Review

Treatment of venous thromboembolism: the single-drug approach

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Practice Points

- An anticoagulant that is effective for both acute and long-term treatment of venous thromboembolism (VTE) is clearly beneficial and avoids the need for any form of bridging therapy.
- Of the old and new anticoagulants, the results of randomized clinical trials in support of the 'single-drug' approach for the treatment of both patients with deep vein thrombosis and those with hemodynamically stable pulmonary embolism are, to date, only available for rivaroxaban and apixaban (direct inhibitors of factor Xa).
- The oral administration of rivaroxaban (15 mg twice a day for the first 3 weeks, followed by 20 mg once daily for 3–12 months) or apixaban (10 mg twice a day for 7 days, followed by 5 mg twice a day for 6 months) in patients with acute VTE, is associated with a benefit-to-risk ratio that is at least comparable with that provided by the conventional treatment with enoxaparin followed by vitamin K antagonists.
- Both rivaroxaban and apixaban qualifiy as suitable compounds for the single-drug treatment of VTE.

SUMMARY An anticoagulant that is effective for both acute and long-term treatment of venous thromboembolism is clearly beneficial and avoids the need for any form of overlapping therapy. Among the emerging oral antithrombotic compounds that have the potential to inhibit either factor Xa (rivaroxaban, apixaban and edoxaban) or factor IIa (dabigatran etexilate), and do not require laboratory monitoring, rivaroxaban and apixaban are the only ones to date for which there is persuasive evidence coming from randomized clinical trials in support of the

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'single-drug' approach for the treatment of both patients with deep vein thrombosis and those with hemodynamically stable pulmonary embolism. The oral administration of rivaroxaban (15 mg twice a day for the first 3 weeks, followed by 20 mg once daily for 3–12 months) or apixaban (10 mg twice a day for 7 days, followed by 5 mg twice a day for 6 months) results in a benefit-to-risk ratio that is at least comparable with that provided by conventional treatment with enoxaparin followed by vitamin K antagonists.

The 'single-drug' approach in the second half of the 20th century

In spite of the availability of intravenous (iv.) or subcutaneous (sc.) adjusted-dose unfractionated heparin (UFH) for the treatment of acute episodes of venous thromboembolism (VTE), in the 1960s, 1970s and first half of the 1980s it has been common practice in several European countries, including The Netherlands [1], to treat a substantial proportion of outpatients with deep vein thrombosis (DVT) of the lower extremities with acenocoumarol alone.

In 1992 the results of the ATHOS study were published [2]. In a randomized, double-blind study the efficacy and safety of iv. UFH plus acenocoumarol were compared with those of acenocoumarol alone in the initial treatment of outpatients with proximal DVT. The study was terminated early because of an excess of both symptomatic (20%) and asymptomatic (39.6%) events in the group that received acenocoumarol alone as compared with less than 6.7 and 8.2%, respectively, in the combined-therapy group. This study provided compelling evidence that patients with proximal DVT require an initial treatment with full-dose heparin, which can safely be combined with acenocoumarol therapy. As a result, the 'single approach' therapy with vitamin K antagonists (VKAs) has been definitively abandoned, and UFH has progressively been replaced by sc. low-molecular-weight heparin (LMWH) or fondaparinux for the initial treatment of acute VTE [3].

The single-drug approach around the 2000s

The discovery of drugs that have the potential to inhibit a single target of the coagulation cascade prompted the use of idraparinux (an anti-Xa compound) and of ximelagatran (an anti-IIa compound) for the initial treatment of VTE.

■ Idraparinux & idrabiotaparinux

With the introduction of idraparinux, the first long-acting synthetic pentasaccharide, a new class of antithrombotic agent that specifically inhibits factor Xa and lack activity against thrombin became available. Idraparinux has a linear pharmacokinetic profile, and a longer half-life than the short-acting pentasaccharide fondaparinux, allowing a once-weekly administration. Subsequently, a derivative of idraparinux was obtained by the addition of a biotin moiety to a position where it cannot interfere with antithrombin binding, and was called idrabiotaparinux. The high affinity of biotin for avidin leads to the creation of avidin–biotin complexes, allowing idrabiotaparinux to be eliminated in case of overdose or bleeding events.

After the promising results of a Phase II study [4], two randomized, open-label trials enrolling patients with primary DVT or pulmonary embolism (PE; the van Gogh DVT and PE studies) compared the efficacy and safety of idraparinux (2.5 mg once weekly sc.) to conventional treatment with either iv. UFH or sc. LMWH (at the physicians' discretion) overlapped and followed by adjusted-dose VKA for 3–6 months [5]. In the former study enrolling almost 3000 patients, the incidence of recurrent events after 3 months was 2.9% in the idraparinux group and 3.0% in the standard-therapy group (odds ratio [OR]: 0.98). At 6 months, the OR for idraparinux was virtually unchanged (1.01). The rates of clinically relevant bleeding after 3 months were 4.5% in the idraparinux group and 7.0% in the standard-therapy group ($p = 0.004$). At 6 months, the bleeding rates were 8.3 and 8.1%, respectively. In the latter study enrolling 2215 patients with primary PE, the incidence of recurrent events after 3 months was 3.4% in the idraparinux group and 1.6% in the standard-therapy group (OR: 2.14; 95% CI: 1.2–3.8), a finding that did not meet the noninferiority requirement. In conclusion, while in DVT patients the once-weekly sc. administration of 2.5 mg of idraparinux for 3 or 6 months had an efficacy that was similar to that of heparin/VKA, it did not in patients with primary PE.

In the Equinox study, idrabiotaparinux (3 mg once weekly sc.) was found to be at least as effective and safe as idraparinux (2.5 mg once weekly) for the initial and 6-month treatment of patients with acute DVT [6]. Indeed, during the 6-month treatment period recurrent thromboembolism occurred in nine of 386 patients (2.3%) in the idrabiotaparinux group and in 12 of 371 patients (3.2%) treated with idraparinux (difference of -0.9%; 95% CI: 3.2–1.4%). Clinically relevant bleeding developed in 5.2 and 7.3%, respectively (difference of -2.1%; 95% CI: 5.6–1.4%).

The promising results of the Equinox study prompted the execution of the Cassiopea study, where the efficacy of idrabiotaparinux (3 mg once weekly sc.) was compared with dose-adjusted warfarin (international normalized ratio: 2.0–3.0) for 3–6 months after 5–10 days of treatment with enoxaparin (1 mg/kg twice a day [b.i.d.]), in patients with acute symptomatic PE [7]. Interestingly enough, at variance with results obtained in the van Gogh PE study, idrabiotaparinux was found to be noninferior to warfarin in the reduction of recurrent VTE at day 99 (2 and 3%, respectively; OR: 0.79; 95% CI: 0.50–1.25), and was associated with significantly fewer cases of clinically relevant bleeding compared with warfarin (5 vs 7%, respectively; OR: 0.67; 95% CI: 0.49–0.91). Moreover, patients who received idrabiotaparinux had additional protection against the development of VTE recurrence, which persisted for up to 6 months after treatment discontinuation compared with VTE recurrence in patients who had received warfarin.

The results of available studies make the sc. injection of fixed-dose idrabiotaparinx (3.0 mg once weekly) a valuable alternative to the old and new oral anticoagulants for the treatment of both patients with primary DVT and those with primary PE. However, while the former can be treated with this interesting compound from the beginning, the latter cannot. Indeed, the proper treatment conduction in the category of patients with primary PE requires an initial (7–10 days) therapy with either LMWH or fondaparinux. Thus, idraparinux cannot be regarded as an ideal compound for the single-drug approach to patients with acute VTE.

Of note, in all studies performed with either idraparinux or idrabiotaparinux, adverse events other than bleeding complications were infrequently reported [5–7].

Ximelagatran & dabigatran etexilate

The introduction of ximelagatran, a direct thrombin inhibitor that can be administered orally in fixed doses, opened the era of the new oral antithrombotic compounds.

In order to assess the value of ximelagatran in comparison with standard treatment for the initial and long-term treatment of acute VTE, 2500 patients with acute DVT, alone or associated with hemodynamically stable PE (that was detected in approximately a third of patients), were randomized to receive either ximelagatran, (36 mg b.i.d.) or sc. enoxaparin overlapped and followed by adjusted-dose warfarin for a 6-month period (THRIVE study) [8]. Recurrent VTE events occurred in 26 of the 1240 patients assigned to ximelagatran (2.1%) and in 24 of the 1249 (2.0%) allocated to conventional therapy (difference of 0.2%; 95% CI: -1.0–1.3%). Corresponding values for major bleeding were 1.3 and 2.2% (difference: -1.0%; 95% CI: -2.1–0.1%). In conclusion, oral ximelagatran administered from the beginning in fixed doses was found to be as effective and safe as conventional enoxaparin/VKA therapy in patients with acute DVT (alone or associated with PE). However, the increased levels of liver enzymes, also shown in the studies addressing the treatment of atrial fibrillation, in combination with a definite risk of acute coronary syndromes led to the withdrawal of this drug from the market. Interestingly enough, a careful timely assessment of VTE recurrences could not exclude an excess of these events in the first weeks of treatment, thus raising concerns on the use of this compound as a single-drug approach in all patients with acute VTE.

Failure of ximelagatran prompted the identification of a derivative, dabigatran etexilate, free from the side effects and inconveniences that had led to the withdrawal of its precursor. The main pharmacokinetic and pharmacodymamic properties of dabigatran are illustrated in **Table 1.**

In order to assess the value of dabigatran in comparison with VKA for the treatment of acute VTE, more than 2500 patients with DVT and/or hemodynamically stable PE were randomized to receive either oral fixed-dose dabigatran (150 mg b.i.d.), or adjusted-dose VKA for a 6-month period (the RECOVER study) [9]. Most likely because of concerns raised by the use of ximelagatran [8], all patients were initially given parenteral anticoagulation therapy with UFH, LMWH or fondaparinux. Recurrent VTE events occurred in

30 of the 1274 patients (2.4%) assigned to dabigatran and in 27 of the 1265 (2.1%) allocated to warfarin (difference in risk: 0.4; 95% CI: -0.8–1.5; hazard ratio [HR]: 1.10; 95% CI: 0.65–1.84). Major bleeding episodes occurred in 20 (1.6%) and 24 patients (1.9%), respectively (HR: 0.82; 95% CI: 0.45–1.48); overall bleeding – including clinically relevant non-major events – in 205 (16.1%) and 277 patients (21.9%), respectively (HR: 0.71; 95% CI: 0.59–0.85).

In a confirmatory randomized, double-blind trial (RECOVER II) whose results have recently been presented, 2568 patients with acute VTE treated with UFH, LMWH or fondaparinux for the first 8–10 days, were then randomized to receive dabigatran 150 mg b.i.d. or dose-adjusted warfarin, each given for 6 months [10]. The main study results were fully consistent with those of the previous study [9].

The two RECOVER studies clearly show that dabigatran etexilate is as effective as warfarin in the treatment of acute VTE and is associated with a lower risk for bleeding, provided that patients have received an initial parenteral treatment with either heparin or fondaparinux. Thus, while ximelagatran is no longer available, its derivative, dabigatran etexilate, cannot be regarded, for the present time, as a suitable compound for the single-drug approach to patients with acute VTE. Studies addressing the value of dabigatran etexilate for this indication are warranted.

Of note, in the two RECOVER studies a higher incidence of dyspepsia was observed in patients receiving dabigatran etexilate, as well as a slightly higher rate of acute myocardial infarction [9,10].

The single-drug approach in recent years

In contrast with the new oral thrombin inhibitors, a few oral inhibitors of factor Xa have the potential to be used as a single-drug approach.

Rivaroxaban

Rivaroxaban is an oral, direct Factor Xa inhibitor. Its main pharmacokinetic and pharmacodymamic properties are displayed in **Table 1**.

Based on the findings from two dose-finding studies [11,12], an initial intensified regimen (15 mg b.i.d. for 3 weeks) not preceded by any parenteral therapy was selected for investigation in Phase III studies involving approximately 9000 patients.

The EINSTEIN DVT [13] and the EINSTEIN PE [14] studies had a comparable study design. They were Phase III, randomized, open-label clinical trials designed to evaluate whether the immediate administration of rivaroxaban (15 mg b.i.d. for 3 weeks followed by 20 mg once daily) was at least as effective and safe as sc. enoxaparin (1 mg/kg b.i.d. for at least 5 days) overlapping with and followed by a VKA for a period ranging between 3 and 12 months (at the discretion of investigators) for the prevention of recurrent VTE events in patients with primary DVT or PE, respectively. In the EINSTEIN DVT study, 3449 patients with isolated DVT were randomized to receive either

Table 1. Comparison of the main pharmacokinetic and pharmacodynamic characteristics of oral compounds for the treatment of venous thromboembolism.

Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa (thrombin)	Xa	Xa	Xa
Time to C_{max} (h)	1.25–3	2–4	3–4	1–2
Half-life (h)	14–17	7–11	8–15	8–10
Bioavailability (%)	6	80	60	62
Renal elimination (%)	80	33	25	35
CYP450 metabolism (%)	None	32	Minimal	<4
Transporters	P-gp	P-gp/BCRP	P-gp/BCRP	P-gp
Protein binding (%)	35	93	87	50
Influence on PT	+	+	+	+
Influence on aPTT	+	+	+	+
Influence on TT	++	No	No	No
Reversal agent	None	None	None	None

+: Weak influence; ++: Moderate influence.
aPTT: Activated partial thromboplastin time; C_{max}: Maximal concentration; P-gp: P-glycoprotein; PT: Prothrombin time; TT: Thrombin time.
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rivaroxaban or enoxaparin/VKA [13]. Recurrent VTE occurred in 2.1% of patients receiving rivaroxaban and in 3.0% of those allocated to conventional therapy (HR: 0.68; 95% CI: 0.44–1.04). Clinically relevant bleedings occurred in 8.1% of the patients in each group.

In the EINSTEIN PE study 4832 patients with clinically symptomatic and hemodynamically stable PE (alone or associated with DVT) were randomized to receive either rivaroxaban or enoxaparin/VKA [14]. The primary efficacy end point of symptomatic recurrent VTE occurred in 2.1% of patients receiving rivaroxaban and in 1.8% of patients receiving conventional therapy (HR: 1.12; 95% CI: 0.75–1.68). At the end of the intensified rivaroxaban treatment period (day 21), the rate of recurrent VTE events was similar between rivaroxaban and enoxaparin/VKA groups (0.7 vs 0.9%, respectively). Clinically relevant bleedings occurred in 10.3% of patients receiving rivaroxaban and in 11.4% of those receiving enoxaparin/VKA (HR: 0.90; 95% CI: 0.76–1.07); however, the rate of major bleeding was significantly lower in the former group (1.1 vs 2.2%, respectively; HR: 0.49; 95% CI: 0.31–0.79). Interestingly enough, intracranial bleeding developed in only one patient receiving rivaroxaban as compared with ten treated with conventional therapy, and retroperitoneal bleeding in one and seven, respectively.

The EINSTEIN Extension trial randomized 1197 patients who had received up to 12 months of anticoagulant therapy for an acute VTE event to an additional 6–12 months of therapy with either rivaroxaban, 20 mg once daily, or placebo [13]. Recurrent VTE events developed in 1.3% of patients receiving rivaroxaban group and in 7.1% of those allocated to placebo (relative risk reduction: 82%). Major bleeding occurred in four patients (0.7%) treated with rivaroxaban, and in none allocated to placebo ($p = 0.11$).

According to the results of the EINSTEIN studies, rivaroxaban definitely shows the potential of a single-drug approach for the treatment of patients with VTE, including those with primary PE. Indeed, the EINSTEIN PE showed that a single-drug regimen of rivaroxaban starting with a higher dose (15 mg b.i.d.) for 3 weeks, followed by 20 mg once daily, is as effective as enoxaparin/VKA for the treatment of acute symptomatic PE with an associated significant reduction in the number of major bleeding events [14].

Of note, in all studies performed with rivaroxaban adverse events other than bleeding complications were infrequently reported [13,14].

Apixaban

Apixaban is an oral, direct inhibitor of factor Xa. The main pharmacokinetic and pharmacodynamic properties of apixaban are displayed in **Table 1.**

After the favorable results of a dose-finding Phase II study (the Botticelli study) in patients with acute DVT [15], the efficacy of apixaban for VTE treatment, using a single-drug approach, was investigated in the AMPLIFY trial.

The AMPLIFY study was a randomized, double-blind trial comparing apixaban (10 mg twice a day for 7 days, followed by 5 mg twice a day for 6 months) with enoxaparin followed by warfarin for the treatment of 5400 patients with acute VTE [16]. A total of 59 patients (2.3%) in the apixaban group and 71 patients (2.7%) in the conventional therapy group (RR: 0.84; 95% CI: 0.60–1.18) experienced an outcome event. Major bleeding occurred in 15 patients (0.6%) in the apixaban group and 49 patients (1.8%) in the conventional therapy group (RR: 0.31; 95% CI: 0.17–0.55). Major and clinically relevant nonmajor bleeding occurred in 4.3 and 9.7% of patients in the apixaban and enoxaparin/warfarin groups, respectively (RR: 0.44; 95% CI: 0.36–0.55). The results of the study showed that apixaban was noninferior in preventing recurrent VTE or VTE-related death and superior in avoiding major bleeding as well as the composite of major and clinically relevant nonmajor bleeding as compared to enoxaparin/warfarin.

The AMPLIFY-Extension was a 12 month randomized clinical trial investigating apixaban 2.5 and 5 mg b.i.d. compared with placebo for extended treatment to prevent recurrent VTE in approximately 2500 patients who had completed 6–12 months of treatment for DVT or PE [17]. Apixaban demonstrated superiority versus placebo in the reduction of the composite end point of symptomatic, recurrent VTE and death from any cause ($p < 0.001$), and in the reduction of recurrent VTE and VTE-related death (8.8% in the placebo group, compared with 1.7% in both the apixaban 2.5 and 5 mg groups; $p < 0.001$). Major bleeding events developed in 0.1% of patients receiving 5.0 mg of apixaban, 0.2% of those receiving 2.5 mg and in 0.5% of those allocated to placebo; the composite of major and

clinically relevant nonmajor bleeding in 4.3, 3.2 and 2.7%, respectively. Of note, adverse events other than bleeding complications were infrequently reported in patients receiving either dose of apixaban.

According to the results of the AMPLIFY studies, apixaban appears a suitable compound for the single-drug treatment of acute VTE, while offering a two-dose regimen that can help tailor the long-term antithrombotic treatment to the individual exigencies of patients with these thrombotic disorders [17].

Edoxaban

Edoxaban is an oral, direct inhibitor of factor Xa. The main pharmacokinetic and pharmacodymamic properties of apixaban are displayed in **Table 1.**

Edoxaban is currently being investigated in a Phase III randomized clinical trial (the Hokusai study) in comparison to warfarin in patients with VTE initially treated with parenteral drugs [101]. The results of this trial will become available in September 2013. However, whatever the study results, because of the study design edoxaban cannot qualify for the single-drug treatment of acute VTE in substitution for rivaroxaban or apixaban.

Conclusion & implications

After 50 years without any substantial progress, antithrombotic treatment of patients with VTE has finally evolved. The availability of antithrombotic compounds that can be administered orally in fixed dose, without the need for laboratory control, owing to their predictable pharmacokinetics and pharmacodynamics, has opened new horizons for the treatment of patients with VTE disorders. Dabigatran etexilate, rivaroxaban and apixaban are effective and safe enough to qualify as ideal oral anticoagulants for the treatment of patients with acute VTE. In the next few months we will know whether edoxaban can be added to this array of new oral drugs.

Can one anticoagulant provide initial and long-term treatment of patients with VTE? An anticoagulant that is effective for both acute and long-term treatment of VTE is clearly beneficial and avoids the need for any form of bridging therapy. In the EINSTEIN and AMPLIFY studies similar efficacy was observed for patients receiving rivaroxaban or apixaban from the beginning of therapy and those receiving standard therapy with a considerable reduction in the haemorrhagic risk [13,14,16]. We can conclude that at least two antithrombotic compounds, rivaroxaban and apixaban, qualify as agents that allow for the treatment of VTE disorders with a single-drug approach.

Is all that glitters gold? A number of issues will need to be carefully addressed by Phase IV studies or clinical registries. The optimal management of bleeding complications occurring in patients while on new anticoagulants remains unclear. The use in patients with severe renal failure requires caution. There is the need for studies addressing the benefit and the risks in cancer patients with VTE as well as in pregnancy. One additional major concern is the absence of a specific antidote. In spite of these limitations, we can conclude that the availability of antithrombotic compounds that are not only effective and generally safe, but also simple enough for all physicians to use for most of their patients outside of the hospital has opened a new era for the treatment of VTE disorders.

Future perspective

The demonstration that a few emerging compounds make it suitable to treat effectively and safety patients with VTE from the beginning, without the need for initial parenteral therapy, opens new interesting scenarios for the management of VTE disorders in the next 5–10 years. Most patients will be treated directly at home, irrespective of the modality of the clinical presentation, without the need for undesirable and expensive hospital admissions. The treatment of these disorders will become immediately feasible with out-of-pocket compounds whenever the clinical suspicion arises, without the need for inconvenient parenteral drugs that, in addition, may require laboratory monitoring or surveillance and expertise for their administration. We expect that in the future this highly rewarding modality of VTE treatment will become accessible also for pregnant patients and for those with cancer, who at present can only be managed with the initial and longstanding administration of parenteral heparins. We expect that formulations that make this new modality of VTE treatment suitable for patients with severe renal failure will be identified, as well as antidotes that can promptly counteract their effect wherever made necessary by bleeding complications or by emergency aggressive procedures.

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- ▪▪ of considerable interest

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▪▪ **In this randomized clinical trial, the immediate oral administration of rivaroxaban (15 mg twice a day for 3 weeks followed by 20 mg once daily) was found to be at least as effective and safe as conventional anticoagulation (enoxaparin/VKA) for the initial and long-term treatment of patients with acute proximal deep vein thrombosis.**

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▪▪ **In this randomized clinical trial, the immediate oral administration of apixaban (10 mg twice a day for 7 days followed by 5 mg twice a day for 6 months) was found to be at least as effective as conventional anticoagulation (enoxaparin/VKA) for the initial and long-term treatment of patients with acute venous thromboembolism, and was associated with a highly significant reduction in the risk of overall and major bleeding complications.**

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