

# New oral anticoagulant drugs in cardiovascular disease

Ingo Ahrens<sup>1</sup>; Gregory Y. H. Lip<sup>2</sup>; Karlheinz Peter<sup>3</sup>

<sup>1</sup>Innere Medizin III, Kardiologie und Angiologie, Universitätsklinik Freiburg, Freiburg, Germany; <sup>2</sup>Haemostasis Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK; <sup>3</sup>Atherothrombosis & Vascular Biology, Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia

## Summary

Oral anticoagulation has been limited to vitamin K antagonists (VKAs) for over 60 years. VKAs are effective and recommended for the prevention of venous and arterial thromboembolism in cardiovascular disease, but their pharmacodynamics are difficult to predict and the highly variable interindividual and intraindividual response to treatment accounts for the need of continuous monitoring. This prompted the intensive exploration of numerous substances within the last decade in an attempt to meet the shortcomings of current oral anticoagulation with VKAs. The development and clinical investigation of two novel groups of oral anticoagulants targeting central factors of the coagulation system either factor Xa or thrombin (factor IIa) has now reached the daily clinical practice with the approval of the oral direct thrombin inhibitor da-

bigatran etexilate and the oral direct factor Xa inhibitor rivaroxaban. Ongoing clinical trials are investigating these substances and other novel oral anticoagulants with similar mechanisms of action in patients with atrial fibrillation and acute coronary syndromes. This review article discusses the clinical evaluation and pharmacological properties of novel oral anticoagulants in late and earlier stages of clinical development, thereby providing a critical analysis and an outlook on the future of oral anticoagulation in cardiovascular disease.

## Keywords

Novel oral anticoagulants, direct thrombin inhibitor, Xa-inhibitor, vitamin-k-antagonist, cardiovascular disease

## Correspondence to:

Dr. Ingo Ahrens  
Innere Medizin III, Kardiologie und Angiologie  
Universitätsklinik, Hugstetter Str. 55  
79106 Freiburg, Germany  
Tel.: +49 761 270 3401, Fax: +49 761 270 7045  
E-mail: ingo.ahrens@uniklinik-freiburg.de

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## 1. Oral anticoagulation with vitamin K antagonists (VKAs)

Oral anticoagulation was first established in 1941 with the introduction of dicoumarol which was discovered and characterised by Karl Paul Link, from the Department of Biochemistry at the University of Wisconsin, USA. Link isolated the coumarin derivative out of spoiled hay that mainly consisted of sweet clover which had apparently caused a series of bleeding events among cattle in the northern United States and Canada in the early 1920s (1). During the late 1940s Dr. Link initiated the development of one of the many related compounds to dicoumarol that was then called *warfarin* [after the Wisconsin Alumni Research Foundation and the *-arin* coming from the word coumarin]. Although primarily successfully used as a rat poison, warfarin entered the clinic as an oral anticoagulant in the 1950s and largely replaced dicoumarol as it was more potent and had greater bioavailability (1).

It took until 1978 before the mechanism by which warfarin affected the vitamin K-dependent coagulation factors II, VII, IX and X was discovered. Warfarin inhibits the  $\gamma$ -carboxylation of the aforementioned clotting factors by inhibiting the responsible enzyme vitamin K epoxide reductase complex subunit 1 (VKORC1) (2). Nowadays, warfarin (with a half-life of 35–45 hours [h]) is the most frequently prescribed oral anticoagulant

worldwide. However, phenprocoumon (with a substantially longer half-life of 80–270 h) and acenocoumarol (shorter half-life of 8–24 h) are preferentially used in European countries. Phenprocoumon was introduced in Europe in the early 1950s and is still commonly used in Europe, as its longer half-life that was thought to lead to less variability in international normalised ratio (INR) values compared to the shorter acting warfarin (3). The anticoagulation intensity of these VKAs is monitored by measurement of the INR. This test has proven to provide a high technical reproducibility. However in addition to variations based on changes in nutrition, co-medications and concomitant diseases, a within-individual biological variation of up to 11% has to be taken into account (4).

The reduction of thromboembolic events that has been achieved with all of the VKAs comes at the cost of the unresolved problem of associated bleeding complications. These can be as high as 10–17% for all bleeding complications per 100 patient-years, of which 2–5% account for serious bleeding events, and 0.5–1% per 100 patient-years for fatal bleedings (5). The bleeding events are usually linked to overanticoagulation (INR>3.0) (5), although serial INRs are generally poor predictors of subsequent bleeding events.

The observed inter-individual variability in response (as measured by INR values) to treatment with the VKAs is in part ex-

plained by genetic variability, caused by mutations in the genes coding for the cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9) and the VKORC1 (5-7). CYP2C9 is one of the major hepatic enzymes responsible for the metabolic clearance of VKAs and VKORC1 is the pharmacological target of the VKAs. Two single nucleotide polymorphisms (Arg 144 Cys, CYP2C9\*2 and Ile 359 Leu, CYP2C9\*3) have been described as being the most relevant mutations in CYP2C9 that are linked with decreased activity in metabolising warfarin, phenprocoumon and acenocoumarol, hence leading to a prolonged half-life and overanticoagulation if no dose adjustments are made (5). In a recent meta-analysis, homozygosity for CYP2C9\*3 had the strongest impact on measured INR values, whereas heterozygosity or CYP2C9\*2 still resulted in higher INR values but substantially lower than the values obtained with homozygosity for CYP2C9\*3 (5). Interestingly the INR can be differentially affected depending on the type of VKA used. For example, compared to wild-type CYP2C9, the highest prolongation in INR caused by the CYP2C9 polymorphism, is seen with warfarin and the lowest INR prolongation found with phenprocoumon (5). The most common polymorphism in VKORC1 affecting the required dose of VKA to reach a defined INR is 1173C>T (also referred to as VKCOR1\*2). Indeed, patients with the VKCOR1\*2 polymorphism needed less VKA dose compared to patients with the wild-type VKCOR1; however, the difference in response between the VKAs observed with the CYP2C9 polymorphisms appears less pronounced with the VKCOR1 polymorphisms (5) and could potentially be explained by a class effect of the VKAs in inhibiting VKCOR1. More recently, a pharmacogenetic algorithm has been proposed to prevent over- or underanticoagulation (7), but large scale clinical studies utilising pharmacogenetic algorithms are needed to determine whether this more costly and elaborate approach would lead to less bleeding events.

## 2. Novel oral anticoagulants

Although the VKAs are very effective in preventing thromboembolic events they do have a narrow therapeutic window and significant inter/intra individual variability. The latter imposes the need for regular anticoagulation monitoring, leading to ineligibility for such therapy. VKAs are also affected by diet (e.g. green vegetables), drugs and alcohol, leading to some lifestyle restrictions. The limitations associated with the VKAs has prompted research into many novel anticoagulants. The two largest drug groups interfere with pathways central to the coagulation system, such as factor IIa (thrombin) or factor Xa.

The first novel oral anticoagulant that was approved for clinical use was the direct thrombin inhibitor ximelagatran. In May 2004, ximelagatran was approved in Europe for thromboembolic prophylaxis in patients undergoing hip surgery. Due to a significant number of patients with increased liver enzyme plasma levels and a number of acute hepatic failures under long-term therapy (8), ximelagatran was withdrawn from the market in February 2006.

### 2.1. Oral direct thrombin inhibitors

#### Dabigatran etexilate (Pradaxa<sup>®</sup>, Boehringer Ingelheim)

This is an orally available, small-molecule direct thrombin inhibitor (DTI). It has a high affinity for thrombin with reversible binding. Dabigatran etexilate is a prodrug that is converted into the active metabolite dabigatran, which displays a low bioavailability (approx. 6%) accounting for the high doses that are needed to maintain therapeutic plasma concentrations (9). Of note, the intestinal absorption of dabigatran etexilate is pH sensitive; therefore decreasing its absorption in the presence of proton pump inhibitors. Peak plasma concentrations are reached within 2–3 h after oral administration. The half-life of dabigatran has been described with 12–17 h with 80% of the drug excreted renally, which has to be considered when patients have impaired renal function. On the other hand, this makes dabigatran potentially safe for the administration in patients with moderate hepatic impairment as its metabolism is independent of cytochrome P450 (10).

Following successful phase III clinical studies in patients undergoing total hip replacement or total knee replacement (conditions associated with a high rate of venous thromboembolism (VTE) of around 50%) dabigatran etexilate was approved for this clinical indication in Europe by the EMEA in April 2008, in Canada in June 2008, and in Australia in November 2008. Following the approval, dabigatran etexilate (Pradaxa<sup>®</sup>) is recommended at a dose of 220 mg once daily (QD) after total knee or hip replacement. Initiation of the treatment should be with half the dose (110 mg) administered orally between 1 and 4 h after surgery for a period of 10 days after total knee replacement and a period of 28–35 days after total hip replacement. Patients at increased risk for bleeding, including patients over 75 years of age or patients with renal impairment, should receive a reduced daily dose of 150 mg administered as 75 mg twice a day (BID).

The important major double-blind randomised phase III clinical trials in orthopaedic surgery were RE-NOVATE (total hip replacement), RE-MODEL (total knee replacement), and RE-MOBILIZE (total knee replacement). The design of RE-NOVATE and RE-MODEL was similar with regard to dosages of dabigatran of 220 mg or 150 mg QD compared to enoxaparin 40 mg QD, and both trials showed non-inferiority to enoxaparin (11, 12). The RE-NOVATE trial used the same oral doses of dabigatran but a higher dose of enoxaparin (30 mg twice a day), and this trial failed to show non-inferiority for dabigatran (20). However there was also a difference in the timing of the administration of dabigatran (6–12 h postoperatively compared to 1–4 h postoperatively in RE-NOVATE and RE-MODEL, respectively), which may have caused the different outcome in the RE-NOVATE trial.

Recently published landmark phase III trials for clinical conditions that demand long-term oral anticoagulation are the RE-LY and the RE-COVER trials.

The randomised phase III clinical trial RE-LY finished treatment of all enrolled 18,113 patients with non-valvular atrial fibrillation in March 2009. The mean age of the patients was 71 years (63.6% were men), half the patients had received long-term oral anticoagulation with VKA before, and the mean CHADS<sub>2</sub> score

**Table 1: Oral anticoagulants currently clinically approved or under clinical investigation.**

Substance	Mechanism of action	Typical efficient dose	Half-life	Stage of development
<b>Vitamin K antagonists (VKA)</b>				
Warfarin (Coumadin®)	Inhibition of VKORC1	INR guided	35 – 45 hours	Approved for OAC
Acenocoumarol (Sinthrome®)	Inhibition of VKORC1	INR guided	8 – 24 hours	Approved for OAC
Phenprocoumon (Marcumar®)	Inhibition of VKORC1	INR guided	80 – 270 hours	Approved for OAC
Anisindione (Miradon®)	Inhibition of VKORC1	INR guided	72 – 120 hours	Approved for OAC
ATI-5923 (ARYx Therapeutics)	Inhibition of VKORC1	INR guided	Data not available	In phase II/III clinical trials for OAC
<b>Factor IIa (thrombin) inhibitors</b>				
Dabigatran etexilate (Pradaxa®, Boehringer-Ingelheim)	Competitive binding of FIIa	150 mg or 220 mg once a day (VTE prophylaxis)	12 – 17 hours	Approved for VTE after hip/knee surgery* + in phase III clinical trials for OAC
AZD-0837 (AstraZeneca)	Competitive binding of FIIa	150 mg – 450 mg (in phase II trials)	Data not available	In phase II clinical trials for OAC
Sofigatran (MCC 977, Mitsubishi Pharma)	Competitive binding of FIIa	Data not available	Data not available	In phase II clinical trial for DVT
<b>Factor Xa inhibitors</b>				
Rivaroxaban (Xarelto®, Bayer Healthcare and Johnson & Johnson)	Competitive binding of FXa	10 mg once a day (VTE prophylaxis)	5 – 9 hours	approved for VTE after hip/knee surgery* + in phase III clinical trials for OAC
Apixaban (Bristol-Myers-Squibb and Pfizer)	Competitive binding of FXa	2.5 mg or 5 mg twice a day (in phase III trials)	9 – 14 hours	In phase III clinical trials for OAC
Betrixaban (Portola Pharmaceuticals)	Competitive binding of FXa	40 mg – 80 mg daily (in phase II trials)	19 hours	In phase II clinical trials for OAC
Edoxaban (DU-176b, Daiichi Sankyo)	Competitive binding of FXa	30 mg or 60 mg once a day (in a phase III trial)	Data not available	In a phase III clinical trial for OAC
Eribaxaban (PD0348292, Pfizer)	Competitive binding of FXa	0.1 – 2.5 mg once a day (in a phase II trial)	Data not available	In a phase II clinical trial for VTE after TKR
YM150 (Astellas)	Competitive binding of FXa	30 mg or 60 mg once a day (in phase II trials)	Data not available	In phase II clinical trials for VTE and OAC
LY517717 (Eli Lilly)	Competitive binding of FXa	100 mg – 150 mg once a day (in a phase II trial)	27 hours	In phase II clinical trials for VTE
TAK-442 (Takeda Pharmaceutical)	Competitive binding of FXa	20 mg – 240 mg daily (in phase II trials)	Data not available	In phase II clinical trials for VTE
<b>Others</b>				
Anti IXa: TTP889 (Transtech Pharma)	Reversible binding of FIXa	300 mg daily (one phase II trial)	21 – 25 hours	In phase II clinical trials for VTE

\* FDA approval still pending (June 2010).

was 2.1. The RE-LY trial compared two blinded doses of dabigatran etexilate (110 mg or 150 mg both twice daily) against controlled open-label warfarin for secondary prevention of stroke and systemic embolism. The primary outcome of stroke or systemic embolism occurred in 1.69% of patients per year in the warfarin group compared to 1.53% of patients per year in the 110 mg BID dabigatran group ( $p < 0.001$  for non-inferiority) and 1.11% of patients per year in the 150 mg BID dabigatran group ( $p < 0.001$  for superiority). The rate of major bleeding was lower in the 110 mg BID dabigatran group (2.71% vs. 3.36% per year with warfarin,  $p = 0.003$ ) and similar to warfarin in the 150 mg BID dabigatran group (3.11% vs. 3.36% per year with warfarin,  $p = 0.31$ ) (14).

Recently presented subgroup analysis of data from the RE-LY were done in patients with prior temporary ischaemic attack (TIA) or stroke, patients undergoing cardioversion, patients with low, moderate and high CHADS2 score, elderly patients and patients with renal dysfunction (15–18).

Among the 3,623 patients with prior TIA or stroke a significant reduction of haemorrhagic stroke was observed with both dabigatran treatments (2 for 110 mg BID and 5 for 150 mg BID vs. 18 for warfarin,  $p = 0.003$  and  $p = 0.009$ , respectively) (15). Similar low stroke rates (4 for 110 mg BID, 2 for 150 mg BID and 4 for warfarin, respectively) were shown in the subgroup of 1,257 patients undergoing cardioversions (17).

In low-risk patients (CHADS<sub>2</sub> score 0–1) both dabigatran dosing regimens (110 mg BID and 150 mg BID) demonstrated a favourable risk-benefit profile compared to warfarin when patients whereas the absolute reduction in stroke or systemic embolism was strongest in the highest risk group (CHADS<sub>2</sub> score 3–6) (18).

Another subgroup analysis of 7,258 patients aged ≥75 years and 3,505 patients with a creatinine clearance of 30–50 ml/min found a significant interaction for age and renal function on treatment with dabigatran etexilate. After adjustment for age, the treatment interaction for renal function was no longer evident. The rates of major bleedings with dabigatran etexilate treatment were similar or higher in patients ≥75 years (4.17% for 110 mg BID, 4.81% for 150 mg BID and 4.09% for warfarin, respectively) (16).

Hepatotoxicity was not observed with dabigatran treatment. The only significant side effect of dabigatran was dyspepsia (5.8% of patients on warfarin vs. 11.8% and 11.3% in the dabigatran treatment groups, respectively). This might be attributable to the formulation of dabigatran, which contains a tartaric acid core to enhance intestinal absorption (the optimal bioavailability requires a low pH) (19). Furthermore, this could explain the observed higher rate of gastrointestinal bleedings with 150 mg BID of dabigatran compared to warfarin (14).

The randomised, double-blind, clinical phase III study RECOVER examined whether oral dabigatran 150 mg BID was as effective as warfarin for the secondary prevention of VTE in 2,564 patients with confirmed deep-vein thrombosis (DVT) or pulmonary embolism (PE) (20). After six months 2.4% of all patients in the dabigatran group vs. 2.1% of all patients in the warfarin group had recurrent VTE, thereby establishing non-inferiority of dabigatran 150 mg BID for the secondary prevention of VTE compared to the current standard oral anticoagulation with VKAs (20). There was no significant difference in major or any bleeding between dabigatran 150 mg BID and warfarin (20). However, significantly more patients (9%) discontinued dabigatran treatment due to adverse events (driven by significantly more dyspepsia) than warfarin treatment (6.8% of patients) (20).

The clinical assessment of dabigatran in cardiovascular disease is still ongoing as part of the RE-VOLUTION clinical trial program, including clinical trials named, RE-MEDY (the extension of the RE-COVER study) and RE-SONATE (secondary prevention of VTE), and RE-DEEM (secondary prevention of cardiac events in patients with acute coronary syndrome [ACS]). The phase II clinical trial RE-DEEM has recently been reported and was a dose finding study examining 50, 75, 110 and 150 mg dabigatran BID compared to placebo in 1,861 patients after STEMI or NSTEMI for a duration of six months in addition to dual antiplatelet therapy. The overall increase in major bleeding between placebo and dabigatran was 1% and a dose-dependent increase in major bleeding events was observed (0.5% for placebo, 0.8% 50 mg BID, 0.3% 75 mg BID, 2.0% 110 mg BID and 1.2% for 150 mg BID) (21).

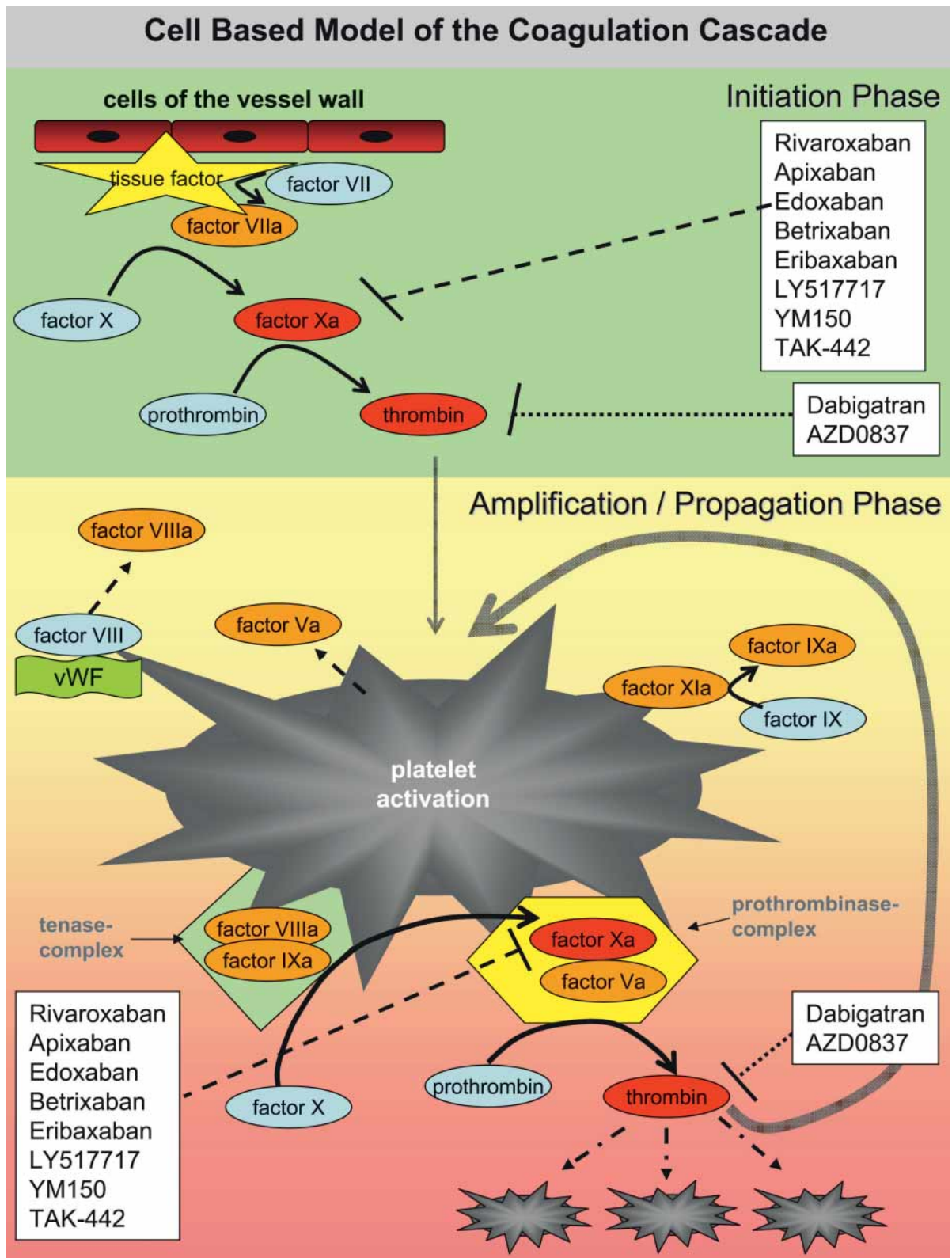
Another phase II pilot trial explores dabigatran compared to enoxaparin as an anticoagulant in the setting of percutaneous coronary intervention (PCI) with a planned enrolment of 50 patients (www.clinicaltrials.gov identifier: NCT00818753).

### AZD-0837(AstraZeneca)

This is an oral antagonist of thrombin and a follow-up compound of ximelagatran with different pharmacologic properties. No safety issues regarding elevated liver enzymes have been reported during the current clinical phase II development. In cardiovascular medicine, AZD-0837 has been investigated in a phase II trial in 955 patients with atrial fibrillation (AF), where the drug was administered as 150 mg, 300 mg, 450 mg QD, or 200 mg BID compared to warfarin (INR 2.0–3.0) over a period of 3–9 months. Bleeding events were reported to be similar between AZD-0837 and warfarin with a trend towards less bleeding events with AZD-0837 (22). There was a higher rate of drug related adverse events (mainly gastrointestinal disorders) with AZD-0837 compared to warfarin.

AZD-0837 has also been investigated in a phase II trial in 250 patients with atrial fibrillation and at least one additional risk factor for stroke. In this trial, patients received AZD-0837 at dosages of 150 mg BID or 350 mg BID compared to warfarin. The patients

**Figure 1: Cell-based model of the coagulation system with the two key factors (factor Xa and thrombin) that are the targets of the novel oral anticoagulants.** Vessel injury leads to the exposure of membrane bound tissue factor (upper left corner) which activates factor VII to factor VIIa. Tissue factor-factor VIIa complex then catalyses the activation of factor X to factor Xa (filled blue circles depict non-activated coagulation factors and filled orange or red circles represent activated coagulation factors). Factor Xa catalyses the proteolytic activation of prothrombin (factor II) which leads to the formation of small amounts of thrombin (factor IIa). The aforementioned steps illustrated in the upper section of the figure summarise the main events in the so called initiation phase. The amplification / propagation phase (responsible for the vast majority of thrombin generation) is characterised by local, thrombin-mediated activation of platelets leading to the release of activated coagulation factors (such as factor Va) from platelet alpha-granules and the conversion of factor VIII (which is normally bound to its carrier molecule von Willebrand factor, vWF) to factor VIIIa. Furthermore, on the surface of activated platelets, activated factor XIa catalyses the conversion of factor IX to factor IXa. In subsequent steps, the platelet-bound prothrombinase complex consisting of factor Xa and factor Va, phospholipid and calcium, is formed. The activation of factor X, which is a prerequisite for the formation of the prothrombinase complex, is mediated by the tenase complex which consists of platelet bound factor IXa and factor VIIIa, phospholipid and calcium. The prothrombinase complex leads to a massive increase in the local production of thrombin. The latter will eventually increase platelet activation and recruit further platelets, thereby amplifying the local production of coagulation factors. The novel oral anticoagulants (white text boxes) are characterised by their specific inhibition of one of the two central factors in the coagulation system, factor Xa and thrombin (both depicted in filled red circles). Dabigatran and AZD0837 are directly inhibiting thrombin thereby interfering in the early (initiation phase) and late stage (amplification / propagation phase) of the cell based model of the coagulation system. Rivaroxaban, apixaban, edoxaban, betrixaban, eribaxaban, LY517717, YM150, and TAK-442 bind to either free factor Xa or factor Xa bound within the prothrombinase complex thereby blocking the conversion of prothrombin to thrombin in the early (initiation phase) and late (amplification / propagation phase) stages of the cell based model of the coagulation system.



were treated for a period of three months. With total bleeding events of six for AZD-0837 150 mg BID compared to eight with warfarin, AZD-0837 at a dosage of 150 mg BID appeared to be safe. There was a numerically higher number of bleeding events (15) in the group of patients receiving the 350 mg BID dosage of AZD-0837 (23).

A recently finished but not yet reported phase II trial examined the safety of long-term (follow up period of 5 years) administration of AZD-0837 compared to warfarin in patients with atrial fibrillation ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00645853). Clinical phase III trials have not yet been initiated ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), database accessed June 2010).

## 2.2. Oral factor Xa inhibitors

### Rivaroxaban the former BAY 59-7939 (Xarelto<sup>®</sup>, Bayer Healthcare and Johnson & Johnson)

This is an oral direct inhibitor of factor Xa with a competitive and reversible binding to factor Xa (24). Rivaroxaban has a high oral bioavailability of 60–80% and reaches peak plasma concentrations after approximately 3 h (25). There is evidence that rivaroxaban may bind not only to free factor Xa but also to factor Xa bound in the prothrombinase complex, which could translate into clinical advantages over heparin, which is too large to bind factor Xa within the prothrombinase complex (24). In contrast to dabigatran etexilate, the intestinal absorption of rivaroxaban is not affected by the pH. However, a higher but delayed maximum plasma concentration of rivaroxaban was observed in patients, who were fed compared to fasting patients, which translates to a slightly lower anti-Xa activity in fasting patients (26), and therefore, rivaroxaban was administered within 2 h of food intake in clinical trials.

The half-life of rivaroxaban is between 5–9 h in patients with normal renal and hepatic function (25, 27). Thus, higher plasma levels of rivaroxaban are expected in patients with impaired renal function (which to a certain extent naturally occurs in elderly patients) or impaired hepatic function as one third of the drug is excreted unchanged renally and about two thirds are metabolised in the liver primarily via cytochrome P450 (28). The major phase III clinical trials that led to the approval of rivaroxaban (Xarelto<sup>®</sup>) in Canada in September 2008, in Europe by the EMEA in October 2008, and in Australia in November 2008 are summarised under the RECORD clinical trial program which assessed the efficacy of rivaroxaban compared to enoxaparin in patients in nearly 10,000 patients undergoing total knee or total hip replacement. In March 2009 an Food and Drug Administration (FDA) expert panel recommended the approval of rivaroxaban but the FDA put the approval of rivaroxaban on hold asking for more information on the drug's safety. A formal decision of the FDA is not expected before February 2010 as the developing company will not deliver additional information on rivaroxaban before February 2010 (Bayer HealthCare press release December 6, 2009). The currently approved dosage of rivaroxaban in Canada, Europe and Australia for VTE prophylaxis in patients undergoing hip or knee surgery is 10

mg QD with the initial dose to be taken 6–10 h post surgery for up to five (hip surgery) or two weeks (knee surgery).

The currently approved dosage regimen for rivaroxaban is based on the doses that were used in the double-blind, randomised RECORD1, -2, -3, and -4 clinical trials. RECORD1 (29) and RECORD2 (30) investigated rivaroxaban in patients undergoing hip surgery, whereas RECORD3 (31) and RECORD4 (32) were knee surgery trials. RECORD1 and RECORD2 both demonstrated superiority of rivaroxaban compared to enoxaparin 40 mg QD. However, RECORD2 used a short-term administration of enoxaparin compared to extended duration of rivaroxaban of 31–39 days after surgery, thereby favouring rivaroxaban through the extended duration of VTE prophylaxis, which generally appears to be superior after hip surgery. The duration of VTE prophylaxis in RECORD3 and RECORD4 was only 10–14 days which is the recommendation after knee surgery. In RECORD4, the North American dose of enoxaparin of 30 mg BID was used [compared to other RECORD trials done with 40 mg enoxaparin QD]. However, rivaroxaban showed superiority compared to enoxaparin in both, RECORD3 and RECORD4, trials. Overall rivaroxaban was superior to enoxaparin in all of the RECORD trials but was also associated with a slightly, but non-statistically significant increase in major bleeding events.

In cardiovascular disease, rivaroxaban is still under clinical investigation in phase III clinical trials for the prevention of thromboembolic events in patients with non-valvular AF (ROCKET-AF), for the secondary prevention of VTE (EINSTEIN studies), for the primary prevention of VTE in hospitalised acute medically ill patients (MAGELLAN), and for the secondary prevention of cardiovascular adverse events in patients with ACS (ATLAS 2 TIMI 51). The MAGELLAN trial is using rivaroxaban at a dose of 10 mg QD for a period of 31–39 days (similar to the dose used in the RECORD trials) compared to enoxaparin 40 mg QD for a shorter period of 6–14 days in 8,000 patients medically ill hospitalised patients ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00571649).

The ROCKET-AF trial investigates rivaroxaban at 20 mg per day compared to daily warfarin with a target INR range of 2.0–3.0 for the prevention of thromboembolic events in 14,000 patients with non-valvular AF ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00403767). Whether rivaroxaban does have an additional effect on top of standard treatment with aspirin or aspirin and clopidogrel for the prevention of cardiovascular adverse events in patients with recent acute coronary syndromes is currently under investigation in the phase 3 ATLAS-2-TIMI51 clinical trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00809965). Rivaroxaban will be given as either 2.5 mg or 5 mg BID. This dosage regimen is based on the dose finding clinical phase IIb ATLAS-ACS-TIMI46 trial, which showed a trend towards a reduction in cardiovascular adverse events but also a dose dependent increase of clinically significant bleeding (33).

The EINSTEIN-DVT study examined rivaroxaban given at a dose of 15 mg BID for a period of three weeks followed by 20 mg QD for up to 12 months. The trial included 2,900 patients with acute DVT but without PE and rivaroxaban was compared to initial enoxaparin 1 mg BID switched to INR-guided oral anticoagu-

**Table 2: Completed and published phase III clinical trials with novel oral anticoagulants.**

Substance / clinical trial	Comparators	Patient number	Doses	Outcome
<b>Dabigatran</b>				
RE-NOVATE (hip surgery)	Dabigatran vs. Enoxaparin	3505	150 mg or 220 mg Dabigatran qd vs. Enoxaparin 40 mg qd s.c.	Dabigatran non-inferior to Enoxaparin
RE-MODEL (knee surgery)	Dabigatran vs. Enoxaparin	2076	150 mg or 220 mg Dabigatran qd vs. Enoxaparin 40 mg qs s.c.	Dabigatran non-inferior to Enoxaparin
RE-MOBILIZE (knee surgery)	Dabigatran vs. Enoxaparin	2615	150 mg or 220 mg Dabigatran qd vs. Enoxaparin 30 mg bid s.c.	Dabigatran inferior to Enoxaparin
RE-LY (atrial fibrillation)	Dabigatran vs. Warfarin	18113	110 mg or 150 mg bid vs. Warfarin (INR 2.0–3.0)	Dabigatran at 110 mg bid non-inferior, at 150 mg bid superior to Warfarin
RE-COVER (acute VTE)	Dabigatran vs. Warfarin	2564	150 mg Dabigatran bid vs. Warfarin (INR 2.0–3.0)	Dabigatran at 150 mg bid non-inferior to Warfarin
<b>Rivaroxaban</b>				
RECORD 1 (hip surgery)	Rivaroxaban vs. Enoxaparin	4541	10 mg Rivaroxaban qd vs. Enoxaparin 40 mg qd s.c.	Rivaroxaban superior to Enoxaparin
RECORD 2 (hip surgery)	Rivaroxaban vs. Enoxaparin	2509	10 mg Rivaroxaban qd vs. Enoxaparin 40 mg qd s.c.	Rivaroxaban superior to Enoxaparin
RECORD 3 (knee surgery)	Rivaroxaban vs. Enoxaparin	2531	10 mg Rivaroxaban qd vs. Enoxaparin 40 mg qd s.c.	Rivaroxaban superior to Enoxaparin
RECORD 4 (knee surgery)	Rivaroxaban vs. Enoxaparin	3148	10 mg Rivaroxaban qd vs. Enoxaparin 30 mg bid s.c.	Rivaroxaban superior to Enoxaparin
EINSTEIN-EXT (VTE)	Rivaroxaban vs. Placebo	1197	20 mg Rivaroxaban qd vs. Placebo	Extended OAC with Rivaroxaban superior to placebo

lation with warfarin within 48 h of randomisation (www.clinicaltrials.gov identifier: NCT00440193). The EINSTEIN-PE trial was identical in design despite the inclusion of 3,300 patients with PE only (www.clinicaltrials.gov identifier: NCT00439777). The results of either EINSTEIN-DVT or EINSTEIN-PE have not been reported yet (June 2010). The results of the EINSTEIN-EXTENSION (www.clinicaltrials.gov identifier: NCT00439725), which tested an extended duration of oral anticoagulation with rivaroxaban 20 mg QD against placebo after patients from either EINSTEIN-DVT or EINSTEIN-PE completed the respective treatment periods, have recently been reported at the 2009 Annual Meeting of the American Society of Hematology (34). A total of 1,197 patients were included in the EINSTEIN-EXTENSION trial, the mean duration of study treatment was 190 days. Recurrent VTE occurred in 7.1% of placebo-treated patients and in 1.3% of rivaroxaban-treated patients ( $p < 0.001$ ) (34). There was no significant difference in major bleeding, while clinically relevant non-major bleeding was noted in 1.2% of placebo-treated patients and in 5.4% of rivaroxaban-treated patients, respectively (34).

### Apixaban (Bristol-Myers-Squibb and Pfizer)

This is an oral direct factor Xa inhibitor with a reversible binding and an oral bioavailability of approximately 50%. Apixaban achieves its peak plasma level at around 3 h after oral administration and has a half-life of 9–14 h. Similar to rivaroxaban, the drug is metabolised in the liver in a cytochrome P450-dependent

way. Approximately 25% of the drug is eliminated via the kidneys and the remainder by intestinal excretion via the faeces (35). Apixaban binds both, the free factor Xa and the factor Xa that is bound within the prothrombinase complex thereby sharing another feature with rivaroxaban.

Most of the major double-blind, randomised clinical phase III trials with apixaban are in the setting of orthopaedic surgery (ADVANCE trials). The ADVANCE-1 clinical phase III trial failed to show non-inferiority of apixaban compared to heparin because of an unexpected lower event rate in the enoxaparin treatment group but suggested a lower rate of major or clinically relevant non-major bleeding with 2.5 mg of apixaban BID compared to enoxaparin 30 mg BID after total knee replacement (2.9% with apixaban vs. 4.3% with enoxaparin,  $p = 0.03$ ) (36, 37). The ADVANCE-2 trial was recently reported and showed superiority of apixaban 2.5 mg BID over enoxaparin given only QD at a dose of 40 mg (38). The bleeding rates in ADVANCE-2 were 3.5% in the apixaban group vs. 4.8% in the enoxaparin group, respectively ( $p = 0.09$ ) (38).

A phase II dose-ranging trial of apixaban (5 mg, 10 mg or 20 mg twice daily) in 520 patients with DVT did not show a dose response. This is in contrast to an earlier phase II trial in 1,238 patients undergoing knee surgery, which did show dose response with increased bleeding rates observed in the higher dose apixaban groups (39).

Apixaban was the first of the novel oral anticoagulants to be assessed in patients with recent acute coronary syndromes, on top of

standard therapy with aspirin or aspirin and clopidogrel. The results of this double-blind, randomised clinical phase II trial (APPRAISE-1) showed an increased rate in bleeding events with a dose dependency especially in the 10 mg daily group and a non-significant decrease in cardiac adverse events, which also was dose-dependent (40). The clinical phase III APPRAISE-2 trial is currently investigating a dose of 5 mg apixaban BID for the prevention of acute ischaemic events in 10,800 patients with recent coronary syndromes compared to placebo when added to standard anti-platelet therapy ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00831441). Apixaban is also under clinical investigation for the prevention of stroke and systemic thromboembolism in 15,000 patients with AF (ARISTOTLE trial, [www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00412984). The ARISTOTLE trial investigates apixaban given at a dose of 5 mg BID compared to warfarin (INR 2.0–3.0). AVERROES is another phase III trial of apixaban in 5,000 patients with AF who are not eligible for an oral anticoagulation with warfarin and therefore would normally only receive aspirin. In this trial apixaban will also be given at 5 mg BID but compared to aspirin instead of warfarin ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00496769).

Additionally, apixaban 2.5 mg BID is under clinical investigation for the prevention of VTE in 6,524 acute medically ill hospitalised patients in comparison to enoxaparin 40 mg QD in the ADOPT phase III clinical trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00457002). Finally, apixaban is also being studied in a phase III clinical trial for the prevention of recurrent VTE in 2,900 patients diagnosed with DVT or PE ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00643201).

### Edoxaban (DU-176b, Daiichi Sankyo)

This is an oral direct inhibitor of factor Xa. Interestingly DU-176b was engineered from a parenteral direct factor Xa inhibitor (DX-9065a) by replacing an amidine moiety with less basic moieties (41). Pharmacological data on oral bioavailability, half-life and elimination have not yet been published, but two phase II clinical trials have been reported with oral doses of DU-176b of 5 mg, 15 mg, 30 mg, or 60 mg QD or BID.

In one of the phase II trials, DU-176b was administered to 523 patients undergoing total knee replacement surgery and a dose-dependent decrease of VTE was observed without an increase in bleeding events (42). In the other reported phase II trial, DU-176b was investigated at 30 mg and 60 mg either QD or BID compared to dose-adjusted warfarin in 1,146 patients with AF. The 60 mg BID arm in this study was terminated due to increased bleeding events (43), whilst the 30 mg and 60 mg QD doses appeared to be safe and well tolerated compared to warfarin. The 30 mg twice daily also showed a significant increase in bleeding events (43).

On the basis of these data, Daiichi Sankyo recently announced the commencing of a large double-blind, randomised clinical phase III trial (ENGAGE AF-TIMI 48) in 16,500 patients with AF where DU-176b will be given at 30 mg or 60 mg QD compared to warfarin administered in a double-dummy manner ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00781391).

### Betrixaban (Portola Pharmaceuticals)

This is a direct factor Xa inhibitor with a reversible mechanism of action, an oral bioavailability of 47%, a half-life of approximately 19 h, and an almost exclusively biliary elimination (44, 45). Betrixaban has been investigated in a prospective, randomised phase II clinical trial in 215 patients undergoing total knee replacement (EXPERT trial). The doses of betrixaban that were used in this trial were 15 mg or 40 mg BID compared to enoxaparin 30 mg BID over a period of 10–14 days. Overall, a dose-dependent effect on inhibition of thrombin generation and anti-factor Xa activity was observed and betrixaban was well tolerated (45).

In cardiovascular disease, betrixaban has been studied in a randomised, dose-finding phase II trial in 500 patients with atrial fibrillation (Explore Xa, [www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00742859). The results of the Explore Xa study were recently reported at the 2010 American College of Cardiology Scientific Sessions – Late Braking Clinical Trials in Atlanta, March 14–16, 2010. Betrixaban was administered as 40 mg, 60 mg, or 80 mg QD in comparison to open-label dose adjusted warfarin (INR 2.0–3.0). The primary end point of major or clinically relevant non-major bleeding (CRNM) occurred in 0.8%, 3.9%, 3.9%, and 5.5% for the warfarin group, respectively. There were statistically significant less major and CRNM bleeding with 40 mg QD betrixaban compared to warfarin ( $p=0.035$ ).

### Eribaxaban (PD0348292, Pfizer)

This oral factor Xa inhibitor is currently in phase II clinical trials but data on this substance are sparse (46). A dose ranging clinical trial for the prevention of VTE in patients undergoing total knee replacement has been reported. A total of 1,411 patients were randomised to receive either 0.1, 0.3, 0.5, 1, or 2.5 mg of eribaxaban QD or enoxaparin 30 mg BID. All doses were well tolerated, and a statistically non-significant dose-dependent increase in total bleeding was observed with eribaxaban (47).

### LY517717 (Eli Lilly)

This is an oral direct factor Xa inhibitor with a reversible binding to factor Xa and a long half-life of approximately 27 h (48). The time to peak plasma concentrations has been reported between 0.5–4 h, with the primary route of elimination via the gastrointestinal tract (48). Up to date there is only one phase II clinical trial published and no evidence for any further ongoing trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), database accessed June 2010). The one published phase II trial investigated LY517717 in 507 patients undergoing total knee replacement and compared doses of either 25 mg, 50 mg, 75 mg, 100 mg, or 150 mg QD to enoxaparin 40 mg QD (48). There was a dose-dependent decrease in thromboembolic events with LY517717 treatment and the efficacies of the 100 mg, 125 mg and 150 mg doses of LY517717 were non-inferior to enoxaparin (48).

### YM150 (Astellas)

YM150 is a direct factor Xa inhibitor with oral bioavailability. Apart from preclinical data (49) a detailed assessment of pharmacologic data on YM150 has not been published (June 2010), but YM150 was examined in 174 patients undergoing hip replacement surgery in a phase II clinical trial called ONYX (50). The doses of YM150 in this study ranged from 3 mg to 60 mg QD compared to enoxaparin 40 mg QD for a period of 7–10 days after surgery. There was a dose-dependent decrease in VTE with a trend towards lower rates with YM150 when a daily dose of 30 mg or more was given (50).

In a second phase II study (ONYX-2) in 1,139 patients undergoing hip replacement surgery YM150 was administered at doses ranging from 5 mg to 120 mg QD (www.clinicaltrials.gov identifier: NCT00353678). The primary composite efficacy endpoint of DVT, symptomatic VTE, PE and death within 10 days ranged from 31.7% to 13.3% and decreased significantly with increasing doses of YM150 (51). The phase II evaluation of YM150 in orthopaedic surgery is currently ongoing in a trial (PEARL) with 670 patients undergoing knee replacement surgery (www.clinicaltrials.gov identifier: NCT00595426). In cardiovascular medicine, YM150 has been investigated in a clinical phase II trial in 448 patients with non-valvular AF in three different dosing regimens compared to warfarin (www.clinicaltrials.gov identifier: NCT00448214). The results of this study have not yet been reported (June 2010).

In cardiovascular medicine, YM150 is currently being trialled in phase II studies in the RUBY-1 study in patients with acute coronary syndromes (www.clinicaltrials.gov identifier: NCT00994292) and in the OPAL-2 study in patients with AF (www.clinicaltrials.gov identifier: NCT00938730).

### TAK-442 (Takeda Pharmaceutical)

This is an oral direct inhibitor of factor Xa with a competitive binding mechanism (52, 53). TAK-442 has been investigated in a phase II clinical trial at doses of 40 or 80 mg QD, and 10 mg, 20 mg, 40 mg, or 80 mg BID compared to enoxaparin 30 mg BID over a treatment period of 10 days in 1,038 patients undergoing total knee replacement surgery (www.clinicaltrials.gov identifier: NCT00641732). The minimum effective dose of TAK-442 was determined at 40 mg QD, the maximum dose of 80 mg BID tended to be more effective than enoxaparin 30 mg BID in this study. Interestingly, the frequency of bleeding events was not dose-dependent in this study and similar to the rate occurring in the enoxaparin-treated group (54).

In cardiovascular medicine, TAK-442 is currently under investigation in a phase II dose-ranging trial in 2,250 patients with ACS as an additional therapy to standard care. The doses of TAK-442 investigated in this trial range from 20 mg a day up to 240 mg a day compared to placebo treatment (www.clinicaltrials.gov identifier: NCT00677053).

### 2.3. Other novel anticoagulants in early stages of clinical development

*ATI-5923* (Tecarfarin, ARYx Therapeutics) is a selective oral vitamin K epoxide reductase enzyme inhibitor (VKA), which in contrast to warfarin is not metabolised via the cytochrome P450, thereby avoiding a number of potential drug-drug interactions that warfarin faces. A phase IIA trial, where 66 patients with atrial fibrillation and a low to medium risk for stroke were switched from warfarin to tecarfarin recently demonstrated that tecarfarin may be a safe and more reliable VKA measured by the time within the therapeutic range (INR 2.0–3.0) (55). Tecarfarin is currently undergoing clinical phase II/III testing in 600 patients who require anticoagulation and have either AF or flutter, prosthetic heart valves, VTE, or a history of myocardial infarction or cardiomyopathy. The treatment with tecarfarin will be compared to warfarin with the primary outcome measurement percentage of time within a therapeutic INR range (www.clinicaltrials.gov identifier: NCT00691470).

*TTP889* (Transtech Pharma) is the first orally available direct factor IXa inhibitor. This drug reaches peak plasma concentrations after 3 h and has a half-life of 21–25 h (56). TTP889 has been evaluated in one clinical phase II trial for the prevention of VTE in 260 patients undergoing hip fracture surgery in the FIXIT trial (56). TTP889 has been used at 300 mg QD compared to placebo and failed to show efficacy in preventing VTE in FIXIT (56). In this context it is worth mentioning that there are also other non-orally available direct factor IXa inhibitors in clinical development. Of special interest is the combination of an intravenously administered RNA aptamer against factor IXa with its corresponding antidote currently undergoing early stages of clinical development. A recently published phase Ib trial investigated the intravenous RNA aptamer – antidote combination RB006 and RB007 (Regado Biosciences), respectively, in 50 patients with stable coronary artery disease on chronic therapy with either aspirin or aspirin and clopidogrel. A single bolus-injection of RB006 increased the activated partial thromboplastin time (aPTT) dose-dependently, and the intravenous bolus injection of the antidote reversed the effect on the aPTT within one minute (57). A clinical phase II trial in 26 patients undergoing elective PCI (REVERSAL-PCI) has recently been presented, demonstrating the safety and efficacy of RB006 and the reversal agent RB007 (58). These results prompted the initiation of a phase IIb study (RADAR), which is currently investigating the RB006 and RB007 aptamer anticoagulation system (REG1) versus heparin in patients with ACS (www.clinicaltrials.gov identifier: NCT00932100).

*Idraparinux and biotinylated idraparinux* (Sanofi-Aventis) are long-acting antithrombin-dependent specific inhibitors of factor Xa. Idraparinux is a synthetic pentasaccharide with a very high affinity for antithrombin. Idraparinux is administered subcutaneously and shows peak concentrations after 2.5 h and a half-life of 100–120 days after a single dose. Therefore a once-a-week-only administration is sufficient to achieve a therapeutic level of inhibition of factor Xa (59). However, at steady-state concentrations after repeated weekly doses the half-life is prolonged to 66.3 days

(59). The latter may partially explain the increasing incidence of bleeding events with the duration of treatment that have been observed in the AMADEUS trial.

The AMADEUS trial compared idraparinix (2.5 mg once a week) to oral VKA therapy in patients with AF (60). In addition to the indication for long-term oral anticoagulation, patients needed to have at least one of the following risk factors: previous ischaemic stroke, transient ischaemic attack or systemic embolism, hypertension, left ventricular dysfunction, age over 75 years, or age 65–75 years with either diabetes mellitus or symptomatic coronary artery disease. The trial was stopped after enrolment of 4,576 patients due to an increased bleeding risk associated with idraparinix treatment (60). Data from the AMADEUS trial also demonstrated the efficacy of idraparinix to prevent thromboembolism compared to oral VKA. This and results from the van Gogh extension (long-term prevention of VTE after PE) trial prompted the clinical evaluation of a biotinylated version of idraparinix (idrabioparinix) which can be rapidly reversed by the injection of avidin (59, 61). The first phase III clinical investigation of the biotinylated idraparinix was the EQUINOX trial in patients with symptomatic DVT, which established the bioequipotency of idrabioparinix in comparison to idraparinix and furthermore the reversibility of idrabioparinix after the administration of avidin (62). The clinical evaluation of idrabioparinix vs. oral VKA is currently ongoing in 3,200 patients with PE in the phase III CASSIOPEA study ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00345618) and in 9,600 patients with AF and CHADS<sub>2</sub> score  $\geq 2$  in the phase III BOREALIS-AF study ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier: NCT00580216).

#### 2.4. Monitoring options for novel oral anticoagulants

The task to develop a novel oral anticoagulant was always accompanied by the demand for a safe substance with oral bioavailability that does not need routine monitoring to a similar level as the VKAs. Now that two novel oral anticoagulants just entered the clinical routine, many patients and clinicians would feel more comfortable with the novel agents if monitoring options would be available.

There are currently no standardised monitoring tests for the novel oral anticoagulants. However, if necessary special coagulation tests may be applied to estimate the extent of factor Xa or thrombin inhibition caused by the intake of oral Xa or thrombin inhibitors.

The ecarin clotting time (ECT) directly assesses the activity of thrombin in a plasma sample and displayed a linear dose-response to therapeutic concentrations of dabigatran (19). Therefore, the anticoagulative effect of oral dabigatran may be estimated by measuring the ECT. However, unfortunately no major clinical trial has yet established the optimum ECT to achieve the best possible anticoagulation with the lowest possible bleeding risk. Therefore, routine measurement of ECT cannot be recommended at this stage.

The neoplastin-induced prothrombin time (PT) showed a dose-dependent correlation to rivaroxaban plasma levels and may therefore be used to estimate the anticoagulative effect of rivaroxaban (63). Similar to the ECT with dabigatran, no major clinical trial has yet established the optimum PT for patients treated with oral rivaroxaban. Routine measurement of PT can not be recommended at this stage, since data to draw conclusions in regard to dosing are not available. In general, pharmaceutical companies could support clinical practise, if drug monitoring by plasma level measurements and/or coagulation tests would parallel clinical trials.

### 3. The future of oral anticoagulation in cardiovascular disease

After almost 60 years of oral anticoagulation with VKAs, two novel oral anticoagulants with distinct mechanisms of action were approved in 2008 in Canada, Europe and Australia (a decision by the FDA is expected in 2010) for the prophylaxis of thromboembolism in patients undergoing total hip or knee replacement. Both drugs are currently under extensive clinical investigations in patients with cardiovascular disease with the emphasis on the prevention of thromboembolism in patients with AF. The addition of oral anticoagulants to single or dual anti-platelet therapy in patients with ACS is another current focus in the development of the novel oral anticoagulants.

In comparison to oral VKA, either direct inhibitors of thrombin or factor Xa have overall favourable pharmacologic profiles. They are direct acting, reversible, small-molecules with predictable pharmacodynamics thereby allowing QD or BID fixed dosing regimens without the need for routine monitoring of their respective anticoagulant effects. However, the current “one size fits it all” hypothesis may not hold when the novel oral anticoagulants are applied to the general population outside well controlled clinical trials. Therefore further clinical trials and registries are needed to examine the effect of the novel oral anticoagulants in special patient groups (e.g. non-adolescent patients, elderly patients, patients with renal insufficiency, or patients with liver impairment). The short half-life of the novel oral anticoagulants may help to prevent clinically relevant bleeding events (which are observed in over-anticoagulated patients treated with oral VKA) but also requires a good patient compliance, because missing 2–3 doses leads to ineffective anticoagulation. However, patient compliance with oral anticoagulant drugs appears to be problematic in general. This is also reflected by the rates of drug discontinuation in the RE-LY trial. A total of 7.3%, 7.8%, and 6.2% of the dabigatran 110 mg BID, 150 mg BID, and warfarin-treated patients, respectively, discontinued study drug intake without any specific reason (14). Therefore, the new oral anticoagulant drugs may open up long-term oral anticoagulation for patients that could not be treated with warfarin for safety reasons (e.g. inability to monitor INR for any reason), but may not reach patients in compliant to warfarin treatment.

Another issue that warrants careful evaluation of the eligibility of a patient for treatment with the novel oral anticoagulants are direct drug interactions that may occur. For example dabigatran interferes with amiodarone, verapamil and quinidine belonging to the group of P-glycoprotein inhibitors. Therefore, dose reductions of dabigatran may be necessary in patients on treatment with the aforementioned drugs. Also rivaroxaban appears to be not without any drug interactions. Strong inhibitors of either CYP3A4 or P-glycoprotein (e.g. ketoconazole, erythromycin, clarithromycin, rintonavir) increased, whereas strong inducers of CYP3A4 (e.g. rifampicin) decreased rivaroxaban plasma levels. Therefore, similar to warfarin treatment, concomitant drugs and potential interactions with the novel oral anticoagulants have to be carefully explored and discussed with the patient.

Another potential problem that needs to be addressed in the future is the reversibility of the novel oral anticoagulants in clinical situations that require immediate reconstitution of the coagulation system (e.g. severe bleeding events). There are currently no recommendations or antidotes available to reverse the action of direct thrombin inhibitors or direct factor Xa inhibitors. However, the application of recombinant factor VIIa (NovoSeven®) and activated prothrombin complex concentrate (FEIBA®) have been discussed to reverse the effects of direct factor Xa inhibitors, but there are no sufficient data to routinely recommend their clinical usage for this purpose (28). Also, a novel potential antidote for factor Xa inhibitors is currently in preclinical development, which consists of plasma derived factor Xa, in which the active site has been chemically modified to render it inactive but retaining its ability to bind small-molecule inhibitors of factor Xa, thereby reversing the effect of direct factor Xa inhibitors by competitive binding (64). Furthermore, promising strategies to reverse anticoagulation have been pursued. DNA or RNA aptamers blocking coagulation factors can be inhibited by specific DNA- or RNA-based antidotes (57). Furthermore, the biotin/avidin system offers a fast approach to inactivate drugs and thus to antagonize anticoagulation (59, 61). In the future, novel biotechnological developments may provide further promising switch on/off approaches in anticoagulative therapy.

It is likely that both strategies, the direct inhibition of thrombin and the direct inhibition of factor Xa with orally available drugs, will be established as alternatives for the current practice of oral anticoagulation with the VKAs. Furthermore, the different pharmacological properties, especially metabolism and route of elimination, could lead to the preferred usage of a particular drug in a special patient group (e.g. patients with impaired liver or renal function).

The current global market for anticoagulants (2008) has been declared at around 6 billion US\$ and interestingly warfarin accounts for just 300 million US\$, whereas low molecular weight heparins account for almost 4.5 billion US\$ (65). At the end, the overall usage of novel oral anticoagulants will depend on the balance of cost for the individual therapy and benefit created for the individual patient in direct comparison not only to VKAs but potentially also to low-molecular-weight heparins (especially in indications where bridging of an otherwise oral VKA therapy is required).

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