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The potential role of new oral anticoagulants in the prevention and treatment of thromboembolism

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ABSTRACT

Thromboembolic disorders are among the major causes of morbidity and mortality, and anticoagulation remains the cornerstone of prevention and treatment of these disorders. Although effective, the well-established agents have significant drawbacks. Heparin, low molecular weight heparin, and fondaparinux must be given parenterally, which is inconvenient for long-term or home use. The orally administered vitamin K antagonists (such as warfarin) have a slow onset of action, thus requiring bridging therapy with a parenteral agent when immediate anticoagulation is needed (e.g. inpatients with acute deep vein thrombosis). Because vitamin K antagonists produce a variable anticoagulant response as a result of multiple drug–drug and food–drug interactions and genetic polymorphisms, frequent coagulation monitoring and dose adjustment are required to ensure a therapeutic level of anticoagulation, which is inconvenient for both patients and physicians. In the search for new agents to overcome the drawbacks associated with traditional agents, direct Factor Xa inhibitors (e.g. rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitors (e.g. dabigatran etexilate) have been developed and are undergoing late-stage clinical evaluation for the prevention and treatment of thromboembolic disorders. These new oral agents have already shown promise in large-scale clinical studies and data suggest that we have entered a new era with novel drugs that are closer than ever to the 'ideal anticoagulant'. Because these new oral agents have a rapid onset of action and can be given at fixed doses without the need for routine coagulation monitoring, they may simplify treatment paradigms and are expected to improve overall clinical outcome.

Contents

1. Introduction

Venous thromboembolism, comprising deep vein thrombosis and pulmonary embolism, is one of the leading causes of mortality and morbidity. In the US, pulmonary embolism causes almost 250,000 deaths per annum (Heit et al., 2005), and it is estimated that 12% of deaths occurring annually in the European Union are associated with venous thromboembolism (Cohen et al., 2007). Hospitalized patients are at risk of developing venous thromboembolism, with most of them having one or more risk factors (Geerts et al., 2008). Without thromboprophylaxis, the incidence of objectively confirmed deep vein thrombosis varies between 10% and 20% in patients in a general medical ward, between 15% and 40% in those undergoing major

Abbreviations: bid, twice daily; od, once daily.

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general, gynecologic, and urologic surgery or neurosurgery, and between 40% and 60% after hip or knee replacement surgery (Geerts et al., 2008). Furthermore, pulmonary embolism is the most common preventable cause of hospital death, and the prevention of pulmonary embolism is the number one strategy to improve patient safety in hospitals (Geerts et al., 2008).

Venous thromboembolism should be considered as a chronic rather than an acute illness (Zhu et al., 2009). Patients with a first episode of venous thromboembolism are at increased risk of recurrence. The cumulative incidence of recurrence is approximately 18% after 2 years, 25% after 5 years, and 30% after 8 years (Prandoni et al., 1996). Recurrent deep vein thrombosis is associated with the development of post-thrombotic syndrome (Pesavento et al., 2006), with a frequency of 15–50% after symptomatic proximal deep vein thrombosis. Post-thrombotic syndrome—a long-term complication of deep vein thrombosis—is characterized by chronic, persistent pain, swelling, skin discoloration, and the potential to result in venous ulceration in the affected limb (Biondi et al., 2010). In most cases, post-thrombotic syndrome develops within 1–2 years after deep vein thrombosis (Kahn, 2006). Pulmonary embolism predisposes patients to chronic pulmonary hypertension. It has been found that symptomatic chronic thromboembolic pulmonary hypertension affects up to 4% of patients within 2 years after the first episode of symptomatic pulmonary embolism (Pengo et al., 2004).

Effective thromboprophylaxis can reduce the incidence of venous thromboembolism in high-risk patient populations, and providing adequate intensity and duration of anticoagulation for the treatment of deep vein thrombosis can prevent recurrence and, thus, its associated consequences. Evidence-based guidelines strongly recommend the use of anticoagulants for the prevention and treatment of venous thromboembolism (Geerts et al., 2008; Kearon et al., 2008).

Currently available anticoagulants for the treatment of venous thromboembolism include unfractionated heparin, low molecular weight heparin, fondaparinux, and vitamin K antagonists. The currently recommended treatment strategies are illustrated in Fig. 1. Conventional anticoagulant treatment comprises three stages: acute treatment (i.e. ≥5 days)—to stabilize the thrombus, prevent extension and possibly subsequent fatal pulmonary embolism; secondary prevention of recurrent venous thromboembolism (≥3 months); and long-term maintenance treatment (>3 months/indefinite). With the currently available agents, immediate anticoagulation can only be achieved with parenteral anticoagulants (such as unfractionated heparin, low molecular weight heparin, or fondaparinux). Extended anticoagulant therapy currently involves the use of vitamin K antagonists (mainly warfarin). The dose of vitamin K antagonists should be adjusted to maintain a target international normalized ratio of 2.5 (range, 2.0–3.0) in most patients (Kearon et al., 2008).

Atrial fibrillation is the most common cardiac arrhythmia of clinical significance and a major risk factor for cardioembolic stroke (Lloyd-Jones et al., 2004; Singer et al., 2004). It is becoming more prevalent with the increasing elderly population. Atrial fibrillation affects 1% of the general population and up to 10% of those >80 years of age. The risk of ischemic stroke is increased four- to fivefold in patients with atrial fibrillation (Wolf et al., 1991). Acetylsalicylic acid, an antiplatelet agent, is recommended for patients with atrial fibrillation who have a low to intermediate risk of stroke, but it only provides modest protection. Although the vitamin K antagonists (such as warfarin) can reduce the risk of atrial fibrillation-related stroke by approximately 70% (Singer et al., 2004; Hart et al., 2007), they have a narrow therapeutic window, with a risk of stroke or bleeding with insufficient anticoagulation and over-anticoagulation, respectively. In addition, routine coagulation monitoring and frequent dose adjustment are burdensome for both patients and physicians (Ansell et al., 2008).

It is apparent that traditional anticoagulants are all associated with drawbacks (Table 1), and there is an increasing unmet need for new, better oral anticoagulant agents. The desired properties of such an agent are shown in Table 2 (Bauer, 2006; Haas, 2008; Bounameaux, 2009; Laux et al., 2009). In the search for an 'ideal anticoagulant', new oral agents that directly target Factor Xa (such as rivaroxaban, apixaban,

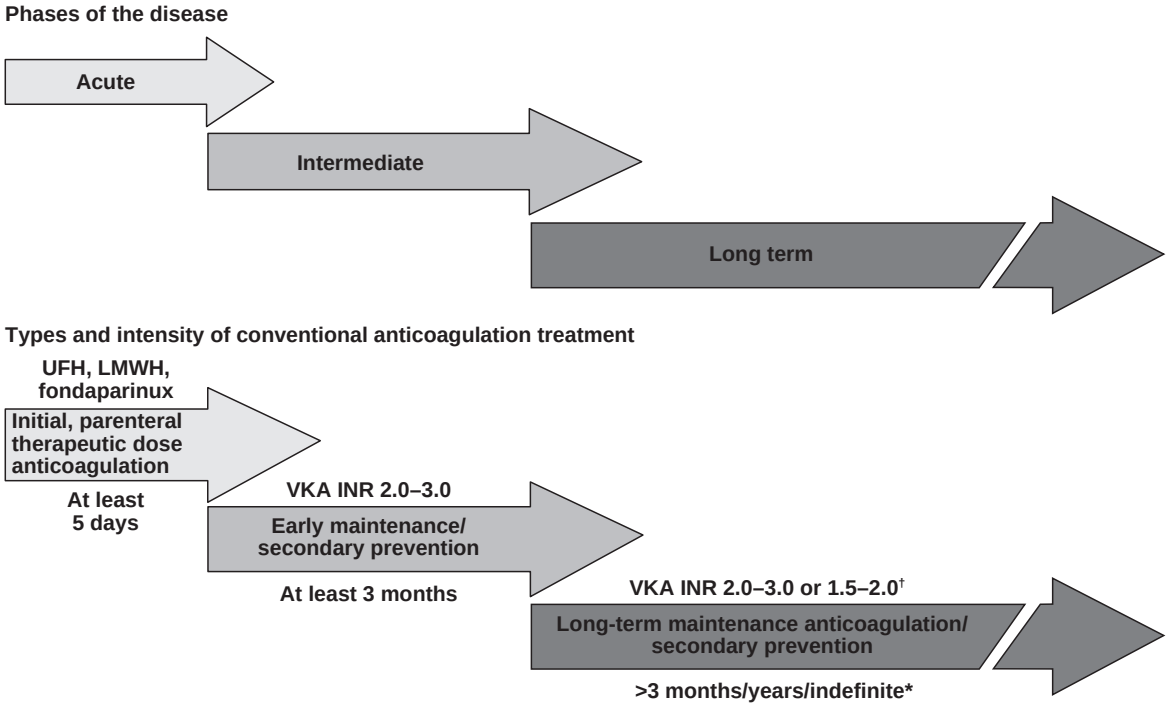

Fig. 1. Phases of venous thromboembolism and conventional treatment with anticoagulants (Kearon et al., 2008). *With re-assessment of the individual benefit–risk at periodic intervals. †International normalized ratio (INR) range of 1.5–2.0 is recommended for patients who have a strong preference for less frequent INR monitoring after the first 3 months of conventional-intensity anticoagulation (INR range: 2.0–3.0). LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist. Acute and intermediate phases of the disease/treatment are sometimes grouped under 'initial' phase.

Table 1
Disadvantages of current anticoagulation therapies (Stangier et al., 2007; Haas, 2008; Laux et al., 2009).

Warfarin	Unfractionated heparin	Low molecular weight heparin	Fondaparinux
• Slow onset and offset of action	• Potential for severe heparin-induced thrombocytopenia	• Parenteral administration	• Parenteral administration
• Unpredictable patient response	• Parenteral administration	• No inhibition of clot-bound coagulation factors	• Bleeding complications in patients with renal insufficiency
• Monitoring and dose adjustment required	• Unpredictable response due to non-specific protein and cell binding	• Risk of heparin-induced thrombocytopenia	
• Narrow therapeutic window	• Variable bioavailability	• Bleeding complications in patients with renal insufficiency	
• Multiple food and drug interactions	• No inhibition of clot-bound coagulation factors	• Animal origin (potential contamination)	
	• Laboratory monitoring required at higher doses		
	• Animal origin (potential contamination)		

edoxaban, betrixaban, and YM150) or thrombin (such as dabigatran etexilate and AZD0837) have shown promise (Weitz et al., 2008a; Perzborn, 2009; Olsson et al., 2010). After a brief description of the traditional anticoagulants currently in clinical use, this article will focus on the new agents that are in the most advanced stages of clinical development—the direct Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban and the direct thrombin inhibitor dabigatran etexilate. Their pharmacological profiles and up-to-date clinical trials for the prevention and treatment of venous thromboembolism and stroke prevention in patients with atrial fibrillation will be presented. The potential role of these new oral agents for the prevention and treatment of thromboembolic disorders will also be discussed.

2. Traditional anticoagulants

Heparins are indirect anticoagulants that bind to antithrombin, enhancing its ability to inhibit Factor Xa, thrombin, and other coagulation factors (Hirsh et al., 1998). However, clot-bound thrombin is relatively protected from inhibition by heparin–antithrombin, possibly because the heparin-binding site is inaccessible when thrombin is bound to fibrin (Weitz et al., 1990). Unfractionated heparin binds to a number of plasma proteins, which contribute to its variable anticoagulant response. In addition, unfractionated heparin is associated with the risk of developing heparin-induced thrombocytopenia and osteoporosis. Consequently, rigorous and frequent coagulation monitoring is required (Hirsh et al., 2008).

Low molecular weight heparins, derived from unfractionated heparin by chemical or enzymatic depolymerization, exhibit more predictable anticoagulation and can be given at fixed doses without coagulation monitoring. However, both unfractionated heparin and low molecular weight heparins require parenteral administration, which limits their use in the outpatient setting. Although low molecular weight heparins can also cause heparin-induced thrombocytopenia, this risk is lower compared with unfractionated heparin (Hirsh et al., 2008).

Table 2
Characteristics of an 'ideal anticoagulant' (adapted from Bauer, 2006; Haas, 2008; Bounameaux, 2009; Laux et al., 2009).

Characteristics required for an 'ideal anticoagulant'
Oral administration
No requirement for routine coagulation monitoring and dose adjustment
Wide therapeutic window
Rapid onset of action
Predictable pharmacokinetics and pharmacodynamics
Minimal interactions with foods and other drugs
Ability to inhibit free and clot-bound coagulation factors
Low non-specific binding
Availability of an antidote
No unexpected toxicities
Acceptable costs

Fondaparinux is a synthetic analog of the antithrombin-binding pentasaccharide found in unfractionated heparin or low molecular weight heparins. The pentasaccharide structure is too short to enable bridging between antithrombin and thrombin. Thus, fondaparinux selectively potentiates the anti-Factor Xa activity of antithrombin and has no effect on thrombin. Fondaparinux produces a predictable anticoagulant response (lack of variability) that precludes the need for routine coagulation monitoring or dose adjustment and does not cause heparin-induced thrombocytopenia (Hirsh et al., 2008). However, fondaparinux is contraindicated in patients with renal failure (creatinine clearance <30 mL/min). As with low molecular weight heparins, fondaparinux must also be administered subcutaneously.

Vitamin K antagonists, first introduced more than 60 years ago, were until recently the only orally active anticoagulants available for clinical use. They produce an anticoagulant effect by interfering with the γ-carboxylation of vitamin K-dependent coagulation Factors II, VII, IX, and X (Ansell et al., 2008). In addition to their slow onset of action, vitamin K antagonists are also challenging to use in clinical practice because they have a narrow therapeutic window, unpredictable pharmacokinetics and pharmacodynamics, and multiple food–drug and drug–drug interactions. Therefore, their use necessitates frequent coagulation monitoring and dose adjustment (Ansell et al., 2008). Maintaining a therapeutic anticoagulation level requires a good understanding of their pharmacokinetics and pharmacodynamics as well as optimal physician–patient communication.

3. Pharmacological profiles of the new oral anticoagulants

Factor Xa has emerged as a particularly attractive target for effective anticoagulation because it is positioned at the convergence point of the intrinsic and extrinsic coagulation pathways. Factor Xa catalyzes the conversion of prothrombin to thrombin—one molecule of Factor Xa resulting in the generation of more than 1000 thrombin molecules (Mann et al., 2003). Thus, inhibition of Factor Xa diminishes the burst of thrombin generation and thrombin-mediated coagulation activities (including the activation of platelets). However, because direct inhibition of Factor Xa does not affect the activity of the existing thrombin, it may preserve hemostasis. This, in clinical terms, may translate to efficacy with a low bleeding risk (Kubitza & Haas, 2006), although this is still controversial.

The main characteristics of the new agents that have reached phase III clinical development are summarized in Table 3.

3.1. Rivaroxaban

3.1.1. Pre-clinical studies

Rivaroxaban is an oral, highly selective, direct Factor Xa inhibitor. *In vitro* kinetic studies showed that rivaroxaban inhibits human Factor Xa competitively (inhibitory constant [K_i] 0.4 nM), with >10,000-fold

Table 3
Main pharmacological characteristics of selected new oral anticoagulants.

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran etexilate
Type of drug	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct thrombin inhibitor
Half-life (hours)	7–11	8–15	6–11	14–17
Bioavailability (%)	80–100	34–88	~50	~6
Renal elimination (%)	33 (unchanged) 33 (inactive metabolites)	~22	~40	~80
Dosage	od	bid	od	bid
T_{max} (after oral ingestion) (hours)	2–4	1.5–3.5	1.5	1.5

bid, twice daily; od, once daily; T_{max}, time to peak plasma concentration.

greater selectivity for Factor Xa than for other serine proteases (Perzborn et al., 2005). It inhibits prothrombinase (half maximal inhibitory concentration [IC_{50}]: 2.1 nM) (Perzborn et al., 2005) and clot-bound Factor Xa (IC_{50} 75 nM), with almost complete inhibition (85–97%) of clot-bound Factor Xa at concentrations ≥ 500 nM (Depasse et al., 2005). In a recent study investigating the effect of rivaroxaban on whole blood clot structure and degradability by tissue plasminogen activator, rivaroxaban was shown to increase clot permeability and degradability in whole blood and plasma clots (Varin et al., 2009). In animal models, rivaroxaban exhibited a favorable efficacy/bleeding ratio. In rat and rabbit models of arterial and venous thrombosis, rivaroxaban inhibited thrombus formation at doses that did not significantly increase bleeding times (Perzborn et al., 2005).

3.1.2. Clinical pharmacology

Rivaroxaban has been found to have predictable pharmacokinetics and pharmacodynamics, and its absolute oral bioavailability is high (80–100%) after a 10 mg dose. Rivaroxaban is rapidly absorbed with a maximum concentration appearing 2–4 h after dosing. Food (a high-fat, high-calorific meal) does not affect the area under the plasma concentration–time curve and the maximum concentration for the 10 mg dose. Plasma protein binding in humans is approximately 92–95%, with serum albumin being the main binding component (Bayer Schering Pharma AG, 2009). In healthy subjects, median inhibition levels of Factor Xa activity range from 20% to 61% for 5–80 mg doses. Maximum inhibition of Factor Xa activity occurs 1–4 h after administration. Factor Xa activities do not completely return to baseline at 24 h for doses above 5 mg (Kubitza et al., 2005). Inhibition of Factor Xa activity and prolongation of the prothrombin time correlate with rivaroxaban plasma concentrations (Mueck et al., 2007). Rivaroxaban has a dual mode of elimination, with approximately two-thirds undergoing metabolic degradation in the liver, of which half is excreted via the kidneys and the other half via the hepatobiliary route. The final one-third of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion (Bayer Schering Pharma AG, 2009). Rivaroxaban is metabolized via cytochrome P450 enzymes (3A4, 2J2) and cytochrome P450-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation (Bayer Schering Pharma AG, 2009).

Rivaroxaban has no clinically relevant drug–drug interactions with frequently used concomitant medications, such as the non-steroidal anti-inflammatory drug naproxen (Kubitza et al., 2007a) and acetylsalicylic acid (Kubitza et al., 2006a). Preliminary studies also indicate that there is no clinically relevant interaction of rivaroxaban with clopidogrel (Kubitza et al., 2007b) and the cardiac glycoside digoxin (Kubitza et al., 2006b), suggesting that these drugs can be co-administered with rivaroxaban. However, it should be noted that an increased bleeding tendency is to be expected if acetylsalicylic acid, clopidogrel, or non-steroidal anti-inflammatory drugs are administered concomitantly with any anticoagulant drugs. Rivaroxaban can also be co-administered with atorvastatin; the pharmacokinetics and pharmacodynamics of rivaroxaban are not affected by co-administration with atorvastatin and the pharmacokinetics of atorvastatin are not affected by co-administration with rivaroxaban (Kubitza et al., 2008). Because rivaroxaban is metabolized via cytochrome P450 3A4 and 2J2, and is a substrate of the transporter protein P-glycoprotein, it is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics, such as ketoconazole, itraconazole, voriconazole, and posaconazole, or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both cytochrome P450 3A4 and P-glycoprotein and can increase the plasma concentration of rivaroxaban to a clinically relevant degree, which may lead to an increased bleeding risk (Bayer Schering Pharma AG, 2009). However, agents that strongly inhibit only one of the rivaroxaban elimination pathways (either cytochrome P450 3A4 or P-glycoprotein) are expected to increase rivaroxaban plasma concentration to a lesser extent. For example, clarithromycin, considered to be a strong cytochrome P450 3A4 inhibitor but moderate P-glycoprotein inhibitor, increases the mean rivaroxaban maximum plasma concentration and the mean area under the curve to a lesser degree than ketoconazole and ritonavir. The increase in the plasma concentration of rivaroxaban with co-administration of clarithromycin is not considered clinically relevant (Bayer Schering Pharma AG, 2009). In addition, strong cytochrome P450 3A4 inducers should also be co-administered with caution (Bayer Schering Pharma AG, 2009).

3.2. Apixaban

3.2.1. Pre-clinical studies

Apixaban is a highly selective, reversible, direct Factor Xa inhibitor (Raghavan et al., 2009) that inhibits both free Factor Xa (K_i 0.08 nM) and prothrombinase activity (Shantsila & Lip, 2008; Wong et al., 2008), as well as clot-bound Factor Xa activity (Jiang et al., 2009). Preclinical studies have shown that apixaban was absorbed well in chimpanzees, dogs, and rats; the mean oral bioavailability was 51%, 88%, and 34%, respectively (Shantsila & Lip, 2008). In a rabbit arteriovenous shunt model, apixaban inhibited thrombus formation in a dose-dependent manner (Pinto et al., 2007).

3.2.2. Clinical pharmacology

In healthy subjects, apixaban was absorbed relatively rapidly, with a maximum plasma concentration achieved approximately 3 h post-dose. The mean terminal half-life of apixaban ranged between 8 and 15 h (Frost et al., 2007). Apixaban is eliminated via multiple pathways, including oxidative metabolism, renal, and intestinal routes. After oral administration, the majority (56%) of the recovered dose is in feces, with urinary excretion also representing a significant elimination pathway (approximate 22% of the recovered dose). The parent compound is the major component in plasma, urine, and feces in humans. There are also several metabolites that account for approximately one-third of the total recovered dose, the most prominent being O-demethyl apixaban sulfate (Raghavan et al., 2009). Concomitant administration of ketoconazole or other potent

cytochrome P450 3A4 inhibitors with apixaban should be avoided because they substantially increase apixaban levels. The effects of apixaban and moderate cytochrome P450 3A4 inhibitors (i.e. cimetidine, diltiazem, selective serotonin receptor inhibitors) should be used with caution. The effect of concomitant administration of apixaban and the statins, which are also metabolized by cytochrome P450 3A4, has not been reported (Carreiro & Ansell, 2008).

3.3. Edoxaban

3.3.1. Pre-clinical studies

Edoxaban (DU-176b) is an oral, direct, specific Factor Xa inhibitor (K_i 0.56 nM), with an approximate 10,000-fold selectivity for Factor Xa over thrombin (Morishima et al., 2004). Its antithrombotic efficacy was initially examined in a venous stasis thrombosis model. Edoxaban dose-dependently inhibited thrombus formation, prolonged prothrombin time, and inhibited Factor Xa activity. It also exerted a significant anticoagulant effect in a rat model of tissue factor-induced disseminated intravascular coagulation (Morishima et al., 2004). In rat and rabbit thrombosis models, edoxaban dose-dependently inhibited thrombus formation and bleeding time in rats was not significantly prolonged at an antithrombotic dose. A subsequent *in vitro* study confirmed the concentration-dependent and competitive inhibition of human Factor Xa by edoxaban, without affecting platelet aggregation (Furugohri et al., 2008).

3.3.2. Clinical pharmacology

In a single-dose (60 mg) study in healthy subjects, the maximum plasma concentration of edoxaban was observed at 1.5 h after administration, corresponding to the maximum inhibition of Factor Xa activity, which returned to baseline levels by 12 h. The inhibition of Factor Xa led to a corresponding reduction in thrombin generation and prolongation of clotting times (Zafar et al., 2007). In a multiple-dose study, edoxaban prolonged the activated partial thromboplastin time and the prothrombin time in a dose-dependent manner (Ogata et al., 2010). The half-life ranged from 5.8 to 10.7 h, and the rate of plasma protein binding was 40–59%. Urinary excretion of unchanged edoxaban was 36% and 45% of the dose administered (90 and 120 mg daily doses, respectively). There are currently no data available on drug–drug interactions for edoxaban. Food had no clinically significant effects on the pharmacokinetics and pharmacodynamics of edoxaban (Ogata et al., 2010).

3.4. Dabigatran etexilate

The serine protease thrombin is the final mediator in the coagulation cascade that leads to the production of fibrin (Fig. 2) (Mann, 1984). Thrombin is also a potent activator of platelets. Direct thrombin inhibitors may offer potential efficacy advantages over indirect thrombin inhibitors (such as heparins or low molecular weight heparin). In addition to inactivating free thrombin, direct thrombin inhibitors are also able to inactivate fibrin-bound thrombin—an important trigger of thrombus expansion (Kumar et al., 1995; Weitz, 2010). Synthetic, small-molecule, direct thrombin inhibitors represent a new therapeutic class of antithrombotic agents. Ximelagatran, a prodrug of the active metabolite melagatran, was the first oral direct thrombin inhibitor to be evaluated (Weitz & Bates, 2005). Ximelagatran underwent extensive phase III studies for several indications, including the prevention and treatment of venous thromboembolism and stroke prevention in patients with atrial fibrillation (Francis et al., 2003; Schulman et al., 2003; Albers et al., 2005; Fiessinger et al., 2005). It was briefly launched in Europe for the prevention of venous thromboembolism after total hip or total knee replacement surgery, and also demonstrated potential for preventing thromboembolic events in patients with atrial fibrillation. However, it was withdrawn from the market because of hepatotoxicity (Testa et al., 2007). Nevertheless, the ximelagatran studies provided proof of principle that effective anticoagulation could be achieved with fixed-dose, unmonitored oral agents, which set the stage for dabigatran etexilate.

3.4.1. Pre-clinical studies

Dabigatran etexilate is an oral prodrug of dabigatran, a specific, reversible thrombin inhibitor. Human thrombin is dose-dependently and competitively inhibited by dabigatran with a Ki of 4.5 nM (Eisert et al., 2010). Dabigatran was well tolerated and showed a dose-dependent prolongation of activated partial tissue thromboplastin time in conscious rats and rhesus monkeys. In a rat model of thrombosis, maximum inhibition of thrombus formation was observed 30 min after

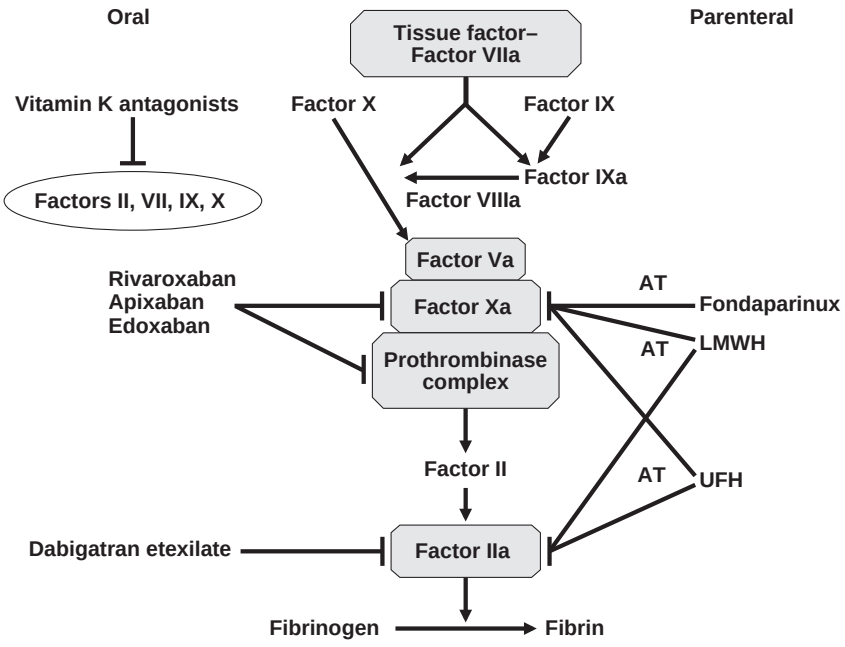

Fig. 2. Targets of conventional and new anticoagulant drugs. AT, antithrombin; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

oral administration of dabigatran, and when tested in rabbits dabigatran resulted in a dose-dependent inhibition of thrombus weight. In a rat tail bleeding model, bleeding time was not prolonged by dabigatran at an antithrombotic effective dose (Eisert et al., 2010).

3.4.2. Clinical pharmacology

After oral administration, dabigatran etexilate is absorbed rapidly and completely converted by esterases to dabigatran, with an oral bioavailability of approximately 6% (Stangier et al., 2007). Peak plasma concentrations are reached within 2 h of administration. Dabigatran has a half-life of approximately 14–17 h, and this is not dose dependent (Stangier et al., 2007). Dabigatran etexilate and dabigatran are not metabolized by the cytochrome P450 enzymes to any significant extent (Stangier, 2008). Elimination of dabigatran occurs predominantly via the kidneys, with approximately 80% excreted unchanged in the urine (Stangier, 2008). Because of its predictable pharmacokinetics and pharmacodynamics, routine coagulation monitoring is not required. There is no clinically relevant influence of atorvastatin, digoxin, or diclofenac on the pharmacokinetics of dabigatran etexilate or vice versa (Stangier, 2008; Stangier et al., 2009). The only drugs that should not be co-administered with dabigatran etexilate are quinidine and amiodarone because of competition for the P-glycoprotein transporter (Boehringer Ingelheim International GmbH, 2009).

4. Current state of clinical development of new oral anticoagulants

4.1. Prevention of venous thromboembolism in major orthopedic surgery

4.1.1. Rivaroxaban

The efficacy and safety of rivaroxaban has been evaluated in four phase III studies (REgulation of Coagulation in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism [RECORD]) for the prevention of venous thromboembolism after total hip replacement or total knee replacement surgery in a total of more than 12,500 patients. In all of the RECORD studies, rivaroxaban was given as 10 mg once daily (od). The primary efficacy endpoint was the composite of deep vein thrombosis, as detected by mandatory, bilateral venography, non-fatal pulmonary embolism, and all-cause mortality (total venous thromboembolism), and the main secondary efficacy endpoint was the composite of proximal deep vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolism-related death (major venous thromboembolism). The primary safety endpoint was major bleeding, defined as clinically overt bleeding that was fatal, occurred in a critical organ (e.g. retroperitoneal, intracranial, intraocular, or intraspinal), required re-operation, or extra-surgical-site bleeding that was associated with a fall in hemoglobin of 2 g/dL or more or required an infusion of ≥2 units of blood.

The RECORD1 study showed that extended-duration rivaroxaban (beginning 6–8 h after surgery and continuing for 31–39 days) was significantly more effective than extended-duration enoxaparin (40 mg od, beginning 12 h before surgery and continuing for 31–39 days) in patients undergoing total hip replacement surgery, with an absolute risk reduction of 2.6% ($P<0.001$) and 1.7% ($P<0.001$) for total and major venous thromboembolism, respectively. The rate of major bleeding was not significantly different between the groups (Eriksson et al., 2008).

In the RECORD2 study, extended-duration thromboprophylaxis for 31–39 days with rivaroxaban (beginning 6–8 h after surgery) was compared with a short-term regimen of enoxaparin 40 mg (starting 12 h before surgery) for 10–14 days followed by placebo in patients undergoing total hip replacement surgery. The primary efficacy endpoint occurred in significantly fewer patients receiving extended-duration thromboprophylaxis with rivaroxaban than in those receiving short-term enoxaparin plus placebo (absolute risk reduction 7.3%, $P<0.0001$). Similarly, extended thromboprophylaxis with rivaroxaban was more effective than short-term enoxaparin plus placebo in reducing the incidence of major venous thromboembolism, with an absolute risk reduction of 4.5% ($P<0.0001$). Rates of bleeding were low and not significantly different between the rivaroxaban and enoxaparin regimens (Kakkar et al., 2008).

The efficacy and safety of rivaroxaban for the prevention of venous thromboembolism have also been investigated in patients undergoing total knee replacement surgery. RECORD3 compared oral rivaroxaban 10 mg od (beginning 6–8 h after surgery) with subcutaneous enoxaparin 40 mg od (beginning 12 h before surgery) for 10–14 days. Rivaroxaban was significantly more effective than enoxaparin in reducing total venous thromboembolism (absolute risk reduction 9.2%; $P<0.001$) and major venous thromboembolism (absolute risk reduction 1.6%; $P=0.01$). Moreover, rivaroxaban reduced the incidence of symptomatic venous thromboembolism (absolute risk reduction 1.3%; $P=0.005$). There was no significant difference in the incidence of major bleeding between the two groups (Lassen et al., 2008).

The RECORD4 study compared rivaroxaban with the enoxaparin regimen normally used in North America (30 mg twice daily [bid], starting 12–24 h after surgery) in patients undergoing total knee replacement surgery. Rivaroxaban showed significantly better efficacy for the primary endpoint than enoxaparin, with an absolute risk reduction of 3.19% ($P=0.0118$). There was no statistically significant difference in the incidence of major venous thromboembolism or major bleeding between rivaroxaban- and enoxaparin-treated patients (Turpie et al., 2009).

Taken together, rivaroxaban is the only new oral anticoagulant that has demonstrated superiority to both enoxaparin regimens (40 mg od and 30 mg bid) for the prevention of venous thromboembolism in patients undergoing total hip or total knee replacement surgery. Rivaroxaban has been approved in more than 100 countries worldwide for the prevention of venous thromboembolism after elective hip or knee replacement surgery in adults. However, there has been some debate regarding the different definitions of major bleeding used in phase III trials for the prevention of venous thromboembolism. The exclusion of surgical-site bleeding from the major bleeding definition in the RECORD studies has caused some concern (Ufer, 2010). Nonetheless, when surgical-site bleeding events were included in the analysis of the major bleeding rates, the rivaroxaban regimens showed a rate that was comparable with that of the enoxaparin regimens. There also seems to be a difference between the definitions of major bleeding that surgeons would use in clinical practice from those used in clinical studies reporting the safety profiles of newer anticoagulants. Furthermore, bleeding definitions may differ from study to study. Findings from a recent international survey suggest that misperceptions about the benefit-to-harm profiles of thromboprophylactic therapies may incorrectly inform treatment choices in patients at high risk of postoperative venous thromboembolism (Ginzburg & Dujardin, in press).

4.1.2. Apixaban

Apixaban has been evaluated in three phase III studies (Apixaban Dose Orally vs. Anticoagulation with Enoxaparin [ADVANCE]) for the prevention of venous thromboembolism in more than 11,600 patients undergoing major orthopedic surgery. ADVANCE-1 investigated the efficacy and safety of apixaban 2.5 mg bid (with the first dose started on the morning of the day after surgery), compared with enoxaparin 30 mg bid (starting 12–24 h after surgery) in patients undergoing total knee replacement surgery (both regimens were administered for 10–14 days). The results indicated that apixaban did not meet the prespecified criteria for non-inferiority compared with enoxaparin ($P=0.06$ for non-inferiority) with respect to the primary efficacy endpoint (a composite of symptomatic or asymptomatic deep

vein thrombosis, pulmonary embolism, and all-cause mortality). The rates of major bleeding (International Society of Thrombosis and Hemostasis definition: fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a fall in hemoglobin of 20 g/L or more, or required an infusion of ≥2 units of blood) were 0.7% and 1.4% for apixaban and enoxaparin, respectively (P = 0.053). The rate of major and clinically relevant non-major bleeding was lower compared with the enoxaparin regimen (P = 0.03) (Lassen et al., 2009).

The ADVANCE-2 study compared apixaban 2.5 mg bid with enoxaparin 40 mg od (starting 12 h before surgery) in patients undergoing total knee replacement surgery. The results showed that apixaban was superior to enoxaparin for the prevention of the primary efficacy endpoint (the composite of adjudicated asymptomatic or symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality), with an absolute risk reduction of 9.3% (P<0.0001 for non-inferiority). Apixaban was also more effective than enoxaparin for the prevention of major venous thromboembolism (symptomatic or asymptomatic proximal deep vein thrombosis, non-fatal pulmonary embolism, and venous thromboembolism-related mortality; P = 0.0186 for superiority). The frequency of major or clinically relevant non-major bleeding events did not differ between treatment groups (Lassen et al., 2010a).

The ADVANCE-3 study evaluated apixaban (2.5 mg bid) compared with enoxaparin 40 mg od for the prevention of venous thromboembolism after total hip replacement surgery. The trial has been completed and the results were presented at the International Congress on Thrombosis, in July 2010, Milan, Italy. The results showed that apixaban was more effective than enoxaparin in reducing the primary efficacy endpoint (composite of asymptomatic and symptomatic deep vein thrombosis, pulmonary embolism, and all-cause mortality during treatment; P<0.0001 for both non-inferiority and superiority), without increasing major or clinically relevant bleeding (Lassen et al., 2010b).

4.1.3. Edoxaban

Edoxaban has shown promising results in two phase II studies for the prevention of venous thromboembolism in a total of 1426 patients undergoing total knee replacement or total hip replacement surgery (Fuji et al., 2010; Raskob et al., 2010). In the first study, edoxaban (5–60 mg) was administered for 11–14 days in patients undergoing total knee replacement surgery. There was a dose-dependent reduction in venous thromboembolism (the composite of asymptomatic and symptomatic deep vein thrombosis and symptomatic pulmonary embolism) versus placebo, without increases in major or clinically relevant bleeding (Fuji et al., 2010).

A subsequent study in patients undergoing total hip replacement surgery compared different doses of edoxaban with dalteparin. Both drugs were administered 6–8 h postoperatively and continued for 7–10 days. Edoxaban was more effective than dalteparin in preventing venous thromboembolism (defined as deep vein thrombosis or pulmonary embolism during the treatment period). A clear dose–response relationship for efficacy was demonstrated. The observed incidence of bleeding was similar across study groups (Raskob et al., 2010).

A phase IIb study evaluated the efficacy, safety, and dosage regimen of edoxaban in patients undergoing total hip replacement surgery. Double-blind edoxaban 15 mg or 30 mg od (starting within 6–24 h after surgery), or open-label, subcutaneous enoxaparin 20 mg bid (starting within 24–36 h after surgery) was administered for 11–14 days. The primary efficacy endpoint was the composite of asymptomatic deep vein thrombosis, symptomatic pulmonary embolism, or symptomatic deep vein thrombosis. The primary safety endpoint was the incidence of major and clinically relevant non-major bleeding. Edoxaban showed potential efficacy similar to enoxaparin for the prevention of thromboembolic events in patients undergoing total hip replacement surgery. The incidence of major and clinically relevant non-major bleeding was comparable with that of enoxaparin (Fuji et al., 2009).

4.1.4. Dabigatran etexilate

The efficacy and safety of dabigatran etexilate in thromboprophylaxis after total knee replacement and total hip replacement surgery have been evaluated in three double-blind, randomized phase III studies (Eriksson et al., 2007a, 2007b; The RE-MOBILIZE Writing Committee, 2009) in a total of 8210 patients. In all three studies, dabigatran etexilate at doses of 150 mg or 220 mg od, starting with a half dose, was compared with subcutaneous enoxaparin. The primary efficacy endpoint was total venous thromboembolism (a composite of venographically detected or symptomatic deep vein thrombosis and/or symptomatic pulmonary embolism and all-cause mortality). The primary safety endpoint was the occurrence of bleeding events during treatment. Major bleeding events were defined as: fatal, retroperitoneal, intracranial, intraocular, or intraspinal bleeding; or bleeding warranting treatment cessation or leading to re-operation; clinically overt bleeding (including surgical-site bleeding) associated with a ≥2 g/dL fall in hemoglobin; or clinically overt bleeding leading to a transfusion of ≥2 units of packed cells or whole blood.

The RE-NOVATE study compared the efficacy and safety of two doses of dabigatran etexilate (starting 1–4 h after surgery) with enoxaparin 40 mg od (starting the evening before surgery), in patients undergoing total hip replacement surgery, with a duration of prophylaxis of 28–35 days (Eriksson et al., 2007b). Both doses of dabigatran etexilate were non-inferior to enoxaparin (P<0.0001 for non-inferiority). There was no significant difference in the frequency of major bleeding events during treatment between both dabigatran etexilate doses and enoxaparin (P = 0.60 for dabigatran 150 mg and P = 0.44 for dabigatran 220 mg).

The RE-MODEL study compared the efficacy and safety of dabigatran etexilate (starting 1–4 h after surgery), with enoxaparin 40 mg od (starting the evening before surgery), for the prevention of venous thromboembolism after total knee replacement surgery. The treatment duration was 6–10 days. Both doses of dabigatran etexilate were non-inferior to enoxaparin (P = 0.0003 for the dabigatran 220 mg and P = 0.017 for the dabigatran 150 mg dose groups for non-inferiority). There was no significant difference in bleeding events between either dose of dabigatran etexilate and enoxaparin (P = 1.0 for dabigatran 150 mg and P = 0.82 for dabigatran 220 mg) (Eriksson et al., 2007a).

However, in the RE-MOBILIZE study in patients undergoing total knee replacement surgery (duration of prophylaxis 12–15 days), both doses of dabigatran etexilate (starting 6–12 h after surgery) failed to meet non-inferiority compared with enoxaparin 30 mg bid for the primary efficacy endpoint (The RE-MOBILIZE Writing Committee, 2009), possibly due to the higher dose of enoxaparin (30 mg bid) and the later starting time with dabigatran compared with the RE-MODEL trial.

In all three trials in patients undergoing total hip replacement or total knee replacement surgery, dabigatran etexilate had a similar safety profile to that of enoxaparin. There was no significant difference in the frequency of major bleeding events during treatment between the dabigatran etexilate doses and the enoxaparin regimens. Dabigatran etexilate has been approved in the European Union and several other countries for the prevention of venous thromboembolism after total hip replacement or total knee replacement surgery. In the US, it has also been approved recently for stroke prevention in patients with atrial fibrillation.

4.2. Prevention of venous thromboembolism in medically ill patients

4.2.1. Rivaroxaban

Rivaroxaban is undergoing a phase III study for the prevention of venous thromboembolism in hospitalized medically ill patients

(NCT00571649). The Multicenter, rAndomized, parallel Group Efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically iLL patients comparing rivaroxabAN with enoxaparin (MAGELLAN) study is investigating the efficacy and safety of venous thromboembolism prophylaxis with rivaroxaban 10 mg od for 35 days, compared with short-term enoxaparin 40 mg od administered for 10 days, followed by oral placebo in hospitalized acutely ill medical patients. This study was completed in October 2010.

4.2.2. Apixaban

Apixaban is also undergoing a phase III study for the prevention of venous thromboembolism in hospitalized medically ill patients (ADOPT; NCT00457002). This study is comparing apixaban 2.5 mg bid for 30 days with enoxaparin 40 mg od for 6–14 days followed by placebo for the prophylaxis of venous thromboembolism in acutely ill medical patients during and after hospitalization. This study is currently recruiting and is due to complete in May 2011.

4.3. Treatment of venous thromboembolism

4.3.1. Rivaroxaban

Two phase II studies have been conducted with rivaroxaban for the treatment of deep vein thrombosis. In the ODIXa-DVT (Oral DIrect Factor Xa inhibitor BAY 59-7939 in patients with acute symptomatic Deep Vein Thrombosis) study, 613 patients with proximal deep vein thrombosis were randomized to receive either rivaroxaban (10, 20, or 30 mg bid, or 40 mg od) or enoxaparin followed by vitamin K antagonists for 12 weeks (Agnelli et al., 2007). Enoxaparin was administered for at least 5 days and until the international normalized ratio had reached 2–3 for 2 consecutive days. Thrombotic burden at day 21 was consistently reduced with each rivaroxaban regimen to a similar extent as with enoxaparin/vitamin K antagonist therapy. Major bleeding occurred in 1.7–3.3% of patients in the rivaroxaban group compared with none in the standard therapy group.

In the phase II EINSTEIN DVT study, 543 patients with acute symptomatic deep vein thrombosis were randomized to receive one of three dose regimens of rivaroxaban (20, 30, or 40 mg od) or the combination of low molecular weight heparin and vitamin K antagonist for 3 months (Buller et al., 2008). The minimum duration of heparin treatment was 5 days and was continued until a stable international normalized ratio of >2 was observed on two measurements at least 24 h apart. The primary efficacy outcome was the composite of symptomatic, recurrent deep vein thrombosis, symptomatic fatal or non-fatal pulmonary embolism, and asymptomatic deterioration in thrombotic burden, as assessed by compression ultrasound and perfusion lung scan at 3 months. The primary efficacy endpoint occurred in 5.4–6.6% of patients receiving rivaroxaban versus 9.9% in the standard treatment group. The study did not demonstrate a dose trend for the primary efficacy endpoint in rivaroxaban-treated patients. The primary safety endpoint (any clinically relevant bleeding) occurred in 2.2–6.0% of patients receiving rivaroxaban versus 8.8% in the standard therapy group. Overall, the results of this study demonstrated that rivaroxaban 20–40 mg od had good efficacy and safety for the treatment of acute symptomatic deep vein thrombosis.

The EINSTEIN program consists of three multicenter, randomized, open-label, phase III studies: EINSTEIN DVT (the second study with this study name; www.clinicaltrials.gov; NCT00440193), EINSTEIN PE (NCT00439777), and EINSTEIN Extension.

EINSTEIN DVT, involving over 3400 patients, investigated the efficacy and safety of rivaroxaban in patients with acute symptomatic deep vein thrombosis without symptomatic pulmonary embolism. Rivaroxaban 15 mg bid was given for the first 3 weeks, followed by 20 mg od, compared with enoxaparin (1.0 mg/kg bid) for ≥5 days, plus a vitamin K antagonist with a target international normalized ratio of 2.5 for a predefined treatment period of 3, 6, or 12 months. The primary efficacy outcome was the cumulative incidence of symptomatic recurrent venous thromboembolism. The principal safety outcome was the composite of major and clinically relevant non-major bleeding. This study has been completed recently and the results were recently published (Einstein Investigators, 2010). The results showed that rivaroxaban (15 mg bid for 21 days followed by 20 mg od) was non-inferior for the prevention of recurrent symptomatic venous thromboembolism versus the current standard of care (enoxaparin 1.0 mg/kg bid for ≥5 days followed by a vitamin K antagonist titrated to an international normalized ratio of 2.0–3.0).

EINSTEIN PE is currently ongoing and evaluating rivaroxaban in patients with confirmed acute symptomatic pulmonary embolism with or without symptomatic deep vein thrombosis. The rivaroxaban regimen used is the same as that in the EINSTEIN DVT study, with a predefined treatment duration of 3, 6, or 12 months. This study is currently recruiting with an estimated enrollment of 4000 patients.

EINSTEIN Extension, a randomized, double-blind, placebo-controlled, superiority study in 1197 patients, evaluated the efficacy and safety of rivaroxaban 20 mg od for 6 or 12 months compared with placebo in patients completing 6 or 12 months of anticoagulant treatment for their acute episode of venous thromboembolism (Einstein Investigators, 2010). The primary efficacy outcome was symptomatic recurrent venous thromboembolism (i.e. the composite of recurrent deep vein thrombosis, non-fatal pulmonary embolism, and fatal pulmonary embolism). The principal safety outcome was major bleeding. During the treatment period, symptomatic recurrent venous thromboembolism occurred in 1.3% of the rivaroxaban recipients compared with 7.1% of placebo-treated patients ($P<0.0001$)—a relative risk reduction of 82% with rivaroxaban. The incidence of symptomatic recurrent venous thromboembolism was similar between the study groups during the 1-month observation period after the cessation of study medication. Major bleeding did not occur in placebo patients and was observed in 0.7% of rivaroxaban recipients ($P=0.106$). However, there was no incidence of fatal bleeding or bleeding in a critical site. Clinically relevant non-major bleeding occurred in 1.2% and 5.4% of the placebo and rivaroxaban recipients, respectively. There was no evidence of liver toxicity. It was concluded that, based on the estimated cumulative incidence rates, approximately 15 patients need to be treated to prevent one recurrent venous thromboembolic event.

4.3.2. Apixaban

BOTTICELLI was a phase II study in patients with acute symptomatic proximal deep vein thrombosis or extensive calf vein thrombosis (Buller et al., 2008). Five-hundred-and-twenty patients were randomized to receive either different doses of apixaban or the standard treatment (low molecular weight heparin/vitamin K antagonist for 84–91 days). The primary efficacy endpoint (the composite of symptomatic recurrent venous thromboembolism and asymptomatic deterioration on bilateral compression ultrasound or perfusion lung scan) occurred in 4.2% of patients receiving conventional therapy (low molecular weight heparin or fondaparinux followed by a vitamin K antagonist), and was similar in the apixaban 5 mg and 10 mg bid groups (6.0% and 5.6%, respectively), and lower in the apixaban 20 mg od group (2.6%). The incidence of major and clinically relevant non-major bleeding was similar between apixaban-treated patients and those receiving conventional therapy.

Two phase III studies are currently ongoing with apixaban for the treatment of venous thromboembolism (the AMPLIFY program). The AMPLIFY study is assessing apixaban (10 mg bid for 7 days, followed by 5 mg bid for 6 months) versus conventional treatment (enoxaparin plus warfarin) for the treatment of patients with deep vein thrombosis or pulmonary embolism (NCT00643201). The AMPLIFY-EXT study is evaluating apixaban 2.5 mg or 5.0 mg bid compared with placebo for 12 months in patients with deep vein thrombosis or

pulmonary embolism who have completed their intended treatment (NCT00633893). Both studies are currently recruiting participants.

4.3.3. Edoxaban

A phase III study (HOKUSAI) is currently ongoing, investigating the efficacy and safety of edoxaban 60 mg od (with low molecular weight heparin/unfractionated heparin), versus low molecular weight heparin/unfractionated heparin followed by warfarin (target international normalized ratio of 2.0–3.0), in the treatment of venous thromboembolism in patients with acute symptomatic deep vein thrombosis and/or pulmonary embolism. The maximum treatment duration is 12 months. The primary efficacy endpoint is the recurrence of symptomatic venous thromboembolism (i.e. the composite of deep vein thrombosis, non-fatal pulmonary embolism, and fatal pulmonary embolism). The primary safety endpoint is the incidence of major and clinically relevant non-major bleeding during treatment. This study is currently recruiting participants (NCT00986154).

4.3.4. Dabigatran etexilate

The RE-COVER study was a randomized, double-blind, non-inferiority trial that evaluated the efficacy and safety of dabigatran etexilate (150 mg bid) versus warfarin for 6 months in the treatment of acute venous thromboembolism involving a total of 2564 patients (Schulman et al., 2009). Recurrent symptomatic venous thromboembolism occurred in 2.4% of patients receiving dabigatran etexilate compared with 2.1% of those receiving dose-adjusted warfarin ($P<0.001$ for non-inferiority). The rate of major bleeding was similar for the dabigatran and warfarin groups (1.6% and 1.9%, respectively). Major or clinically relevant non-major bleeding occurred in 5.6% of patients receiving dabigatran etexilate and in 8.8% of patients receiving warfarin ($P=0.002$). The incidence of death, acute coronary syndrome, and abnormal liver function tests were similar between the two groups. The study drug was discontinued in 9% of patients receiving dabigatran etexilate and in 6.8% of patients receiving warfarin ($P=0.05$). The only adverse effect directly attributable to dabigatran in this study was dyspepsia, occurring in 3% of patients (Schulman et al., 2009).

The ongoing phase III RE-MEDY study is evaluating dabigatran etexilate (150 mg bid) versus warfarin for the secondary prevention of venous thromboembolism (treatment period 18 months) after 3–6 months' treatment with an approved anticoagulant (NCT00329238). The primary outcome is the composite of recurrent symptomatic venous thromboembolism and deaths related to venous thromboembolism during the treatment period.

The RE-SONATE study is assessing dabigatran etexilate (150 mg bid) versus placebo (treatment period 6 months) for the secondary prevention of venous thromboembolism after 6–18 months of treatment with vitamin K antagonist (NCT00558259). The primary endpoints are symptomatic recurrent venous thromboembolism and major bleeding. Both studies are currently recruiting participants.

4.4. Stroke prevention in atrial fibrillation

4.4.1. Rivaroxaban

Rivaroxaban has been investigated in a phase III study in approximately 14,000 patients with non-valvular atrial fibrillation: Rivaroxaban Once daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF; NCT00403767). The efficacy and safety of rivaroxaban (20 mg od, or 15 mg od in patients with a creatinine clearance of 30–49 mL/min) were compared with dose-adjusted warfarin (titrated to a target international normalized ratio of 2.5 [range 2.0–3.0]), for the prevention of stroke and non-central nervous system embolism in patients with non-valvular atrial fibrillation. The primary efficacy endpoint was the composite of stroke and non-central nervous system systemic embolism. The primary safety endpoint was the composite of major and non-major clinically relevant bleeding events (Patel et al., 2009). This study has been completed recently, and the results were presented at the annual American Heart Association congress in November 2010. In this phase III study, rivaroxaban was non-inferior to warfarin for prevention of stroke and non-central nervous system embolism (intention-to-treat population), and rivaroxaban was superior to warfarin when patients were taking study drug (on-treatment population). The rates of major bleeding and the composite of major and non-major clinically relevant bleeding events were comparable between rivaroxaban-treated and warfarin-treated patients. Rivaroxaban actually resulted in fewer intracranial and fatal bleeding events.

4.4.2. Apixaban

Two studies are ongoing with apixaban. In the Apixaban for Reduction In Stroke and Other ThromboembolLic Events in atrial fibrillation (ARISTOTLE) study (NCT00412984), 18,206 patients with atrial fibrillation are randomized to receive either warfarin (target international normalized ratio of 2.0–3.0) or apixaban (5 mg or 2.5 mg bid). The main objective of the study is to determine whether apixaban is non-inferior to warfarin at reducing the combined outcome of stroke (ischemic or hemorrhagic) and systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke (Lopes et al., 2010). This study is currently ongoing but not recruiting participants.

In the AVERROES study (NCT00496769), apixaban 5 mg bid (or 2.5 mg bid in selected patients) was compared with acetylsalicylic acid (81 mg to 324 mg od) for the prevention of stroke or systemic embolism in 5600 patients with atrial fibrillation and at least one risk factor for stroke who are unsuitable for or unwilling to take a vitamin K antagonist. The primary efficacy endpoint was stroke (ischemic or hemorrhagic) or systemic embolism, and the primary safety endpoint was major bleeding (Eikelboom et al., 2010). The results of this study were presented at the European Society of Cardiology annual congress in September 2010. Overall, the data showed that, compared with acetylsalicylic acid, apixaban significantly reduced the risk of stroke or systemic embolism, with no significant increased risk of major hemorrhage ($P=0.33$).

4.4.3. Edoxaban

Edoxaban has been assessed in a phase II study for the prevention of stroke in patients with atrial fibrillation (Weitz et al., 2008b). A total of 1146 patients were randomly assigned to receive either one of four fixed dose regimens of edoxaban (30 mg od, 30 mg bid, 60 mg od, or 60 mg bid) or warfarin dose adjusted to a target international normalized ratio of 2.0–3.0 for 12 weeks. The incidence of major and clinically relevant non-major bleeding events was significantly higher compared with that in the warfarin group (3.2%) for the edoxaban 60 mg bid (10.6%; $P=0.002$) and 30 mg bid (7.8%; $P<0.05$) regimens, but similar to that in warfarin-treated patients for the edoxaban 30 mg od and 60 mg od groups (3.0% and 4.7%, respectively, versus 3.2% in the warfarin group). The incidence of stroke was similar across treatment groups.

The ongoing phase III Effective aNticoaGulation with factor xA next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) trial is comparing edoxaban (30 mg and 60 mg od) with warfarin for the prevention of stroke and systemic embolic events in approximately 20,500 patients. The edoxaban regimens allow for dose reduction in patients with anticipated increased drug exposure. Recruitment began in November 2008 and the expected median follow-up period is 24 months (Ruff et al., 2010).

4.4.4. Dabigatran etexilate

A phase III study with dabigatran etexilate (the Randomized Evaluation of Long-Term Anticoagulation Therapy trial [RE-LY]) has

been completed recently (Connolly et al., 2009, 2010). In this non-inferiority trial, 18,113 patients who had atrial fibrillation and a risk of stroke were randomized to receive fixed doses of dabigatran, 110 mg or 150 mg bid, or adjusted-dose warfarin. Rates of stroke or systemic embolism were 1.71% in the warfarin group, compared with 1.54% in the group that received dabigatran 110 mg bid ($P<0.001$ for non-inferiority) and 1.11% in the group that received dabigatran 150 mg bid ($P<0.001$ for superiority). The rate of major bleeding was 3.57% in the warfarin group, compared with 2.87% in the group receiving dabigatran 110 mg bid ($P=0.003$) and 3.32% in the group receiving dabigatran 150 mg bid ($P=0.32$). The rate of hemorrhagic stroke was 0.38% in the warfarin group, compared with 0.12% with dabigatran 110 mg bid ($P<0.001$) and 0.10% with dabigatran 150 mg bid ($P<0.001$). Therefore, dabigatran etexilate 110 mg bid was non-inferior and dabigatran etexilate 150 mg bid was superior to warfarin for the prevention of stroke and systemic embolism. However, there was a higher rate of treatment discontinuation in the dabigatran etexilate groups (probably due to gastrointestinal adverse effects). The rate of myocardial infarction was also higher in the dabigatran-treated group (Gage, 2009).

5. Potential role of new oral anticoagulants

Most patients with deep vein thrombosis are treated at home, and this outpatient treatment increases the need for a safe, effective, single oral anticoagulant that can be administered at a fixed dose. New oral anticoagulants exhibit many characteristics of the 'ideal anticoagulant', as defined in Table 2. They are administered orally at fixed doses, have a rapid onset of action, predictable pharmacokinetics and pharmacodynamics, and minimal food–drug or drug–drug interactions. Therefore, there is no need for routine coagulation monitoring or dose adjustment.

Adopting the novel oral agents for the treatment of venous thromboembolism will considerably simplify the treatment strategy, as one oral regimen will be sufficient for the whole treatment duration, without the need for bridging therapy from a parenteral anticoagulant in the acute treatment phase (even though this option has not been used in all phase III studies in this indication). A single-drug therapy would provide great convenience both within and out of the hospital setting; this single-drug approach was used in both the EINSTEIN (rivaroxaban) and the AMPLIFY (apixaban) studies. In the phase III EINSTEIN DVT/PE studies, intensified treatment in the first 3 weeks (15 mg bid) is utilized, and this initial dose regimen is to ensure adequate treatment is achieved during this acute period. This is then followed by a once daily regimen for the rest of the treatment period without routine coagulation monitoring and dose adjustment (unlike warfarin). A similar approach is used in the AMPLIFY program with the direct Factor Xa inhibitor apixaban, but the drug is given at 5 mg bid and intensified treatment is given during the first 7 days (10 mg bid). In the edoxaban and dabigatran etexilate programs, an initial period of at least 5 days with a parenteral low molecular weight heparin administration is mandatory (Table 4).

It should be noted that the design of the ongoing trials for the treatment of venous thromboembolism are different, which may impact the use of the different new drugs, as shown in Table 4. Although double-blind designs are considered optimal for phase III randomized trials in general, this paradigm may distort one of the fundamental objectives of phase III studies, i.e. to compare a new regimen with the existing standard under realistic clinical conditions. This becomes especially problematic when the best current therapy is complicated by the need for monitoring and dose adjustments. According to Büller et al., with adequate controls to minimize bias, open-label phase III studies may provide more accurate assessments than trials that adhere to a double-blind design, because they would apply in actual clinical practice, but these views are not shared by all (Büller et al., 2008). Furberg and Soliman (2008) made a strong case for a double-blind design in spite of the many challenges.

The available clinical studies have established non-inferiority or even superiority of several regimens of the new oral agents compared with conventional therapy. The new oral anticoagulants are also associated with similar or lower bleeding rates in comparison with conventional anticoagulants (such as enoxaparin and warfarin). For example, there was no significant difference in the rate of major bleeding in all the completed phase III studies for the prevention and treatment of venous thromboembolism between the new agents and conventional therapy. In addition, there was no indication of sustained hepatoxicity associated with the new oral anticoagulants within the trial periods in these studies (unlike ximelagatran).

The introduction of the new oral anticoagulants may reduce the length of hospital stay, facilitating earlier discharge, particularly in patients who cannot or are unwilling to carry out subcutaneous injection themselves. Because the new oral agents do not require routine coagulation monitoring, adherence to guidelines is also expected to improve. Many physicians have concerns about the administration of vitamin K antagonists because they have a narrow therapeutic window and require routine coagulation monitoring and dose adjustment. A meta-analysis showed that, in community-based practice in the US, patients with atrial fibrillation receiving warfarin treatment only spent 51% of their time within the therapeutic international normalized ratio range (2.0–3.0) (Baker et al., 2009), leaving them at a risk of either thromboembolism or bleeding complications. The new oral anticoagulants may provide a better alternative to warfarin for stroke prevention in patients with atrial fibrillation because they do not require routine coagulation monitoring and dose adjustment. Both dabigatran etexilate (a direct thrombin inhibitor) and rivaroxaban (a direct Factor Xa inhibitor) have demonstrated potential to replace warfarin in this indication Table 5.

In addition, the new oral agents are expected to be more cost-effective than the traditional anticoagulants, partly as a result of their oral route of administration (versus parenteral administration) and the lack of a need for routine coagulation monitoring. A recent cost-effectiveness analysis of rivaroxaban versus enoxaparin for the prevention of postsurgical venous thromboembolism in Canada

Table 4
Comparison of the design of trials for the treatment of established VTE with the new oral anticoagulants using warfarin (target INR: 2.0–3.0) as a comparator.

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran etexilate
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Study acronym	EINSTEIN (NCT00440193; NCT00439777)	AMPLIFY (NCT00643201)	HOKUSAI (NCT00986154)	RE-COVER (Schulman et al., 2009)
Study design	Open, randomized, non-inferiority	Double-blind, randomized, non-inferiority	Double-blind, randomized, non-inferiority	Double-blind, randomized, non-inferiority
Dosage	15 mg bid for 21 days followed by 20 mg od	10 mg bid for 7 days followed by 5 mg bid	60 mg od	150 mg bid
Duration	3, 6, or 12 months	6 months	3–12 months	6 months
Initial UFH or LMWH	Optional (maximum 36 h)	Optional (maximum 36 h)	Mandatory (5–12 days)	Mandatory (≥5 days)

bid, twice daily; INR, international normalized ratio; LMWH, low molecular weight heparin; od, once daily; UFH, unfractionated heparin; VTE, venous thromboembolism.

Table 5
Phase III studies of new oral anticoagulants in stroke prevention in patients with atrial fibrillation.

	Rivaroxaban	Apixaban		Edoxaban	Dabigatran etexilate
Target	Factor Xa	Factor Xa		Factor Xa	Thrombin
Study acronym	ROCKET AF (NCT00403767)	ARISTOTLE (NCT00412984)	AVERROES (NCT00496769)	ENGAGE AF-TIMI 48 (NCT00781391)	RE-LY
Study design	Double-blind, randomized, event-driven, non-inferiority	Double-blind, randomized, non-inferiority	Double-blind, randomized, superiority	Double-blind, randomized, non-inferiority	Randomized, blinded (for dabigatran) with open-label use of warfarin, non-inferiority
Dosage	20 mg od (15 mg od in patients with moderate renal insufficiency)	5 mg bid, or 2.5 mg bid in selected patients	5 mg bid, or 2.5 mg bid in selected patients	30 mg or 60 mg od	110 mg or 150 mg bid
Comparator	Warfarin (target INR range: 2.0–3.0)	Warfarin (target INR range: 2.0–3.0)	Acetylsalicylic acid 81 to 324 mg od	Warfarin (target INR range: 2.0–3.0)	Warfarin (target INR range: 2.0–3.0)
Study duration	Up to 4 years	Up to 4 years	Up to 3 years	2 years	2 years
Current status	Completed	Ongoing	Terminated early	Ongoing	Completed

bid, twice daily; INR, international normalized ratio; od, once daily.

showed that rivaroxaban was associated with improved health outcomes, lower incidence of symptomatic venous thromboembolism, and a lower cost per patient (Diamantopoulos et al., 2010). Similarly, a cost-effectiveness model comparing rivaroxaban and dabigatran etexilate with enoxaparin as thromboprophylaxis after total hip and total knee replacement surgery in the Irish healthcare setting indicated that both new agents had a lower overall cost than enoxaparin, with rivaroxaban being the most cost-effective strategy in this setting (McCullagh et al., 2009).

Potential limitations of these novel drugs do, however, exist. The lack of specific antidotes—in case immediate reversal is needed—is a theoretical rather than practical drawback, because the half-lives of the new oral agents are relatively short (compared with warfarin). Although routine monitoring is not required with these new anticoagulants, a simple assay for quantifying the activity or plasma levels of the drug would be useful in patients with a hemorrhagic or thrombotic event, to determine whether patients are over- or under-anticoagulated (Bounameaux & Reber, 2010; Weitz, 2010) and/or how long the remaining anticoagulant effect is anticipated to last. Periodic coagulation testing, although cumbersome in most cases, may also be helpful to assess compliance even though this has never been demonstrated formally.

6. Conclusions

Both direct Factor Xa inhibitors and direct thrombin inhibitors have shown promising results in recent clinical studies, demonstrating that both Factor Xa and thrombin are viable targets for anticoagulant therapy. Therefore, we are now closer than ever to the 'ideal anticoagulant', and these new agents could improve the benefit–risk balance of extending anticoagulant therapy beyond the usual, limited duration. Moreover, the single-drug approach for the whole treatment duration may revolutionize the therapeutic paradigm and is expected to improve overall clinical outcomes.

Conflict of interest

H Bounameaux has received funding for participating in clinical trials sponsored by Bayer Schering Pharma AG, honoraria for giving lectures from Bayer Schering Pharma, Pfizer, Sanofi-Aventis, GlaxoSmithKline, Servier, and Daiichi Sankyo, and honoraria for participating in advisory boards by Bayer Schering Pharma, Pfizer, Sanofi-Aventis, GlaxoSmithKline, Boehringer-Ingelheim, and Daiichi Sankyo. T Mavrakanas has no conflict of interest to declare.

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