CLINICAL INVESTIGATION

Pharmacotherapy of deep-venous thrombosis: current status and future perspective

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Anticoagulation is the main therapy for acute deep-vein thrombosis (DVT) of the limbs. Over the last five decades there has been little progress in the development of oral anticoagulant therapies. However, recently this area has been experiencing a rapidly changing situation thanks to the development of orally active small molecules that directly target either thrombin or activated factor X. The aim of this article is to highlight the main characteristics of these new classes of anticoagulant drugs, summarize the development program of the most advanced molecules and review the most recent published data on Phase III trials of DVT treatment for both the acute phase and the secondary prevention of the disease. Oral administration, predictable anticoagulant responses, low potential for drug–drug interactions and the positive first published clinical data, render direct thrombin and activated factor X inhibitors good candidates to replace oral vitamin K antagonist and low molecular weight heparins for DVT treatment.

Keywords: activated factor Xa inhibitors • apixaban • dabigatran etexilate • deep-vein thrombosis • edoxaban • idrabiotaparinux • oral anticoagulants • rivaroxaban • thrombin inhibitors

Venous thromboembolism (VTE) encompasses both deep-vein thrombosis (DVT) and pulmonary embolism (PE). Anticoagulation is the main therapy for both DVT and hemodynamically stable PE. The evidence for the need for anticoagulation in patients with DVT is based on studies performed more than 40 years ago [1]. Patients with DVT should be treated with anticoagulants as soon as the diagnosis is confirmed by objective testing. The main objectives of anticoagulant therapy in the initial treatment of DVT are to prevent thrombus extension and embolization to the lungs, and to prevent early recurrences of the disease [2]. Since anticoagulant drugs with a rapid onset of action are needed in this phase, three parenteral treatment options are currently available for the initial treatment of DVT: unfractionated heparin, low-molecular weight heparin (LMWH) and fondaparinux [2].

As soon as possible, most patients are also started on oral anticoagulant treatment with vitamin K antagonists (VKA) for the long-term treatment of DVT [2]. Long-term therapy has two goals: to complete the treatment of the acute episode of DVT and to prevent new episodes of VTE, including recurrent DVT and PE that are not directly related to the acute event [2]. Owing to their slow onset of action, and because of their potential to paradoxically increase the pro-thrombotic state of the patient by also inhibiting endogenous anticoagulants such as protein C and protein S, VKA can not be used as the only treatment strategy during the acute phase of disease and thus requires initial association with parenteral anticoagulants for a minimum of 5 days. After this period, oral anticoagulant therapy alone is continued until its benefits (reduction of recurrent VTE) no longer clearly outweighs its risks (increase in bleeding). The risk of recurrence after

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stopping therapy is largely determined by two factors: whether the acute episode of VTE has been effectively treated; and the patient intrinsic risk of having a new episode of VTE [2]. Therefore, guidelines suggest treating DVT for at least 3 months if transient risk factors are identified and to consider long-term treatment for patients with unprovoked proximal DVT and no risk factors for bleeding, in whom good quality anticoagulant monitoring is achievable [2]. Cancer patients have the highest risk of recurrence, and therefore guidelines suggest long-term secondary prevention, in particular, when the cancer is still active [2]. Uncertainty remains on whether a minor risk factor (such as air flight) is sufficient to define VTE as provoked and thus to support the recommendation to withhold treatment at 3 months. When the risk:benefit ratio remains uncertain, patient preference to continue or to stop treatment should be also taken into account [2]. Long-term treatment with VKAs is certainly a burden for the patient: VKAs require regular monitoring of the international normalized ratio (INR), which occurs at least once a month, if not more frequently, and VKAs are exposed to several food–drug and drug–drug interferences, also with common analgesics and antibiotics. Over the last five decades, there has been little progress in the development of oral anticoagulant therapies. However, recently this area has experienced a rapidly changing situation due to the development of orally active, small molecules that directly target either thrombin or activated factor X (FXa) in the coagulation cascade [3–5]. The aim of this review is to highlight the main characteristics of these new classes of anticoagulant drugs and to review the most recent data on DVT treatment for both the acute phase and the secondary prevention of the disease (Table 1 & 2). For the purpose of this review, we will mainly discuss drugs with already published Phase III trials.

Direct thrombin inhibitors

Direct thrombin inhibitors (DTIs) are a class of anticoagulants that bind selectively to thrombin and block its interaction with its substrates [6]. Older DTIs (i.e, recombinant hirudin, argatroban and bivalirudin) are administered parenterally and are currently approved in specific settings [6]. Newer DTIs have the advantage of being capable of being administered orally. Ximelagatran was the first of this new generation, but it was withdrawn from the world market in 2006 because of potential idiosyncratic severe (even lethal) hepatic toxicity [7]. Dabigatran etexilate, AZD0837 and MCC-977 are now under development [8]. In this review we will focus on dabigatran etexilate, the only one of these new molecules that has been already assessed in the treatment of DVT.

■ Pharmacodynamic & pharmacokinetic properties

Dabigatran etexilate is the prodrug of dabigatran, an univalent, reversible DTI that binds exclusively to the active site of thrombin and that dissociates relatively quickly from thrombin, leaving a small amount of free, enzymatically active thrombin available for control of hemostasis [9]. Dabigatran etexilate is rapidly absorbed from the GI tract with a bioavailability of 5–6% [7,10,11]. Absorption requires an acid microenvironment and is reduced by acid-suppression therapy [11]. Pantoprazole reduces dabigatran etexilate bioavailability by more than 20% [8]. Whether this is clinically relevant is not yet clear. The onset of the anticoagulant activity is rapid, with plasma levels of dabigatran peaking at 2 h. Half-life ranges between 12 and 17 h [7]. Dabigatran produces a predictable anticoagulant effect, requires no coagulation monitoring and can be given once daily (q.d.). At least 80% of dabigatran is excreted unchanged via the kidneys; therefore, use of dabigatran etexilate in patients with severe renal failure, with a creatinine clearance less than 30 ml/min, requires dose reduction and extreme caution [7]. Regarding drug–drug interactions, dabigatran requires caution when used in combination with strong inhibitors or inducers of P-glycoprotein [8]. P-glycoprotein, which is primarily located in the intestine, acts to pump drugs back into the intestinal lumen limiting systemic absorption of xenobiotics. Reduced dosages of drugs that are substrates for P-glycoprotein, such as dabigatran, may be needed when coadministered with strong P-glycoprotein inhibitors (eg, amiodarone, rifampicin, verapamil and quinidine) [8].

■ Clinical data with dabigatran

At present, no Phase III clinical data have been published for new DTIs except for dabigatran [13]. Dabigatran etexilate has been already licensed in the EU, Canada and many other countries for the prevention of VTE in patients undergoing hip- and knee-replacement surgery [14–16,101], with a recommended dose of 220 mg q.d. [101] for all patients but those with moderate renal insufficiency (creatinine clearence between 30 and 50 ml/min) and the elderly (≥75-years old), for whom the recommended dose is 150 mg q.d. [101]. A dose reduction is also recommended for patients on amiodarone treatment [101].

Moreover, the US FDA has recently approved dabigatran etexilate for nonvalvular atrial fibrillation based on results of the RE-LY trial, which compared two dabigatran etexilate doses of 110 and 150 mg twice a day (b.i.d.), with dose-adjusted warfarin in 18,113 patients [17,18]. A dose of 150 mg b.i.d. was approved for patients with a creatinine clearance >30 ml/min, whereas in patients with a creatinine

Table 1. Published Phase III trials on venous thromboembolism.

Trial	Patients	Intervention	Comparison	Primary outcome: recurrent VTE (patients [n])	Ref.
RE-COVER	Acute symptomatic VTE, DVT and/or PE, who were initially given parenteral anticoagulation therapy	Dabigatran etexilate (150 mg b.i.d.)	Dose-adjusted warfarin (INR: 2.0–3.0)	Dabigatran: 30 (2.4%) warfarin: 27 (2.1%)	[19]
EINSTEIN-DVT	Acute symptomatic DVT	Rivaroxaban (15 mg b.i.d. for the first 3 weeks followed by 20 mg q.d.)	LMWH and dose-adjusted VKA (INR: 2.0–3.0)	Rivaroxaban: 36 (2.1%) LMWH/VKA: 51 (3.0%)	[40]
EINSTEIN EXTENSION	Patients who completed an anticoagulant treatment course of 6–12 months after the index VTE event	Rivaroxaban (20 mg q.d. for 6 or 12 months)	Placebo	Rivaroxaban: 8 (1.3%) Placebo: 42 (7.1%)	[40]

b.i.d.: Twice daily; DVT: Deep venous thrombosis; INR: International normalized ratio; LMWH: Low-molecular-weight heparin; PE: Pulmonary embolism; q.d.: Once daily; VKA: Vitamin K antagonist; VTE: Venous thromboembolism.

clearance between 15 and 30 ml/min the approved dose is 75 mg b.i.d., a dose not evaluated in the RE-LY trial [17,18]. Dabigatran etexilate is also licensed in Canada for patients with nonvalvular atrial fibrillation at the two dosages tested in the RE-LY study, 110 and 150 mg b.i.d., and recently received a favorable scrutiny by the Committee for Proprietary Medicinal Products of the EMA.

Dabigatran for the treatment of acute VTE

Dabigatran etexilate is currently undergoing a large Phase III program for the evaluation of its efficacy and safety in the acute treatment in the secondary prevention of VTE [102]. RE-COVER evaluated, and RE-COVER II trial is still evaluating, dabigatran 150 mg b.i.d. versus dose-adjusted warafarin for the treatment of acute symptomatic VTE in a double-blind study [102]. The RE-MEDY and the RE-SONATE trials are recruiting patients who have been successfully treated with standard doses of an approved anticoagulant for 3–6 months or who have completed 6–18 months of treatment with VKA for confirmed acute symptomatic VTE, respectively. In the RE-MEDY trial, patients are randomized to dabigatran 150 mg b.i.d. or to dose-adjusted warfarin for 18 months; in the RE-SONATE trial, patients are randomized to dabigatran 150 mg b.i.d. or to palcebo for 6 months [102].

At the end of 2009, the RE-COVER trial was published [19]. In the RE-COVER study, investigators enrolled patients with acute VTE, DVT and/or PE, who were initially given parenteral anticoagulation therapy, in a randomized, double-blind, noninferiority trial, aimed to compare dabigatran etexilate, administered at a dose of 150 mg b.i.d., with dose-adjusted warfarin (INR: 2.0–3.0). The primary outcome of the study was the 6-month incidence of recurrent symptomatic, objectively confirmed VTE and related deaths. Safety outcomes included bleeding events, acute coronary syndromes, other adverse events and results of liver-function tests. A total of 30 of the 1274 (2.4%) dabigatran patients, as compared with 27 of the 1265 (2.1%) warfarin patients, had recurrent VTE. The difference in risk was 0.4% (95% CI: 0.8–1.5). The hazard ratio (HR) with dabigatran was 1.10 (95% CI: 0.65–1.84). Major bleeding episodes occurred in 20 (1.6%) dabigatran patients and in 24 (1.9%) warfarin patients (HR with dabigatran: 0.82; 95% CI: 0.45–1.48), and episodes of any bleeding were observed in 205 (16.1%) dabigatran patients and in 277 (21.9%) warfarin patients (HR with dabigatran: 0.71; 95% CI: 0.59–0.85). The numbers of deaths and abnormal liver function tests were similar in the two groups. Adverse events leading to discontinuation of the study drug occurred in 9.0% of patients assigned to dabigatran and 6.8% of patients assigned to warfarin ($p = 0.05$), mainly due to dyspepsia (2.9% in the dabigatran group vs 0.6% in the warfarin group). Finally, acute coronary syndromes occurred in five (0.4%) of dabigatran patients and three (0.2%) of warfarin patients ($p = 0.73$), and myocardial infarction in four (0.3%) and two (0.2%), respectively ($p = 0.69$). Further data are certainly needed before definitely concluding on the effect of dabigatran on coronary events [20,21].

Oral FXa inhibitors

Oral FXa inhibitors are a class of anticoagulants that directly inhibit FXa [3,7]. Other selective FXa inhibitors, such as fondaparinux and idraparinux, are administered

Table 2. Ongoing Phase III trials on venous thromboembolism.

Trial	Patients	Intervention	Comparison
RE-COVER II	Acute symptomatic VTE, DVT and/or PE, who were initially given parenteral anticoagulation therapy	Dabigatran etexilate (150 mg b.i.d.)	Dose adjusted warfarin (INR: 2.0–3.0)
RE-MEDY	Patients who have completed their intended 3–6 months of treatment for VTE	Dabigatran etexilate (150 mg b.i.d.)	Dose adjusted warfarin (INR: 2.0–3.0)
RE-SONATE	Patients who have completed their intended 6–18 months of treatment for VTE	Dabigatran etexilate (150 mg b.i.d.)	Placebo
AMPLIFY	Acute symptomatic VTE	Apixaban: 10 mg b.i.d. for 7 days then 5 mg b.i.d.	LMWH and dose adjusted warfarin (INR: 2.0–3.0)
AMPLIFY-EXTENSION	Patients who have completed their intended treatment for VTE	Apixaban: 2.5 or 5 mg b.i.d.	Placebo
EINSTEIN-PE	Acute symptomatic PE	Rivaroxaban (15 mg b.i.d. for the first 3 weeks followed by 20 mg q.d.)	LMWH and dose adjusted VKA (INR: 2.0– 3.0)
HOKUSAI-VTE	Acute symptomatic VTE, who were initially given parenteral anticoagulation therapy	Edoxaban 60 mg q.d.	Dose adjusted warfarin (INR: 2.0–3.0)
CASSIOPEA	Symptomatic PE with or without symptomatic DVT, who were initially given parenteral anticoagulation therapy	Idrabiotaparinux 3.0 mg subcutaneously once-weekly	Dose adjusted warfarin (INR: 2.0–3.0)

b.i.d.: Twice daily; DVT: Deep venous thrombosis; INR: International normalized ratio; LMWH: Low-molecular-weight heparin; PE: Pulmonary embolism; q.d.: Once daily; VKA: Vitamin K antagonist; VTE: Venous thromboembolism.

parenterally and act indirectly on FXa [22,23]. FXa is common to the intrinsic and the extrinsic activation pathways of the coagulation system and is the primary site of amplification of the coagulation cascade [7]. FXa inhibitors are able to inhibit both free and prothrombinase-bound FXa [7]. Several compounds are in different developing stages (e.g., edoxaban, betrixaban, LY517717 and YM150) [7]. As stated previously, we will focus on the two FXa inhibitors with already published data of Phase III trials, apixaban and rivaroxaban, and will briefly report on other upcoming clinical trials on the treatment of DVT.

■ Pharmacodynamic & pharmacokinetic properties

Apixaban is a derivative compound of razaxaban [7]. It is a small molecule able to inhibit, in a selective and reversible manner, the active site of both free and prothrombinase-bound FXa [24,25]. Apixaban has high oral bioavailability (50–85%) and a half-life of approximately 12 h [25]. It is absorbed in the GI tract and its plasma peak is achieved in approximately 3 h [25]. Food does not interfere with its absorption, so the drug generates a predictable anticoagulation effect [8]. Apixaban is metabolized in the liver by cytochrome-dependent and -independent mechanisms, and approximately 25% is cleared through the renal route, whereas the remainder appears in the feces [8].

Rivaroxaban is a potent, selective and reversible oxazolidinone-based, active-site directed FXa inhibitor [7]. It is specific for FXa and does not inhibit related serin proteases [8,26]. It is absorbed in the GI tract and has a bioavailability of 60–80% [8,27]. Plasma levels of the drug peak after 3–4 h, with a half-life ranging from 5 to 9 h in young individuals, and from 11 to 13 h in the elderly [8]. Co-administration of rivaroxaban with food increases the T_{max} from 2.75 to 4 h, with an increase in the C_{max} and overall exposure of 30–40% [8]. C_{max} is unaffected by body weight of more than 120 kg, but it is increased in subjects weighing less than 50 kg (25% increase) [8]. Almost 33% of rivaroxaban is excreted as active metabolites via the kidney [8]. No dose adjustment is required for the elderly, but caution is required for patients with severe renal insufficiency (i.e., creatinine clearance: 15–30 ml/min) [103]. Rivaroxaban is contraindicated in patients with creatinine clearance less than 15 ml/min [103]. Rivaroxaban is metabolized in the liver by cytochrome-dependent and independent mechanisms [8] and is contraindicated in patients with severe liver disease [8,103]. Rivaroxaban is also contraindicated in patients receiving concomitant treatment with strong inhibitors of both cythocrome CYP3A4 and P-glycoprotein, such as azole-compounds and ritonavir [8,103].

Clinical data

Apixaban

There are three completed Phase III clinical trials with apixaban in the setting of major orthopedic surgery, collectively termed the ADVANCE program [28–30]. They compared apixaban 2.5 mg orally b.i.d. with enoxaparin 30 mg b.i.d. and enoxaparin 40 mg subcutaneously q.d. for total knee-replacement surgery (ADVANCE-1 and -2, respectively), and with enoxaparin 40 mg for total hip-replacement surgery (ADVANCE-3). The noninferiority criteria for primary outcome were met in the ADVANCE-2 and -3 study but not in the ADVANCE-1 study. Major bleedings were reduced in ADVANCE-1 study ($p = 0.05$; nonstatistically significant), and were similar in the ADVANCE-3 study [28–30].

Recently, data of a Phase III clinical trial in patients with atrial fibrillation, the AVERROES study, was published [31]. Apixaban 5 mg b.i.d. reduced the risk of stroke or systemic embolism without increasing bleeding risk in comparison with aspirin 81–324 mg q.d. in 5599 patients with atrial fibrillation for whom VKA was unsuitable [31].

Apixaban is currently undergoing extensive evaluation in other settings, such as in the acute treatment and secondary prevention of VTE, prophylaxis of VTE in acutely ill medical patients, prevention of VTE in patients undergoing treatment for advanced cancer and in patients with a recent acute coronary syndrome [102].

Apixaban for the treatment of VTE

In a dose finding Phase II study, the Botticelli DVT study, apixaban has been assessed for the treatment of DVT [32]. In this setting, patients were randomized to receive apixaban (5 mg b.i.d., 10 mg b.i.d. or 20 mg q.d.) or LMWH followed by VKA. The primary efficacy outcome was defined as the composite of symptomatic recurrent VTE and asymptomatic worsening of the thrombotic lesion as assessed by bilateral compression ultrasonography and perfusion lung scan. It occurred in 4.7% of patients treated with apixaban and in 4.2% of LMWH/VKA-treated patients. No dose effect was observed across apixaban doses. The principal safety outcome, defined as the composite of major and clinically relevant nonmajor bleeding, occurred in 7.3% of the apixaban-treated patients and in 7.9% of LMWH/VKA-treated patients. Two Phase III studies, the AMPLIFY and AMPLIFY-extension, were subsequently planned to test apixaban for the acute and long-term therapy of VTE [102]. In the AMPLIFY study, patients with acute VTE were randomized to apixaban 10 mg b.i.d. for 7 days then 5 mg, b.i.d. or to enoxaparin 1 mg/kg b.i.d. until INR >2 then warfarin for 6 months. The AMPLIFY-estension study compares two regimens of apixaban (2.5 or 5 mg b.i.d.) with placebo in patients who have completed their intended treatment for VTE. The AMPLIFY studies are currently ongoing.

Rivaroxaban

Rivaroxaban has been already licensed in the EU, Canada and many other countries for the prevention of VTE in patients undergoing hip- and knee-replacement surgery [33–36,103]. The recommended dose is 10 mg q.d. [103]. The first dose should be administered between 6 and 10 h postoperatively. No dose adjustment is required for moderate renal insufficiency (i.e., creatinine clearance: 30–49 ml/min) [103], whereas rivaroxaban is contraindicated in patients taking azolic antimycotic drugs and HIV protease inhibitors [103]. After the completion of the large RECORD program, which assessed the efficacy and safety of rivaroxaban in patiens undergoing total hip- and total knee-replacement surgery, a number of clinical trials are currently ongoing in other settings [102]. Rivaroxaban is being tested for prophylaxis of VTE in acutely ill medical patients, prevention of stroke and systemic embolism in patients with atrial fibrillation and in patients with a recent acute coronary syndrome [102]. In ROCKET-AF, a total of 14,264 patients with atrial fibrillation were randomized in a double-blind, double-dummy manner to receive either the FXa inhibitor rivaroxaban 20 mg q.d. or dose-adjusted warfarin. Data were available only in abstract form until now [37]. Rivaroxaban was noninferior to warfarin at the on-treatment analysis, but not at the intention-to-treat analysis. Major bleeding occurred in 3.6% of patients in the rivaroxaban group versus 3.45% in the warfarin-treated group [37].

Rivaroxaban for the treatment of VTE

Phase II clinical trials evaluated rivaroxaban for the treatment of DVT with total daily doses ranging from 20 to 60 mg. Rivaroxaban was compared with standard therapy, with LMWH followed by VKA [38,39]. Following the positive results of these studies, rivaroxaban was investigated in Phase III, in the so-called Einstein programme. The Einstein-DVT trial was recently published with the Einstein-Extension study [40]. The Einstein-PE trial is still ongoing [102]. In both Einstein-DVT and -PE, rivaroxaban was administered at the dosage of 15 mg b.i.d. for the first 3 weeks followed by 20 mg q.d., and was compared with the standard therapy, LMWH and VKA, after objective diagnosis of either DVT or PE. In the EINSTEIN DVT study, 3449 patients were included: 1731 given rivaroxaban and 1718 given enoxaparin plus a VKA. The primary outcome measure of symptomatic recurrent VTE occurred in 36 (2.1%) rivaroxaban-treated patients and 51 (3.0%) LMWH/warfarin-treated patients, resulting

in an HR of 0.68 (95% CI: 0.44–1.04, p < 0.0001 for non-inferiority). Bleeding rates were similar between the two groups.

Rivaroxaban was also tested in the long-term secondary prevention of VTE in the Einstein-Extension study [40]. In this randomized, double-blind placebo-controlled study, patients who completed an anticoagulant treatment course of 6–12 months after the index VTE event, were randomized to receive rivaroxaban at a 20 mg q.d. or placebo for an additional 6 or 12 months. The primary efficacy outcome was symptomatic recurrent VTE. A total of 602 patients in the rivaroxaban group and 594 in the placebo group were included. Rivaroxaban had superior efficacy (eight events [1.3%], vs 42 with placebo [7.1%]; HR, 0.18; 95% CI: 0.09–0.39; p < 0.001). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%), versus none in the placebo group (p = 0.11). Clinically relevant nonmajor bleeding was significantly increased in the rivaroxaban group, occurring in seven and in 32 patients, respectively.

Other possible drug options

Several other molecules are under development, but at early stages. The following two drugs, idrabiotaparinux and edoxaban, are in Phase III for VTE indication.

Idrabiotaparinux

In the van Gogh DVT trial, idraparinux, a long-acting synthetic pentasaccharide, highly specific for FXa inhibition, given once weekly by subcutaneous injection for 6 months, was demonstrated to have similar efficacy and safety to standard therapy in patients with symptomatic DVT, but not in patients with PE [41]. Although the idraparinux regimen was simple and convenient, its prolonged anticoagulant effect raised questions about the potential hazard of bleeding from invasive procedures and the appropriate management of patients with major bleeding.

The subsequent addition of a biotin moiety to idraparinux (i.e., idrabiotaparinux) creates the ability to rapidly reverse the anticoagulant activity by infusing avidin.

In the recently published Equinox study, 757 patients with symptomatic DVT were randomized to idrabiotaparinux (3 mg) or to idraparinux (2.5 mg), both given subcutaneously, once weekly for 6 months [42]. It is not a proper Phase III trial because the primary objective of this study was to demonstrate bioequipotency. However, clinical data were available; recurrent VTE during the 6-month treatment period occurred in nine of 386 patients (2.3%) in the idrabiotaparinux group and in 12 of 371 patients (3.2%) in the idraparinux group. The incidence of clinically relevant bleeding was 5.2% in the idrabiotaparinux group and 7.3% in the idraparinux group. In the Cassiopea study, patients with symptomatic PE with or without symptomatic DVT have been randomized to idrabiotaparinux or to warfarin for 3 or 6 months [102]. Data from this study (if positive) have the potential to disclose new scenarios [102].

Edoxaban

Edoxaban tosylate is an oral direct FXa inhibitor. The drug is rapidly absorbed, reaching a C_{max} in 1–2 h with a mean plasma half-life of 8–10 h, and is mainly eliminated via renal excretion [43]. Other than VTE prevention in orthopedic surgery and stroke prevention in atrial fibrillation, edoxaban is undergoing a Phase III study for the treatment of acute symptomatic VTE, named the HOKUSAI-VTE study [102]. Patients with acute symptomatic proximal DVT and/or symptomatic PE confirmed by appropriate diagnostic imaging are treated with parenteral LMWH/unfractionated heparin (minimum 5 days) and are randomized to edoxaban tosylate 60 mg q.d. or to dose-adjusted warfarin to maintain INR between 2.0 and 3.0 [102].

Future perspective

There is an increasing interest on the future role of the new oral anticoagulant drugs, both DTIs and direct FXa inhibitors, in the prevention and treatment of venous and arterial thromboembolism. After decades where only one class of oral anticoagulants (i.e., the VKAs) and few parenteral drugs (in particular unfractionated heparin and low molecular weight heparin) were available, the armamentarium of drugs involved in the prevention and treatment of thromboembolic disorders is finally rapidly getting larger. After the successful development of a parenteral indirect FXa inhibitor (fondaparinux) and the more controversial development of a long-acting Xa inhibitor (idraparinux) and experience with the oral DTI (ximelagatran), new oral DTIs and FXa inhibitors are becoming imminently available. The characteristics of these new agents are clearly favorable. The oral route of administration is a major advantage over unfractionated heparin, LMWH or fondaparinux, in particular when treatment is administered for an extended period of time. The possibility to administer these drugs without the need for laboratory monitoring, thanks to their predictable pharmacodynamic and pharmacokinetic and to the limited food–drug and drug–drug interactions, is a major advantage over unfractionated heparin and VKAs. The favorable results of the first clinical trials support their potential to change current practice and management of patients requiring prophylaxis or treatment of venous and arterial thrombosis. In particular, there is the potential to

change the management of patients with DVT. Many new compounds are administered to DVT patients, according to study protocol, after initial treatment with parenteral drugs. However, in the EINSTEIN-DVT study, rivaroxaban was administered immediately as initial treatment. In a near future, a single oral agent may be sufficient to effectively treat this disease, without the need for initial treatment with parenteral drugs. Data on secondary prevention with dabigatran etexilate and rivaroxaban appears to confirm this scenario.

Of course, only future reports from daily clinical practice over the next months and years will ultimately prove if and when these changes will occur. If the baseline characteristics of these compounds and the results of Phase III studies are substantially positive, a number of issues will need to be carefully addressed in the future. In the expected case of a large prescription of these new agents, additional data from Phase IV studies or clinical registries, possibly promoted and carried out by nonprofit institutions, will become crucial. First, in Phase III trials these drugs are administered to highly selected populations, and in real-life a non-negligible proportion of patients, potentially candidates to receiving the new compounds, will present additional risk factors that would have excluded them from the trials and that may increase their risk for adverse events. At least in the first years, both VKAs and parenteral anticoagulant drugs will certainly maintain an important role in some patient's categories such as in children (no available studies), patients with severe renal insufficiency and pregnant women, among others. Second, no formal conclusion can be drawn on the treatment of cancer patients with thrombosis. Randomized studies using LMWH as control are necessary before concluding that they can replace available drugs for this indication. Third, the optimal management of bleeding complications in patients treated with a new oral anticoagulant remains unclear. There are at least three options when VKAs are used: vitamin K, fresh frozen plasma and prothrombin complexes. Activated factor VII is another potential option. There are no proven strategies available for the management of drug-related hemorrhages with the new compounds [44]. Finally, specific laboratory tests to measure drug activity in the case of an emergency, in case of recurrent events despite ongoing treatment, or just for assessing compliance, will be most welcome to improve the quality of these therapies.

At this initial stage, physicians should find the correct balance between the enthusiasm in favor of the 'brave new world' and the scepticism for any newcomer. On the one hand, the possibility to be free from INR monitoring appears as a relief for the patients. On the other hand, the concept that 'one drug fits all' could be dangerous and certainly still is a chimera. In our opinion, the real step forward in the treatment of DVT is in the availability of several treatment options to help us optimize individual patient management. Correct use of the new compounds and the correct management of particular conditions will be necessary to maintain a favorable balance between risks and benefits.

Conclusion

After decades with only one class of oral anticoagulants we are about to enter a new era in the management of thromboembolic disorders. The two agents in the most advanced stages of development are currently dabigatran etexilate and rivaroxaban, a thrombin and a FXa inhibitor, respectively. Both drugs are approved in the EU and Canada for thromboprophylaxis in patients undergoing elective hip- or knee-replacement surgery, and the FDA has approved dabigatran etexilate also for patients with nonvalvular atrial fibrillation. Several other agents are in earlier stages of development. Thanks to their predictable anticoagulant responses and low potential for drug–drug interactions, these new agents can be given in fixed doses without coagulation monitoring. These properties and the oral administration render these compounds potentially more convenient than both VKAs and low molecular weight heparins.

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Executive summary

- Anticoagulation is the main therapy for acute deep-vein thrombosis of the limbs.
- Direct thrombin and oral factor Xa inhibitors are two new classes of anticoagulants.
- Main advantages are their predictable anticoagulant responses, low potential for drug–drug interactions and administration in fixed doses without coagulation monitoring.
- Direct thrombin and activated factor X inhibitors are predicted to be potentially good candidates to replace oral vitamin K antagonists and low molecular weight heparins for deep-vein thrombosis treatment in the future.

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