

## REVIEW

# New anticoagulants – promising and failed developments

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New direct and indirect acting factor Xa (FXa) and thrombin inhibitors are being developed to overcome the downsides of the conventional anticoagulants – unfractionated and low molecular weight heparins and vitamin K antagonists. Ximelagatran and idraparinux failed to demonstrate an acceptable safety profile. Rivaroxaban and dabigatran are approved for the post-operative prevention of thromboembolic complications after elective hip or knee replacement surgery; dabigatran is approved for the prevention of embolism in patients with atrial fibrillation in an increasing number of countries. Several novel indirect antithrombin-dependent anticoagulants as well as antithrombin-independent oral direct FXa and thrombin inhibitors are investigated in multiple indications for the prophylaxis and treatment of venous thromboembolism and the prophylaxis of arterial thrombotic disorders. Quality-adjusted life years costs and incremental cost-effectiveness ratios are relatively high at present, but may decrease after approval of more new anticoagulants for additional indications.

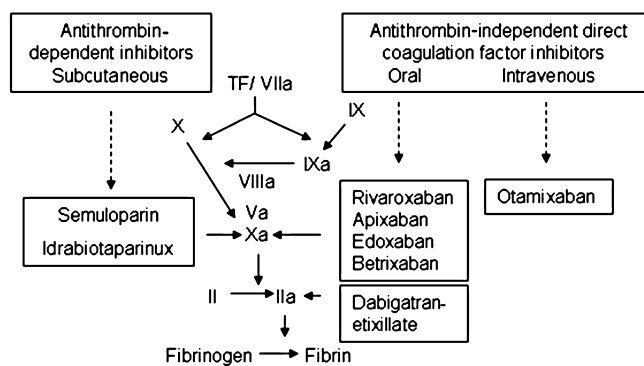
### Abbreviations

AVERROES, Apixaban in patients with atrial fibrillation; BID, twice daily; CHADS, congestive heart failure, hypertension, age > 75 years, diabetes and stroke; CHADS2-VASc, congestive heart failure, hypertension, age > 75 years, diabetes and stroke (2 points), vascular disease; DRIVE, dose ranging study in elective total hip replacement surgery; DTI, direct thrombin inhibitor; EINSTEIN, oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep-vein thrombosis; EMA, European Medicines Agency; FXa, factor Xa; ICER, incremental cost effectiveness ratios; INR, international normalized ratio; LMWH, low molecular weight heparin; NS, not significant; OD, once daily; QALYs, quality adjusted life years; RE-LY, randomized evaluation of long term anticoagulant therapy with dabigatran etexilate; RE-LY-ABLE, dabigatran treatment in patients with atrial fibrillation who completed RE-LY trial; SAVE-ABDO, semuloparin AVE5026 abdominal surgery; SAVE-HIP, semuloparin AVE5026 elective hip replacement surgery; SAVE-ONCO, semuloparin AVE5026 oncology; SAVE-VEMED, semuloparin AVE5026 venous thromboembolism in medical patients study; SHINE, SR123781 in patients with unstable angina; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism

### Introduction

Immediately acting unfractionated heparins (UFHs), low molecular weight heparins (LMWHs), hirudins or argatroban (Hirsh *et al.*, 2008), and slowly acting vitamin K antagonists (VKAs) (Ansell *et al.*, 2008) reduce the morbidity and mortality of patients at risk of recurrent venous thromboembolism (VTE) (Keaton *et al.*, 2008), cerebral and non-cerebral embolism (Singer *et al.*, 2008), and coronary occlusion or reocclu-

sion (Becker *et al.*, 2008). The use of these anticoagulants is limited by several drawbacks. Heparins, LMWHs, hirudins and argatroban have to be administered intravenously or subcutaneously and require dose adjustment guided by monitoring of the anticoagulant effect. LMWHs have to be administered subcutaneously, with the dose being adjusted in older patients and in renal impairment. Severe side effects such as heparin-induced thrombocytopenia or the generation of antibodies to hirudins and other drug-related side effects



**Figure 1**

Overview on the specific mode of inhibition of the new anticoagulants.

limit their administration (Warkentin *et al.*, 2008). The main downsides of VKAs are the requirement of regular dose adjustments by monitoring the anticoagulant effect, the low prevalence of international normalized ratio (INR) values within the therapeutic range (2–3) (Baker *et al.*, 2009), the interactions with food and many drugs, severe intracranial and extracranial bleeding complications, and other severe side effects such as coumarin-induced hepatitis. The slow onset and offset of action of VKAs necessitate simultaneous administration of heparins and LMWHs during the induction of anticoagulation as well as during surgical interventions. New anticoagulants are being developed with initial activities in some instances dating back 10 or more years, to overcome these drawbacks of the conventional anticoagulants and, thereby, help to improve patient care.

In most instances, those novel anticoagulants are synthetic small molecules with specific modes of action. They are inhibitors of relevant coagulation enzymes for almost all of which new compounds are being developed. This review focuses on the most advanced group of inhibitors interacting with factor Xa (FXa) or with thrombin. Results from post-operative prevention of thromboembolism and results of dose-finding studies of all indications are not included. Aptamer-based compounds such as TTP889 (Eikelboom *et al.*, 2010) are not included. The included articles were identified in the PubMed database using the names of the individual anticoagulants. Additional online data were used, especially regarding information on the status or cessation of individual clinical trials, mainly from <http://www.ClinicalTrials.gov>. Data are included as of 1 June 2011.

The new anticoagulants can be grouped by their mode of action that may or may not require antithrombin as cofactor or may involve direct binding and inhibition of coagulation proteases. In this review, pharmacological data and clinical phase III studies for prevention of embolism in patients with atrial fibrillation and for treatment of acute VTE and recurrent thromboembolism are reported in detail. Other studies of earlier clinical phases and in other indications are only shortly reviewed. An overview of the new groups of anticoagulants is shown in Figure 1. Some of the pharmacological effects of the thrombin and FXa inhibitors are compiled in the Table 1.

The indirect FXa specific agents, idrabiotaparinux and semuloparin, inhibit FXa following binding to antithrombin, semuloparin, exerting some inhibition of thrombin, too (ratio anti-FXa to antithrombin inhibition, 80 to 1). The oral direct FXa and thrombin inhibitors act through a reversible binding directly and exclusively to the specific coagulation proteases FXa or thrombin.

An advantage of these new anticoagulants is the fixed dosing without the need for anticoagulant monitoring and dose adjustment. This is important for the oral direct FXa and thrombin inhibitors because VKAs have to be dose adjusted according to the target range of the INR between 2 and 3.

All oral small molecule FXa and thrombin inhibitors have been investigated in clinical trials for the post-operative prevention of VTE. Rivaroxaban and dabigatran have been approved in many countries for the prevention of VTE following total hip and elective knee replacement surgery (Cao *et al.*, 2010; Friedman *et al.*, 2010). Very recently, edoxaban was approved in Japan (<http://www.nelm.nhs.uk/en/NeLM-Area/News/2011---April/26/Edoxaban-receives-first-marketing-approval-in-Japan-for-the-prevention-of-VTE-after-major-orthopaedic-surgery/>) and apixaban received a positive statement of the European Medicines Agency (EMA) for this indication ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Summary\\_of\\_opinion\\_\\_Initial\\_authorisation/human/002148/WC500103875.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion__Initial_authorisation/human/002148/WC500103875.pdf)). The other compounds are in different stages of clinical development and are not part of the present review. Idrabiotaparinux and argatroban are not investigated for post-operative prophylaxis of thromboembolism.

Patients with atrial fibrillation suffer from an increased risk of embolic events that can be significantly reduced by VKAs. The limitations for the use of VKAs lead to an estimated underuse in up to 50% of patients requiring an effective anticoagulation (Tulner *et al.*, 2010). The expected ease to use new oral direct coagulation inhibitors may therefore also help to reduce the underuse threat in patients necessitating an effective anticoagulant therapy.

The incidence of embolic events increases with additional cardiovascular risk factors. These are summarized in a scoring system named congestive heart failure, hypertension, age > 75 years, diabetes and stroke (CHADS2) score which has been used in the studies described next. This score consists of a congestive heart failure, hypertension, age > 75 years, diabetes (each 1 point) and stroke (2 points) (Gage *et al.*, 2001). The newer CHA2DS2-VASc score (Lip *et al.*, 2010) was not used in these studies.

## Indirect, antithrombin-dependent anticoagulants

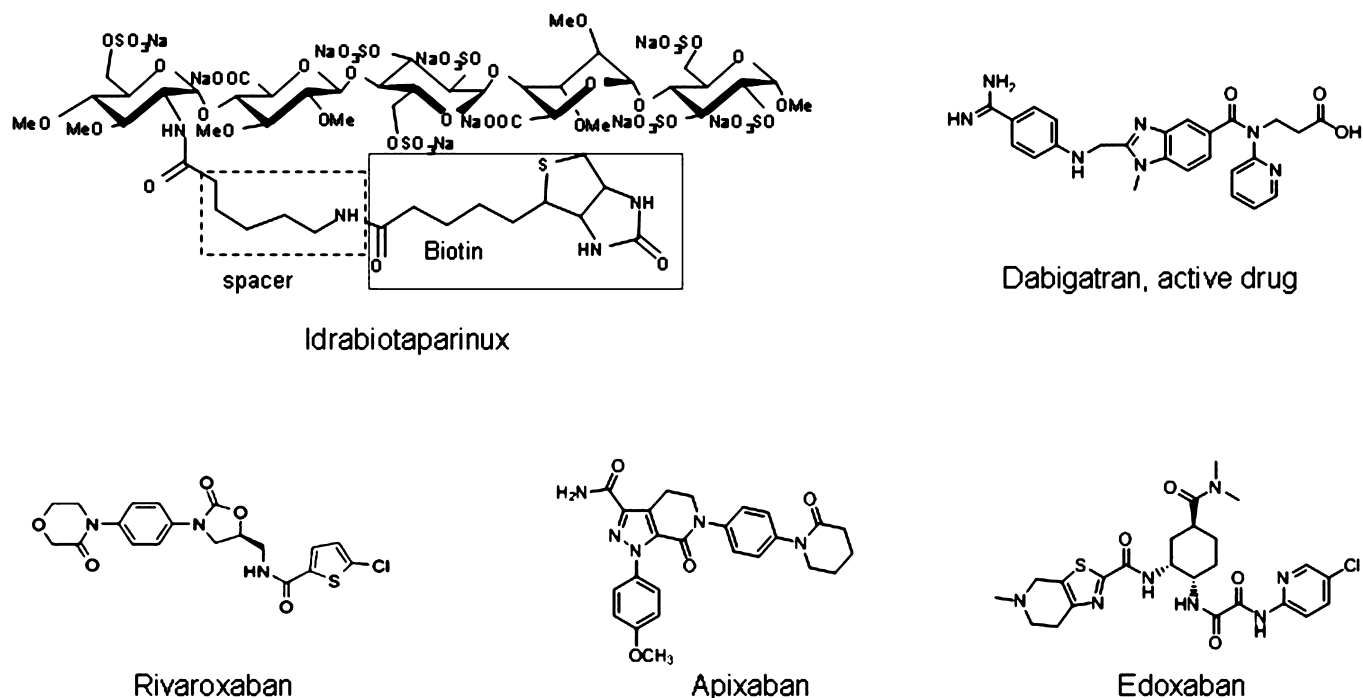
### *Idraparinux and Idrabiotaparinux*

The antithrombin-dependent indirect inhibitors in development are idraparinux, idrabiotaparinux and semuloparin. Idraparinux and idrabiotaparinux are polymethylated derivatives of fondaparinux. Their elimination half-life increases from 7 days after single administration up to 60 days after a 6–12 month treatment period (Harenberg, 2009). The development of idraparinux was terminated due to the very long

**Table 1**  
Pharmacological parameters of the new oral anticoagulants

Parameter	Dabigatran	AZD 0837	Rivaroxaban	Apixaban	DU176b	LY517717	YM 150	Betrixaban
Target	FIIa	FIIa	FXa	FXa	FXa	FXa	FXa	FXa
MW (Da)	628 (pro-drug) 472 (active)	na	436	460	na	459	na	452
Ki (nmol·L <sup>-1</sup> )	4.5	2–4	0.4	0.08	0.56	4.6–6.6	0.03	0.12
Concentration for doubling of PT (μmol·L <sup>-1</sup> )	0.8	>2	0.23	3.6	0.26	na	1.2	0.4
Concentration for doubling of aPTT (μmol·L <sup>-1</sup> )	0.23	0.8	0.69	7.4	0.51	na	na	na
Bioavailability	6.5% in humans	22–52% in humans	57–86% in animals	–66% in humans	50% in monkeys	25–82% in animals	47%	41–82% in animals
t <sub>max</sub> (n)	1.25–3	0.7–1.5	2–4	1–3	1–2	0.5–4	na	na
Vd (l)	60–70	na	–50	Reported as low	na	na	na	na
t <sub>1/2</sub> (h)	12–14	na	9–13	8–15	9–11	27	19	5 in dogs
Potential drug interactions	Quinidine, amiodarone, potent P-gp inhibitors	Potent CYP3A4 inhibitors	Potent inhibitors of CYP3A4 and P-gp	Potent CYP3A4 inhibitors	na	na	Low potential reported	na

aPTT = activated partial thromboplastin time; PT = prothrombin time; CYP = cytochrom P450; P-gp = P-glycoprotein; t<sub>1/2</sub> = terminal elimination half life; t<sub>max</sub> = time to peak plasma concentration; na = not available.



**Figure 2**

Chemical structures of the anticoagulants with published data of phase III trials for treatment of acute venous thromboembolism and prevention of embolism in atrial fibrillation.

elimination half-life and due to increased bleeding after treatment for longer than 6 months.

*Biotinylated Idraparinux*, named idrabiotaparinux, is structurally similar to idraparinus, with the addition of a biotin segment. It has the same anticoagulant activity as idraparinus. Avidin exposes a strong affinity to biotin and can be given intravenously to rapidly bind, neutralize and eliminate idrabiotaparinux (Figure 2, Harenberg, 2009).

*Idrabiotaparinux* was investigated in a randomized double-blind trial in 757 patients with symptomatic deep venous thrombosis, comparing equimolar doses of idrabiotaparinux (3 mg) with idraparinus (2.5 mg) subcutaneously once weekly for 6 months. Inhibition of FXa was similar in the two treatment groups. Recurrent VTE occurred in 2.3% of patients randomized to idrabiotaparinux and in 3.2% of patients randomized to idraparinus (not different). The incidence of clinically relevant bleeding was 5.2% in the idrabiotaparinux group and 7.3% in the idraparinus group (not significant). Deaths were not different between the groups (Equinox Investigators, 2011).

The concentration of the two idraparinus and idrabiotaparinux did not differ in the study. They did not reach steady-state conditions after 6 months of therapy. During a 3 month post-study observation period, the decline of the concentration of the anticoagulants was not determined. An increase of the elimination half-life of idraparinus up to 60 days was described during 6 to 12 months' treatment with idraparinus (Harenberg *et al.*, 2008a). This long half-life may be related to the observed bleeding complications (Harenberg *et al.*, 2008b). Such information was not generated during administration of idrabiotaparinux.

Idrabiotaparinux (3.0 mg) once weekly subcutaneously compared with INR-adjusted warfarin for 6–12 months was investigated for the prevention of embolic events in patients with atrial fibrillation. The study was prematurely stopped most probably due to a lack of efficacy/bleeding ratio during therapy with idrabiotaparinux ([http://www.en.sanofi.com/binaries/20091221\\_rdupdate\\_en\\_tcm28-26977.pdf](http://www.en.sanofi.com/binaries/20091221_rdupdate_en_tcm28-26977.pdf)).

### Semuloparin

*Semuloparin*, previously named AVE5026, is an ultra-low molecular weight heparin with a mean molecular weight of 2500 Da (range of conventional LMWH 2000–10 000 Da) and an anti-FXa/antithrombin ratio of >30. The following studies using 20 mg semuloparin once daily (OD) subcutaneously have been completed: prophylaxis of post-operative thromboembolism following elective knee or hip surgery or hip fracture (Lassen *et al.*, 2009), extended prophylaxis of VTE in patients having undergone hip fracture surgery (SAVE-HIP3, NCT00709904), prevention of VTE in acutely ill medical patients with restricted mobility (SAVE-VEMED, NCT00714597), prevention of VTE in patients undergoing major abdominal surgery (SAVE-ABDO, NCT00679588), prevention of VTE in cancer patients undergoing chemotherapy (SAVE-ONCO, NCT00694382). Currently, no additional clinical studies are ongoing.

### SR123781

SR123781 is a short-acting synthetic hexadecasaccharide for OD injection, which is an indirect antithrombin-dependent inhibitor of Xa coagulation factor (de Kort *et al.*, 2005). The

DRIVE phase IIb study evaluating the hexadecasaccharide in the prevention of venous thromboembolic events in patients undergoing total hip replacement demonstrated a correlation between dose and clinical response, with a positive efficacy/safety ratio (Lassen *et al.*, 2008). The SHINE phase IIb study evaluated SR123781 in patients with non-ST elevated acute coronary syndrome. The study demonstrated good safety, with a bleeding rate similar to UFHs with or without abciximab (Harenberg, 2008). New studies are currently not ongoing.

## Direct FXa inhibitors

### Intravenous direct FXa inhibitor

*Otamixaban* is a direct potent and selective inhibitor of FXa for intravenous administration. Its half-life is 0.5–1.5 h and it is renally excreted by up to 30%. A phase IIb dose-finding study showed similar TIMI bleeding (major or minor) for all dose groups of otamixaban as compared with intravenous laboratory-adjusted UFH (two to threefold prolongation of the activated partial thromboplastin time) (Cohen *et al.*, 2007). Ongoing studies investigate the influence of renal (NCT01120314) and hepatic impairment (NCT01126086) on the metabolism of otamixaban, and the efficacy compared with UFH plus eptifibatide in patients with unstable angina (NCT01076764).

### Oral direct FXa inhibitors

The largest group of anticoagulants consists of direct FXa and direct thrombin inhibitors (DTIs). Direct FXa inhibitors are given intravenously as otamixaban or orally such as rivaroxaban, apixaban, edoxaban, betrixaban. All compounds directly and selectively bind to free FXa and to FXa bound to phospholipids.

*Rivaroxaban* is a competitive, reversible, direct FXa inhibitor with a  $K_i$  of 0.4 nM for purified human FXa and a molecular mass of  $M_r = 435.89$  (Figure 2). After oral administration in man, 60 to 80% are absorbed. Peak plasma levels are achieved in 3 h, and the drug circulates with a half-life of 9 h. Rivaroxaban is excreted by the kidney (66%) and the liver (28%) mainly as unchanged drug. Co-administration of rivaroxaban with food increased the peak plasma concentrations slightly. No additive effects on platelet aggregation were observed during intake of aspirin or the non-steroidal anti-inflammatory drug naproxen, antacid drugs or digoxin. The half-life of rivaroxaban is prolonged in the elderly and in patients with renal impairment (Kubitza and Haas, 2006).

*Rivaroxaban* was investigated in two independent dose-finding studies for the treatment of acute deep vein thrombosis. It was decided to treat patients with 15 mg twice daily (BID) rivaroxaban for 3 weeks followed by 20 mg OD rivaroxaban over 3–12 months in a large phase III clinical trial. This intervention was compared with body-weight adjusted enoxaparin (1 mg/kg body weight bid) followed by warfarin adjusted to an INR of 2–3 (The EINSTEIN Investigators, 2010). The trial was open, prospective and randomized in patients with acute deep vein thrombosis. During 3–12 months' therapy, 2.1% of patients initially randomized to rivaroxaban developed recurrent VTE (deep vein thrombosis or pulmo-

nary embolism) as compared with 3.0% of patients initially randomized to enoxaparin/warfarin ( $P < 0.001$  for non-inferiority). Major and clinically relevant bleeding complications occurred in 8.1% of patients in both treatment groups.

After termination of prophylaxis of recurrent VTE after initial acute deep vein thrombosis or pulmonary embolism, thromboembolic events re-occur in up to 10 patients within 1 year (Kearon *et al.*, 1999; Schulman *et al.*, 2003). Therefore, the benefit of a prolonged prophylaxis of VTE was investigated in patients following a 6 months' anticoagulation of acute deep vein thrombosis using 20 mg OD rivaroxaban compared with placebo over 12 months for prevention of recurrent VTE in a double-blind study. Patients (7.1%) initially randomized to placebo ( $n = 594$ ) developed a recurrent VTE during 12 months compared with 1.3% of patients initially randomized to rivaroxaban ( $n = 602$ ,  $P = 0.001$  for superiority). Severe bleeding complications occurred in 0.7% of patients on rivaroxaban, but in no patient receiving placebo ( $P = 0.05$ ) (The EINSTEIN Investigators, 2010).

The benefit of an oral anticoagulation with rivaroxaban has been demonstrated for the treatment of acute deep vein thrombosis and recurrent events over a period of 3–12 months as well as the prolonged prophylaxis of recurrent VTE for additional 12 months. The safety of rivaroxaban is comparable with that of warfarin. The benefit on mortality remains to be investigated.

*Rivaroxaban* is currently investigated for the treatment of acute symptomatic pulmonary embolism and the prevention of recurrent events (NCT00439777).

Patients with atrial fibrillation and a CHADS2 score above 2 were randomly assigned to 20 mg OD *rivaroxaban* or warfarin adjusted to an INR of 2–3 in a prospective randomized double-blind study (Aalbers, 2011). Seven thousand one hundred thirty-one patients were randomized to rivaroxaban and 7133 patients to warfarin. The mean follow-up was 706 days for rivaroxaban and 708 days for warfarin. The mean CHADS2 score was 3.5 in both treatment groups. Cerebral and non-cerebral embolism occurred in 1.71% per year in patients initially randomized to rivaroxaban and in 2.16% per year in patients initially randomized to warfarin (non-inferiority,  $P < 0.001$ , hazard ratio 0.79, 95% confidence interval 0.66–0.96). The incidence of the events of the primary endpoint is shown in Figure 2. The superiority of overall safety in the treatment population (total  $n = 14\ 143$ ) was significant ( $P = 0.015$ ). Based on the intention to treat analysis ( $n = 14\ 171$ ), cerebral and non-cerebral embolic events occurred in 2.12% per year in patients initially randomized to rivaroxaban and in 2.42% per year in patients initially randomized to warfarin ( $P = 0.117$ ). Haemorrhagic strokes occurred at rates of 0.26% per year under rivaroxaban and 0.44% per year under warfarin (hazard ratio 0.59, 95% confidence interval, 0.37–0.93  $P = 0.024$ ). Mortality was similar in both treatment groups, with 1.87% per year during treatment with rivaroxaban and 2.21% per year for patients treated with warfarin ( $P = 0.073$ ). Severe bleeding complications were observed in 3.6% on treatment with rivaroxaban and in 3.45% of patients on treatment with warfarin ( $P = 0.576$ ). Other bleeding complications were also similar in both treatment groups: 11.8% per 100 years for patients on rivaroxaban and 11.37% per 100 years for patients on warfarin ( $P = 0.345$ ) (Aalbers, 2011).



The reduction of embolic events by rivaroxaban was less frequently accompanied by bleeding complications compared with warfarin on the basis of the safety analysis. However, using the intention to treat analysis, the incidence of cerebral and non-cerebral embolic events was not different for rivaroxaban compared with warfarin. Intracerebral haemorrhagic bleeding occurred less frequently during treatment with rivaroxaban. This is comparable with the results of the randomized evaluation of long-term anticoagulant therapy (RE-LY) study (see below). Other relevant side effects were not different between the two treatment groups.

Prevention of ischaemic events in patients with unstable angina with rivaroxaban was investigated in a phase IIb study for Mega *et al.* (2009) and is currently investigated in a phase III trial (Rocket AF Study Investigators, 2010).

*Apixaban* is a selective and potent ( $K_i = 0.08$  nM) inhibitor of both free and prothrombinase-bound FXa in human plasma (Figure 2). Following oral administration in human, the compound is absorbed to 80% within 3.5 h and is eliminated with a half-life ranging from 8 to 15 h. It is eliminated to about 25% by urinary excretion (Pinto *et al.*, 2007). *Apixaban* is not a significant inhibitor of CYP enzymes or P-glycoprotein and, therefore, is unlikely to be a significant perpetrator of drug–drug interactions (Wong *et al.*, 2011).

*Apixaban* is investigated for the treatment of acute deep vein thrombosis or pulmonary embolism (NCT00643201), and for the extended prophylaxis of recurrent events (NCT00633893).

*Apixaban* was compared with aspirin for the prevention of cerebral and non-cerebral embolism in 5600 patients with atrial fibrillation in whom VKAs were not indicated according to the case history or the decision of the patient or the treating physician [*apixaban* in patients with atrial fibrillation (AVERROES) study, Connolly *et al.*, 2011]. *Apixaban* (5 mg BID) ( $n = 2808$ ) was compared with acetylsalicylic acid (81–324 mg OD) ( $n = 2791$ ) in a double-blind prospective and randomized trial. A subgroup of patients at an age >80 years, a creatinine clearance <50 mL·min<sup>-1</sup> or a risk factor for bleeding, received 2.5 mg BID *apixaban*. The reasons for unsuitability of VKA therapy were not different between the groups; main reasons were assessment that INR was unlikely to be measured at requested intervals, patients' refusal to take VKAs and multiple reasons for unsuitability of VKA therapy (multiple reasons possible). Patients had a mean CHADS score of 2.0 (*apixaban* group) or 2.1 (*aspirin* group). Cerebral and non-cerebral embolism occurred in 1.6% of patients per year during treatment with *apixaban* and in 3.7% of patients per year under *aspirin* (hazard ratio 0.45, 95% confidence interval, 0.32–0.62,  $P < 0.001$  for superiority). Death rates were 3.5% per year for patients treated with *apixaban* and 4.4% per year for patients treated with *aspirin* (not significant). Major bleeding complications were not different and occurred in 1.4% of patients per year under *apixaban* and in 1.2% under *aspirin* (hazard ratio 1.13, 95% confidence interval, 0.74–1.75,  $P = 0.57$ ). Haemorrhagic stroke, myocardial infarction and death were not different in the treatment groups. Hospitalization for a cardiovascular cause occurred more frequently in patients treated with *aspirin* (15.9% per year) as compared with *apixaban* (12.6% per year) ( $P < 0.001$ ). Minor bleeding complications were higher in patients treated with *apixaban*

(5.0% per year) compared with *aspirin* (3.6% per year,  $P = 0.05$ ).

*Apixaban* was shown to be superior to *aspirin* for the prevention of cerebral and non-cerebral embolism in patients with atrial fibrillation. The CHADS2 score was low for patients included in this study. The reasons for unsuitability of VKAs are not thoroughly convincing.

In patients with unstable angina, *apixaban* was investigated in a phase IIb trial for prevention of ischaemic cardiac events (Alexander *et al.*, 2009). A phase II trial was stopped due to major bleeding complications during therapy of *apixaban* on top of dual antiplatelet therapy ([http://www.investor.bms.com/phoenix.zhtml?c=106664&p=irol-newsArticle\\_print&ID=1498702&highlight=](http://www.investor.bms.com/phoenix.zhtml?c=106664&p=irol-newsArticle_print&ID=1498702&highlight=)).

*Edoxaban* (the name originated from Edo as the earlier name of the capital Tokyo of Japan), earlier named as DU-176b, is another orally available, specific and direct inhibitor of FXa (Figure 2). Preclinical studies have demonstrated bioavailability of approximately 60% in monkeys based on <sup>14</sup>C-*edoxaban* detected in urine (Zafar *et al.*, 2007).

*Edoxaban* (NCT00986154) is investigated for the treatment of acute deep vein thrombosis and pulmonary embolism.

Prophylaxis of embolism in patients with atrial fibrillation is currently investigated using *edoxaban* (NCT not available at present) and *betrixaban* (NCT00742859).

*YM-150*, LY517717 and *TAK-421* are other oral synthetic, low molecular weight, direct FXa inhibitor, with comparable pharmacokinetic properties as the other oral FXa inhibitors (Eriksson *et al.*, 2009; Kawamura *et al.*, 2010). They have been investigated in phase IIb trials in different indications (Agnelli *et al.*, 2007; Eriksson *et al.*, 2007; Turpie *et al.*, 2009; Weitz *et al.*, 2010). At present, no phase III clinical trials are ongoing with these anticoagulants.

## Direct thrombin inhibitors

The most relevant synthetic, small molecule DTIs are *argatroban*, *ximelagatran* and *dabigatran etexilate* (Figure 2), and *AZD 0837*. They bind specifically to the active centre of thrombin and inactivate free and fibrin-bound thrombin (Hauptmann and Stürzebecher, 1999). After inactivation of thrombin, the inhibitors reverse from their binding site, thereby leaving a small amount of free and active thrombin available to control haemostasis (Gustafsson and Elg, 2003). The vascular binding differs from that of the irreversible, non-covalent binding of the DTIs hirudin and hirulogs (Direct Thrombin Inhibitor Trialists' Collaborative Group, 2002). *AZD 0837* is a prodrug of the direct inhibitor AR-H067637, with a concentration that dependently inhibits tissue factor-induced generation of free thrombin. The inhibition constant is in the same concentration range as reported for *melagatran* and *dabigatran* (Deinum *et al.*, 2009).

### Oral direct thrombin inhibitors

*Dabigatran*, an oral direct thrombin inhibitor, has been investigated for the treatment of acute deep vein thrombosis and pulmonary embolism and the prevention of recurrent events over 6 months compared with warfarin in a double-blind

prospective randomized trial (Schulman *et al.*, 2009). Patients were initially treated with 150 mg BID dabigatran or body weight adjusted enoxaparin (1 mg·kg<sup>-1</sup> body weight BID) or with warfarin adjusted to an INR of 2–3. 2.4% of patients initially randomized to dabigatran ( $n = 1274$ ) and 2.1% of patients initially randomized to warfarin ( $n = 1265$ ) developed recurrent thromboembolic events. The study hypothesis of non-inferiority was fulfilled ( $P = 0.001$ , relative risk 1.1, 95% confidence interval 0.65–1.86).

Severe bleeding complications recurred in 1.6% of patients treated with dabigatran and in 1.9% of patients treated with warfarin. Minor bleeding complications occurred in 16.1% of patients treated with dabigatran and in 21.9% of patients treated with warfarin ( $P = 0.01$ ). Dyspepsia was observed in 3.6% of patients treated with dabigatran and in 0.7% of patients treated with warfarin ( $P = 0.001$ ). Other side effects were not different between groups. Liver enzymes over time were not different between the treatment groups. Acute coronary events did not differ between both treatment groups (0.4% vs. 0.2%).

Dabigatran has been proven to be effective and safe for the treatment of acute VTE and prevention of recurrent events. The advantage of this study over the analogous study on rivaroxaban is its double-blind study design. A minor limitation in the study is the occurrence of dyspepsia.

Studies on an extended prophylaxis of recurrent events for additional 18 months are waiting for completion (NCT00558259: dabigatran vs. warfarin; NCT00558259: dabigatran vs. placebo).

AZD 0837 is not investigated for this indication.

In a phase III trial, RE-LY compares the efficacy and safety of two blinded doses of *dabigatran etexilate* with open-label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (Connolly *et al.*, 2009). It was a prospective, multicentre, randomized, open-label, controlled parallel group, non-inferiority trial. Systemic embolic events occurred in 1.69% per year in patients randomized to warfarin, 1.53% per year in patients randomized to 110 mg dabigatran BID and 1.11% per year in patients randomized to 150 mg dabigatran BID [relative risk (RR) 0.91, CI 0.74 to 1.11,  $P < 0.001$  for non-inferiority with 110 mg dabigatran BID; and RR 0.66, CI 0.53 to 0.82,  $P < 0.001$  for superiority with 150 mg dabigatran BID]. Major bleeding occurred in 3.36% of patients per year on warfarin, in 2.71% of patients per year on 110 mg dabigatran BID ( $P = 0.003$ ), and 3.11% of patients per year on 150 mg dabigatran BID [not significant (NS)]. The mortality rates were 4.13, 3.75 and 3.64% per year in the warfarin, 110 and 150 mg dabigatran groups (NS and  $P = 0.051$  vs. warfarin), respectively. Dyspepsia occurred in 348 patients (5.8%) in the warfarin group and in 707 patients (11.8%) and 688 patients (11.3%) in the 110 and 150 mg dabigatran groups, respectively ( $P < 0.001$  each). The rates of myocardial infarction were 0.53% per year with warfarin, 0.72% per year with 110 mg BID dabigatran (RR 1.35, 95% CI 0.98 to 1.87;  $P = 0.07$ ) and 0.74% per year with 150 mg BID dabigatran (RR 1.38, 95% CI 1.00 to 1.91;  $P = 0.048$ ).

The dabigatran treatment in patients with atrial fibrillation who completed RE-LY trial (RE-LY-ABLE) is an extension trial of dabigatran treatment in patients who successfully completed the RE-LY study. The trial will provide an oppor-

tunity for about 8000 patients to remain on blinded 110 mg BID and 150 mg BID dabigatran for 12–36 months without switching to VKA. The data will provide additional safety information on patients with long-term exposure to dabigatran (NCT00808067).

The RE-LY study compares two doses of dabigatran with warfarin. For the first time, an anticoagulant regimen of 150 mg BID dabigatran was proven to be more effective in reducing embolic events in patients with atrial fibrillation compared with warfarin. In addition, cerebral haemorrhage occurred significantly less with both doses of dabigatran compared with INR-adjusted warfarin. The higher incidence of myocardial infarction was outweighed by the benefits of dabigatran on the other endpoints. The continuation of patients in the RE-LY-ABLE study will generate additional safety data for dabigatran. The Food and Drug Administration has approved the 150 mg BID dabigatran dose for the prevention of embolism in patients with atrial fibrillation as well as a dose of 75 mg BID dabigatran for patients with impaired renal function (creatinine clearance 20–50 mL·min<sup>-1</sup>).

Currently, the costs of the drug dabigatran for the prevention of stroke in patients with atrial fibrillation currently exceed that of warfarin by about 7000-fold. Therefore, the quality-adjusted survival, costs and cost-effectiveness of dabigatran were compared with those for warfarin adjusted to an INR of 2–3 using the data of the patients included into the RE-LY study (Freeman *et al.*, 2011). The Markov decision model was used for this analysis. The estimated costs were made on the basis of pricing in the UK. Warfarin targeted at an INR of 2–3, dabigatran 110 mg BID and dabigatran 150 mg BID was compared. Outcome measures were quality-adjusted life years, costs in US\$ (year 2008) and incremental cost-effectiveness ratios. The model was sensitive to the costs of dabigatran but was relatively insensitive to other model inputs. According to this model, high-dose dabigatran was more cost-effective than low-dose dabigatran. The analysis showed that treatment with dabigatran could be cost-effective compared with warfarin for the prevention of cerebral and non-cerebral embolism in patients above 65 years and with an increased risk of stroke. The main limitation of this investigation was the assumption of no change of the costs for dabigatran.

The prevention of ischaemic events in patients with acute coronary syndromes was investigated in a phase IIb study using dabigatran in addition to aspirin and clopidogrel. Dabigatran, in addition to dual antiplatelet therapy, was associated with a dose-dependent increase in bleeding events and significantly reduced coagulation activity in patients with a recent myocardial infarction (Oldgren *et al.*, 2011).

## Comments

The cost-effectiveness analysis provides substantial information for the decision which dose of dabigatran or if warfarin should be used in patients with atrial fibrillation based on the individual risk factors for haemorrhage and thromboembolism. However, the analysis has some limitations:

- The price of dabigatran, presently marketed in Europe for short-term prophylaxis of post-operative prophylaxis of VTE, will drop if the indication for prophylaxis of embolic events in patients with atrial fibrillation will be approved by the EMA.
- The price for dabigatran will drop again after the approval of another direct coagulation inhibitor (rivaroxaban or apixaban or both or more compounds) for this indication.
- The results of the AVERROES study indicate that apixaban will reduce the treatment costs compared with acetylsalicylic acid or compared with no therapy (current underuse).

## Perspectives

At present, several studies have been published recently for the treatment of deep vein thrombosis and the prevention of embolic events in patients with atrial fibrillation. Both are the main new indications for new oral anticoagulants to overcome the drawbacks of conventional anticoagulation.

The major drawbacks of the new oral anticoagulants will become visible only after market approval. They comprise high daily treatment costs, fear of unforeseen and unknown side effects, and – in patients comfortably performing therapy with VKAs – fear of switching to an oral anticoagulant with less experience.

The current underuse of VKAs will be reduced by the availability of new oral anticoagulants. Younger patients will be more prone to be treated with the new anticoagulants due to the simplicity of the treatment. The availability of several new oral anticoagulants should help to competitively reduce the daily price for the drugs. Additional information including meta-analyses will improve the knowledge about the added values of the new oral anticoagulants compared with conventional ones.

## Authors' opinion

The new oral anticoagulants present a new and promising therapeutic option for patients requiring oral anticoagulation. Patients with currently ineffective anticoagulation will specifically benefit from the new classes of anticoagulants. Special attention has to be made to an adequate pricing and for specific indications to determine the anticoagulant effect.

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## Conflict of interest

The authors do not have to declare any conflict of interest relating to the manuscript.

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