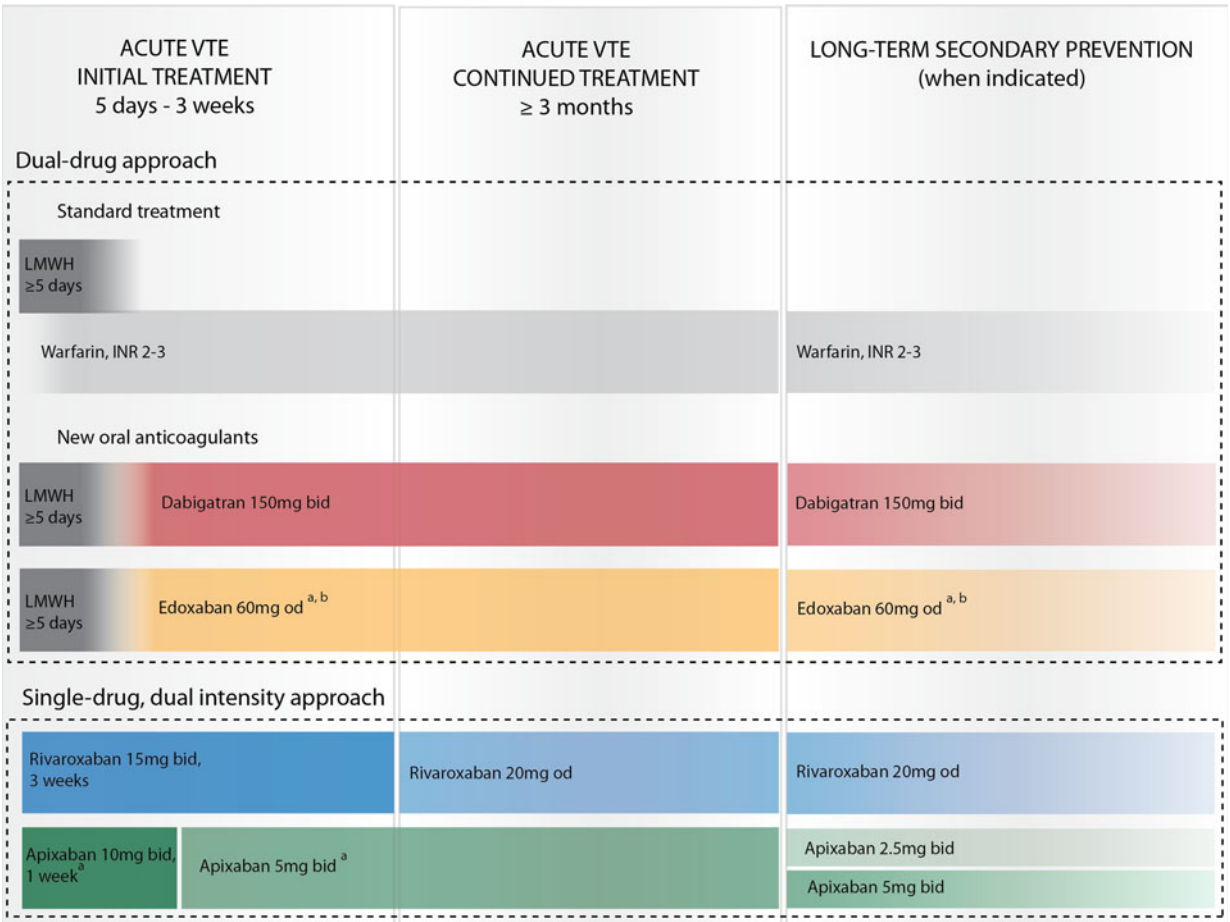

Fig. 2 Overview of different treatment strategies for the initial and continued treatment of acute VTE, and for the long-term secondary prevention of VTE. *bid* twice-daily, *INR* international normalized ratio, *LMWH* low-molecular weight heparin, *od* once-daily, *Pgp* P-glycoprotein, *VTE* venous thromboembolism, [a]trial results not yet published, [b]dose reduction to 30mg od in patients with body weight <60 kg, patients with a creatinine clearance between 30–50 mL/min, and patients with concomitant use of Pgp inhibitors

of routine laboratory monitoring is an advantage, but does not alleviate the need for patient education and a clinical follow-up. Furthermore, the absence of laboratory monitoring could potentially impact on the compliance, which is of the utmost importance in the initial weeks after an acute PE. Indeed, because of their short therapeutic half-life [42], compliance is even more crucial for NOACs, as a treatment interruption as short as a single day will leave the patient without anticoagulant protection. Thus, it seems cautious to shift from routine coagulation monitoring to a clinical path with a follow-up after 3–4 weeks (verifying the appropriate dose change and treatment adherence), after 3 and 6 months, and later on tailored to the individual patient profile.

Impact on Duration of Treatment

All patients with PE should continue anticoagulant treatment for at least 3 months. Anticoagulant treatment can be discontinued after 3 months in patients with a provoked PE secondary to a transient risk factor. In clinical practice, physicians are often inclined to

prolong this treatment phase and prescribe at least a 6-month course of anticoagulation in PE patients. This is also reflected in the EINSTEIN PE study, where the intended treatment duration was 3 months in only 5% of patients [24], versus 12% of patients in the EINSTEIN DVT study [23].

Patients with unprovoked PE or permanent risk factors need to be considered for long-term secondary prevention, taking into account the risk of recurrence, the bleeding risk, and the patient's preferences [33, 35].

The efficacy and safety results of the EINSTEIN PE and EINSTEIN-Extension study, and the more convenient treatment with rivaroxaban or any other approved NOAC will likely impact on the clinical decision to stop or continue anticoagulation treatment, e.g. in patients in whom difficulties related to VKA management drive the decision to stop anticoagulation despite a high risk of recurrent VTE. Anticoagulant therapy is also frequently discontinued in patients with bleeding complications, or patients considered at an increased risk for bleeding. The lower incidence of major bleedings observed with rivaroxaban in the EINSTEIN PE study may lower the threshold for continuing secondary VTE prevention in these patients. The use of bleeding risk scores [43] and more real-life data on the benefit-to-risk profile of NOACs in patients at increased risk of bleeding are needed. An individualized approach for treatment duration and a periodic benefit/risk evaluation remains essential.

Although the results of the EINSTEIN-Extension trial showed a clear reduction in VTE recurrence in patients treated with rivaroxaban versus untreated patients [44], long-term treatment with rivaroxaban was not compared with long-term VKA treatment. Whereas it seems plausible to assume that the efficacy and safety compared to VKA treatment in the acute treatment studies can be extended to prolonged treatment, long-term registries are needed to investigate this assumption. Furthermore, it is of interest that patients with a clear indication for long-term anticoagulant treatment were excluded from the EINSTEIN-Extension trial, and only 5% of patients in the acute treatment trials had a known prothrombotic condition [23, 24]. Patients with a high risk of VTE recurrence may, thus, be underrepresented in the EINSTEIN programme.

Optimal Dose for Long-Term Secondary Prevention?

Based on the EINSTEIN studies and the pharmacokinetic profile of rivaroxaban, the current summary of product characteristics (SmPC) of rivaroxaban stipulates a fixed dose of 20 mg for both the continued treatment and secondary prevention of recurrent VTE, suggesting, however, to consider a dose reduction to 15 mg in patients at high risk of bleeding [42]. The AMPLIFY-extend study has shown that lowering the dose of apixaban for long-term secondary prevention (2.5 mg bid rather than 5 mg bid) improved the benefit-to-risk profile of apixaban, i.e. assured effective prevention of recurrent VTE with a reduced incidence of bleeding complications [12] (Fig. 2).

Hence, also in view of the efficacy of rivaroxaban 10 mg od in the primary prevention of VTE after major orthopaedic surgery [18–20], it is a valid and yet unanswered question whether a dose reduction of rivaroxaban should be considered for long-term secondary prevention, especially for frailer patients or patients at increased bleeding risk.

It is of interest that in the Multicenter, Randomized, Parallel-Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxoparin (MAGELLAN) trial, some bleeding complications were identified with a 10 mg dose of rivaroxaban in acutely ill medical patients [45]. Additional studies are needed to address whether the prolonged use of 'therapeutic' doses of rivaroxaban may lead to an excess of bleeding in the long term, especially in patients with a fluctuating health status.

Impact on the Management of Specific Patient Populations

Patients with special characteristics were often excluded from participation in the EINSTEIN studies and may be unfit for NOAC treatment.

Pregnancy and Breastfeeding

Rivaroxaban is contra-indicated in patients who are pregnant or who are breastfeeding [42]. For female patients on long-term anticoagulant treatment who wish to become pregnant, VKAs are recommended, which should be switched to LMWHs prior to the sixth week of pregnancy [46].

Cancer

PE is a significant cause of morbidity and mortality in patients with most types and stages of cancer [47, 48]. Treatment with VKAs can be complex, due to chemotherapy-related complications, such as drug interactions, nausea, or thrombocytopenia, or the interruption of therapy because of invasive procedures [35]. LMWHs are currently the agents of choice for both acute and continued treatment of VTE in patients with cancer. Clinical data on NOACs are limited; only a small proportion of patients with cancer were included in the EINSTEIN studies (approximately 5–7%) [23, 24, 49]. A clinical trial comparing rivaroxaban (or another NOAC) with LMWHs in patients with cancer would be welcomed.

Elderly Patients

Elderly patients are at increased risk of both recurrent VTE and bleeding. Furthermore, elderly patients are typically underrepresented in clinical trials, and the patients of advanced age who are included in clinical trials are often less frail compared with typical geriatric patients who present with comorbidity and multiple concomitant medications. In general, clinical trial results should be transposed to elderly patients with caution.

The mean age of the EINSTEIN PE patient was approximately 58 years. However, the reduction in major bleeding in the EINSTEIN PE study was also observed in elderly patients [24, 50]. In addition, in the EINSTEIN DVT study, the net clinical benefit of rivaroxaban was largest in frail patients [aged >75 years, with body weight <50 kg or creatinine clearance (CrCl) <50 mL/min] and elderly patients [23]. In a pooled data analysis from both EINSTEIN DVT and EINSTEIN PE, the efficacy was maintained in all different age subgroups [50]. However, this does not exclude that in this higher risk, frail population, a reduced dose could further improve the benefit-to-risk profile.

Patients with Extreme Body Weight

Patients with extreme body weight, both very low and very high, are underrepresented in clinical trials and in preclinical dose-finding studies. As rivaroxaban is given as a single dose independent of therapeutic monitoring or of

body weight, caution is needed in patients with extreme body weight. It is of note that obese patients seem to be reasonably well represented in the EINSTEIN PE study, as 15% of the patients had a body weight >100 kg, without any concern for increased risk of recurrence [24]. However, for patients with extreme body weight, the authors would recommend VKAs or an intermittent monitoring of anti-Xa activity.

Patients on Chronic Antiplatelet Treatment

The concomitant use of anticoagulant and antiplatelet treatment increases the risk of bleeding, and the optimal 'cocktail' of anticoagulant and antiplatelet therapy in patients with an indication for both remains unknown.

Whereas VKAs have been validated both for the secondary prevention of atherothrombotic events and recurrent VTE [51], the efficacy of NOACs for the secondary prevention of atherothrombosis is yet to be established. On the other hand, antiplatelet therapy also has a limited effect on preventing recurrent VTE [52, 53].

Although not formally considered an exclusion criterion, the concomitant use of antiplatelet agents was discouraged for patients in the EINSTEIN trials, and limited to low-dose aspirin, low-dose clopidogrel, or both. However, safety data in patients taking concomitant antiplatelet drugs have not been separately reported [24].

The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction-51 (ATLAS ACS 2—TIMI 51) trial studied the effect of low-dose rivaroxaban on top of dual antiplatelet treatment in patients with recent acute coronary syndromes. While low-dose rivaroxaban (2.5 mg bid or 5 mg bid) successfully reduced recurrent ischemic events, it was at the price of increased bleeding [54]. Notably, the apixaban for Prevention of Acute Ischemic Events (APPRAISE) trial, comparing a standard dose of apixaban (5 mg bid) versus placebo on top of antiplatelet treatment of acute coronary syndromes was halted early due to an increased bleeding rate exceeding the reduction in ischemic events [55]. While these trials report on a very different patient population than PE patients, they illustrate the importance of the balance between anticoagulant and antiplatelet treatment.

In conclusion, the combined use of anticoagulant and antiplatelet agents should be avoided whenever possible, and a critical appraisal of the indication for either treatment is needed. If the combination cannot be avoided, reducing the dose or limiting the duration of anticoagulant therapy seems prudent.

Patients with Reduced Renal Function

In the EINSTEIN studies, patients with a CrCL <30 mL/min (based on the Cockroft–Gault formula) were excluded from participation. However, based on the results and the pharmacokinetic profile, the current approval for rivaroxaban includes patients with moderate (CrCL 30–50 mL/min) and severe (CrCl 15–30 mL/min) renal impairment, without dose reduction [42]. Because of the increased drug levels in patients with severe renal impairment, caution is indicated. The authors would be inclined to propose a dose reduction in patients with severe chronic impairment, and in patients with moderate renal impairment who have additional bleeding risk factors. The potential value of monitoring drug levels or coagulation tests is yet unclear.

Patients with Liver Disease

Patients with significant liver disease were also excluded from the clinical trials of NOACs. It

seems cautious not to use NOACs in patients with liver disease associated with coagulopathy. In contrast to the hepatotoxicity associated with ximelagatran [27], there are currently no known concerns with respect to liver dysfunction for apixaban, rivaroxaban, edoxaban, or dabigatran.

Patients with Known Prothrombotic Conditions

No specific trials have investigated the efficacy of NOACs in relation to genetic or acquired thrombophilia, even though there is currently no evidence that the presence of a prothrombotic state impacts on either the safety or the efficacy of the NOAC. Clinical data of VTE treatment in patients with hypercoagulability are lacking; but there is no evidence that these patients should be treated differently [56]. NOACs may lower the threshold for continuing anticoagulant treatment in patients with thrombophilia, but this requires further study.

Pharmacokinetic Interactions

A list of drugs with potential interactions is given in Table 2 [42]. The use of strong P-glycoprotein (Pgp) inhibitors or certain drugs interfering with cytochrome P450 3A5 (CYP3A4) were exclusion criteria in the EINSTEIN programme. The concomitant use of these drugs with rivaroxaban is not recommended; however, no official recommendation for dose reductions is given [42]. In patients with atrial fibrillation, recently published guidelines from the European Heart Rhythm recommends to consider a dose reduction of rivaroxaban in patients treated with a CYP3A4- or Pgp-inhibitor who have additional bleeding risk factors, such as advanced age, reduced renal function, use of antiplatelet agents, or a known bleeding tendency. However, it should be noted that patients with atrial fibrillation constitute a different population [57].

Although pharmacologically relevant drug interactions are much more frequent and often less predictable with VKAs, the effect of drugs on the anticoagulant effect of VKAs can easily be assessed via monitoring of the INR.

Although the obviation of the need for routine monitoring is welcome both from practical and from health care expenditure perspective, the availability of a reliable coagulation assay can be of help to estimate the intensity of anticoagulation in specific situations, such as potential drug–drug interactions, reduced hepatic and/or renal function, and elderly patients.

DISCUSSION

Over the past decade, the availability of well-validated clinical probability scores, D-dimer assays, and the advances in pulmonary CT angiography have facilitated the diagnostic management of patients with suspected PE. The approval of a new generation of orally available anticoagulants for the treatment of VTE will provide the clinician with a range of convenient treatment options (Fig. 2).

In recent years, several large-scale landmark trials of rivaroxaban as well as other NOACs in the treatment of VTE have been published, demonstrating their efficacy and safety in the studied populations. However, the translation of clinical trial results to clinical practice will generate new questions.

Currently, rivaroxaban is the only NOAC approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for the treatment and secondary prevention of DVT and PE. Although

Table 2 Overview of drugs with relevant pharmacodynamic or pharmacokinetic interactions

Drug	Mechanism of interaction	SmPC recommendation[a]
Major increase in plasma levels (>2-fold)		
Azole antimycotics besides fluconazole (ketoconazole, itraconazole, voriconazole, posaconazole)	Pgp competition and strong CYP3A4 inhibition	Not recommended
HIV protease inhibitors (ritonavir)	Pgp competition and strong CYP3A4 inhibition	Not recommended
Increase in plasma levels (<2-fold)		
Quinidine	Pgp competition	No recommendation
Cyclosporin, tacrolimus	Pgp competition	No recommendation
Fluconazole	Moderate CYP3A4 inhibition	No clinically significant interaction
Clarithromycin	Pgp competition and strong CYP3A4 inhibition	No clinically significant interaction
Erythromycin	Pgp competition and moderate CYP3A4 inhibition	No clinically significant interaction
Possible increased plasma levels (no data available)		
Dronedarone	Pgp competition and CYP3A4 inhibition	Not recommended due to limited data[b]
Decrease in plasma levels		
Rifampicin	Strong CYP3A4 inducer	Use with caution
Phenytoin, carbamazepine, phenobarbital	Strong CYP3A4 inducer	Use with caution
St. John's wort	Strong CYP3A4 inducer	Use with caution
Pharmacodynamic interaction		
Antiplatelet drugs, NSAID	Impaired hemostasis	Use with caution
Warfarin	Additive effect on anticoagulation, no pharmacokinetic interaction	Use with caution[c]
Other anticoagulants	Additive effect on coagulation	Use with caution

CYP3A4 cytochrome P3A4, *ESC* European Society of Cardiology, *NSAID* non-steroidal anti-inflammatory drug, *Pgp* P-glycoprotein, *SmPC* summary of product characteristics

[a] Based on rivaroxaban summary of product characteristics (SmPC)-EU version, November 2012 [42]

[b] Amiodarone is not considered a contraindication in patients with normal-to-mildly reduced kidney function

[c] As rivaroxaban may increase the INR, in order to monitor the pharmacodynamic effect of warfarin, INR should be measured at trough levels (24 h after the last dose of rivaroxaban) for minimal interference. Anti-Xa assays are not affected by warfarin and can be used to monitor the pharmacodynamic effect of rivaroxaban

a comparison of the different clinical development programmes and the results of these studies are beyond the scope of this manuscript, the differences in clinical trial design have important implications, as they lead to different initial treatment strategies

depending on the NOAC of choice (as summarized in Fig. 2).

Clinical trials mainly include a selected patient population with lower-risk patients. Although patients with comorbidities, frailty, and concomitant medications were also included in these trials, real-life experience will need to accumulate in order to better delineate candidates for treatment with the different available NOACs.

Although only a small fraction of patients from EINSTEIN PE was treated entirely with rivaroxaban from the first treatment dose, the efficacy and safety findings are most likely extendable to a rivaroxaban-only treatment in low-risk patients. While it, thus, seems reasonable to start rivaroxaban as a single-drug treatment in most hemodynamically stable patients presenting with PE, current evidence does not support a role for rivaroxaban in the initial treatment of high-risk patients with massive PE. In high- and intermediate-risk patients, especially in patients in whom thrombolysis is still considered a possible treatment strategy, oral rivaroxaban should be withheld until improvement of the patient's clinical condition. Rivaroxaban is also inappropriate for the treatment of PE in pregnant patients, or in patients with significant hepatic or end-stage renal disease. Although there is currently no evidence that the efficacy and safety of rivaroxaban treatment is different in cancer patients or in patients with genetic or acquired prothrombotic conditions, future studies need to better delineate the role of NOACs in these patients.

Frail patients may potentially benefit from the more stable pharmacodynamics of NOACs, as suggested in a subanalysis showing that the largest absolute clinical benefit was obtained in elderly patients. However, it seems cautious to organize a careful follow-up of renal function, concomitant medication, and a frequent re-assessment of other factors contributing to an increased bleeding risk.

CONCLUSION

In conclusion, the development and approval of rivaroxaban represent a true paradigm shift in the management of patients with VTE. While the EINSTEIN programme supports the use of rivaroxaban as an attractive first-line treatment in many PE patients, current evidence is still insufficient to recommend rivaroxaban in specific subpopulations.

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