

New anticoagulant drugs: a turning point in oral anticoagulation management?

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Summary

Heparins and vitamin K antagonists have been the cornerstones of anticoagulant therapy for several decades. Although effective, currently available agents have limitations that have prompted the search for new drugs matching the “ideal” anticoagulant profile. At present, agents targeting factor Xa and thrombin are in the most advanced stages of clinical development. With potential advantages including predictable pharmacological profile, rapid onset of action, low propensity for food and drug interactions, administration of fixed doses and no requirement for therapeutic monitoring, these new agents may potentially improve the management of thromboembolic disorders. However, potential challenges of bringing new anticoagulants to the clinic should be taken into account.

Key-words: new anticoagulants, factor Xa inhibitors, direct thrombin inhibitors.

Riassunto

I nuovi farmaci anticoagulanti: una svolta nel monitoraggio della TAO?

Le eparine e gli inibitori della vitamina K sono stati per vari decenni il caposaldo della terapia anticoagulante. Anche se efficaci, i farmaci attualmente disponibili presentano alcuni limiti che hanno spinto alla ricerca di nuovi agenti che meglio corrispondessero al profilo dell'anticoagulante ideale. Ad oggi, farmaci diretti contro il fattore Xa e la trombina sono nello stadio più avanzato di sviluppo clinico. Questi nuovi farmaci potrebbero migliorare la gestione delle malattie tromboemboliche grazie a potenziali vantaggi, quali un profilo farmacologico prevedibile, una rapida risposta alla somministrazione, scarse interazioni con cibo e altri farmaci, una somministrazione a dosi fisse e senza necessità di monitoraggio di laboratorio. E' importante considerare i potenziali rischi e benefici derivanti dall'introduzione dei nuovi anticoagulanti nella pratica clinica.

Introduction

Currently available anticoagulant drugs include both parenteral and oral agents. Rapidly acting parenteral anticoagulants are commonly used for initial treatment of arterial or venous thromboembolic diseases, whereas oral agents are employed for long-term therapy. Low-molecular-weight heparins (LMWH) have replaced unfractionated heparin (UFH) for most indications because they are more convenient to administer and meta-analyses of clinical trials comparing LMWH with UFH indicate that they are at least as effective and safe. More recently, fondaparinux, a synthetic indirect inhi-

bitor of factor Xa, obtained the licence for venous thromboembolism (VTE) prevention in high-risk orthopaedic surgery patients and, in some countries among which Italy, in general surgical or medical patients. Fondaparinux is also licensed as an alternative to UFH or LMWH for initial treatment of VTE and for patients with acute coronary syndromes. Although LMWH and fondaparinux are important advances, some difficulties persist. The need for once or twice-daily subcutaneous injections renders treatment problematic for some patients¹. This has prompted the development of longer acting parenteral anticoagu-

lants that can be given subcutaneously on a once-weekly basis, and of novel oral anticoagulants with a rapid onset of action². For over 60 years, vitamin K antagonists (VKAs), such as warfarin, have been the only available oral anticoagulants, despite their many limitations. Their slow onset of action necessitates overlap with a parenteral anticoagulant for at least 5 days. Moreover, they have a narrow therapeutic window and exhibit a considerable variability in dose-response among patients, which reflects, at least in part, differences in dietary vitamin K intake, genetic polymorphisms in the enzymes involved in VKAs metabolism, and administration of concomitant medications that suppress or potentiate the anticoagulant effects of VKAs. Regular coagulation monitoring and dose adjustments are therefore necessary to ensure that a therapeutic anticoagulant response is achieved³. The need for frequent coagulation monitoring is burdensome for patients and physicians and costly for the healthcare system. An "improved" oral anticoagulant at least as effective as VKAs in preventing thrombus formation and at least as safe with respect to bleeding risk would be highly desirable. The properties of such an "ideal" agent include a wide therapeutic window, a predictable dose-response relationship (not requiring laboratory monitoring), a rapid onset and offset of action, a readily available antidote or reversal agent, minimal food and drug interactions, and clear efficacy in large trials without adverse effects.

Recently, dabigatran, an oral direct thrombin inhibitor, has been licensed in Europe for VTE prophylaxis in major orthopaedic surgery, and rivaroxaban, an oral direct factor Xa inhibitor, is expected to be available for the same indication during 2009.

In this article new anticoagulant drugs that are in the most advanced stages of development are reviewed, focusing on: 1) their pharmacology; 2) results of clinical trials evaluating their efficacy and safety; 3) their potential advantages and drawbacks in the management of patients with arterial and venous thromboembolic diseases.

Targets of new anticoagulant drugs

When considering candidates for potential new oral anticoagulants, attention must be paid to the three temporal aspects of coagulation, including initiation, propagation, and termination. Most of the so far available anticoagulants inhibit multiple steps in the coagulation cascade, whereas new anticoagulants selectively target one specific coagulation factor. Drugs targeting the tissue factor/factor VIIa complex prevent the initiation of coagulation. The propagation phase can be inhibited by drugs that block factors IXa or Xa, or their respective coenzymes, factors VIIIa and Va. Finally, agents targeting thrombin can prevent fibrin formation (Figure 1). Although drugs targeting factor VIIa-tissue factor⁴ as well as factor IXa⁵ have been develo-

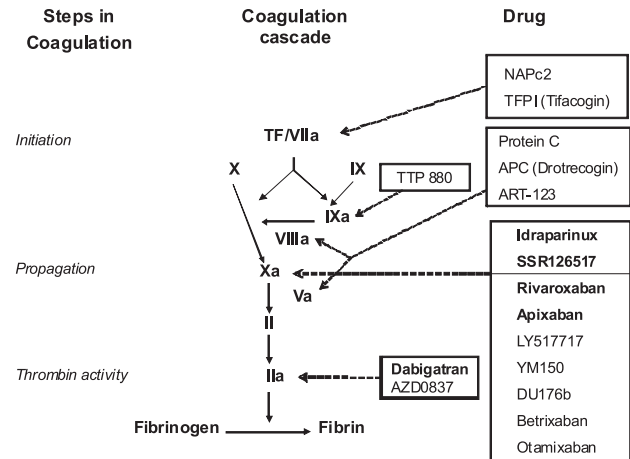


Figure 1. Targets of new anticoagulant drugs.

ped and undergone initial evaluation in the clinic, agents targeting factor Xa and thrombin are in the most advanced stages of clinical development.

Factor Xa is an attractive target for the design of new anticoagulants as it is positioned at the start of the common pathway of coagulation. When bound to factor Va, in the presence of calcium on a phospholipid bilayer, it forms the prothrombinase complex and catalyzes the conversion of prothrombin to thrombin. Factor Xa is also the primary site of serine protease activity amplification, as one molecule gives origin to approximately 1000 molecules of thrombin. Inhibition of factor Xa can occur through direct binding to the factor Xa active site, or indirectly through interaction with antithrombin. Direct factor Xa inhibitors have an advantage because they can bind both free factor Xa and factor Xa within the prothrombinase complex and, therefore, penetrate active thrombus to limit further thrombin generation².

Thrombin plays a central role as a procoagulant by converting fibrinogen to fibrin as well as by activating its other substrates including factor V, factor VIII, factor XI, factor XIII, and the platelet protease activated receptors (PAR-1 and PAR-4). Direct thrombin inhibition is therefore another attractive antithrombotic strategy. Direct thrombin inhibitors inhibit thrombin by directly binding either to exosite 1 for fibrin or the active site of thrombin or both².

Pharmacology of new anticoagulants

Factor Xa inhibitors include indirect inhibitors, such as idraparinux and SSR 126517, parenteral drugs that target factor Xa in an antithrombin-dependent way, and direct inhibitors, such as the orally active agents rivaroxaban and apixaban. Direct thrombin inhibitors include parenteral agents, such as lepirudin, argatroban, and bivalirudin, which have gained approval for limited clinical indications consisting of heparin induced thrombocytopenia and percutaneous coronary in-

Table I. Comparative properties of new anticoagulant agents.

	Idraparinux	Rivaroxaban	Apixaban	Dabigatran etexilate
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Route of administration	Subcutaneous	Oral	Oral	Oral
Frequency of administration	Once-weekly	Once-daily	Twice-daily	Once or twice-daily
Prodrug	No	No	No	Yes
Bioavailability	100%	>80%	>50%	6%
Peak plasma concentration	1-3 h	3 h	3 h	2 h
Half-life	80 h	9 h	9-14 h	14-17 h
Mode of excretion	100% renal	66% renal, 34% hepatic	25% renal, 75% hepatic	80% renal, 20% hepatic
Drug interactions		Potent CYP3A4 and P-glycoprotein inhibitors	Potent CYP3A4 and P-glycoprotein inhibitors	Proton pump inhibitors; potent P-glycoprotein inductors and inhibitors
Antidote	No*	No	No	No
Safe in pregnancy	Unknown	No	No	No

*Available for biotinylated idraparinux.

terventions, and orally active drugs, such as dabigatran etexilate (Figure 1). Table I shows a comparison among the pharmacologic properties of new anticoagulant drugs.

Idraparinux

Idraparinux, a second generation synthetic pentasaccharide, is a hypermethylated derivative of fondaparinux with a longer plasma half-life (about 80 h). Idraparinux exhibits complete bioavailability after subcutaneous injection, binds only to antithrombin in plasma and produces a predictable anticoagulant response. Consequently, it can be given by subcutaneous injection once-weekly and does not require coagulation monitoring. Like fondaparinux, idraparinux is not metabolized and is excreted unchanged via the kidneys. Therefore, the dose must be reduced in patients with renal insufficiency, and it is contraindicated in those with severe renal impairment^{6,7}. The safety of idraparinux in pregnancy is uncertain. No antidote is available to reverse the anticoagulant activity of idraparinux. In order to address this problem SSR 126517 has been developed. This agent is a biotinylated version of idraparinux, which shares the same pharmacological features. The addition of the biotin moiety permits rapid reversal of the anticoagulant effects of SSR 126517 after intravenous injection of avidin, an egg white-derived protein, which binds biotin with high affinity to form a stable complex that is cleared within minutes via the kidneys⁸.

Rivaroxaban

Rivaroxaban, an oxazolidinone derivative, is a potent and selective inhibitor of factor Xa⁹. It binds to

the active site of factor Xa and inhibits the enzyme in a reversible and competitive way regardless of whether factor Xa is free in solution or bound within the prothrombinase complex¹⁰. Rivaroxaban is well absorbed from the gastrointestinal tract with a bioavailability of more than 80%, and food has no major effect on its absorption. Peak plasma levels are achieved in about 3 h. Its terminal half-life is about 5 to 9 h in young individuals, and 11 to 13 h in the elderly. Rivaroxaban exhibits a dual mechanism of excretion: approximately 66% is excreted via the kidneys, and the remainder is excreted in the feces. Intestinal excretion of rivaroxaban appears to be mediated, at least in part, by P-glycoprotein, a transport protein, because potent P-glycoprotein inhibitors increase drug levels. Of that found in the urine, 30% to 40% reflects unchanged drug that is excreted via a combination of glomerular filtration and tubular secretion, whereas the remainder reflects metabolites. Because of its renal clearance, rivaroxaban must be used with caution in patients with renal insufficiency. Rivaroxaban is metabolized in the liver via CYP 3A4, CYP 2J2, and via CYP-independent mechanisms. It is contraindicated in patients with severe liver disease because metabolic inactivation may be impaired. Caution must also be exercised in patients receiving treatment with potent inhibitors of both CYP3A4 and P-glycoprotein, such as ketoconazole or ritonavir, because reduced fecal and renal clearance of rivaroxaban by these drugs can cause an exaggerated anticoagulant effect¹¹. Like other direct factor Xa inhibitors, rivaroxaban prolongs prothrombin time (PT) and activated partial thromboplastin time (aPTT), with PT being more sensitive than aPTT depending on the reagents used for testing. However, the effect of the

drug on these tests is short-lived, with prolongation only seen at peak drug levels. Factor Xa inhibition is the best test to monitor drug concentrations in plasma¹².

Apixaban

Apixaban is a selective and reversible inhibitor of factor Xa and, like rivaroxaban, it inhibits factor Xa bound within the prothrombinase complex as well as the free enzyme. The drug is absorbed from the gastrointestinal tract with a bioavailability over 50%, and peak plasma levels are achieved in about 3 h. With repeated doses, the terminal half-life is between 9 and 14h. Apixaban is metabolized in the liver via CYP3A4 and via CYP-independent mechanisms. It exhibits a dual mechanism of excretion, with about 25% being excreted via the kidneys, whereas the remainder appears in the faeces. Apixaban prolongs International Normalized Ratio (INR) and aPTT in a concentration-dependent way. However, its effect on these tests is minimal at therapeutic concentrations. It can be monitored using a factor Xa inhibition assay or a dilute PT¹³.

Dabigatran etexilate

Dabigatran etexilate is an oral prodrug that, once absorbed from the gastrointestinal tract, is converted by esterases into its active metabolite, dabigatran, a competitive and reversible direct thrombin inhibitor¹⁴. Because bioconversion of dabigatran etexilate to dabigatran begins in the gut, the drug enters the portal vein as a combination of prodrug and active compound. Once in the liver, bioconversion of the prodrug is completed and about 20% is conjugated and excreted via the biliary system. The cytochrome P450 system plays no part in the metabolism of dabigatran etexilate. Therefore, the risk of drug-drug interactions is low¹⁵. Because the bioavailability of dabigatran etexilate is only about 6%, relatively high doses of dabigatran etexilate must be given to ensure that adequate plasma concentrations are achieved. The absorption of dabigatran etexilate in the stomach and small intestine is dependent on an acid environment. To promote such a microenvironment, dabigatran etexilate is provided in tartaric acid-containing capsules. Drug absorption is reduced by 20% to 25% if dabigatran treated patients are given proton pump inhibitors. Peak plasma levels of dabigatran are achieved about 2 h after dabigatran etexilate administration. The half-life of dabigatran is approximately 8 h after single dose administration and up to 14 to 17 h after multiple doses. About 80% of circulating dabigatran is excreted unchanged via the kidneys. Consequently, plasma concentrations increase in patients with renal insufficiency and the drug is contraindicated in patients with renal failure. Dabigatran etexilate prolongs aPTT, but its effects on this test are not dose-dependent. It has minimal effect on PT but prolongs ecarin clotting time in a

concentration-dependent way^{16,17}.

Clinical studies with new anticoagulants

Idraparinux has completed phase III clinical trials for VTE treatment, and trials with its biotinylated form SR 126517 are underway. Phase II trials with rivaroxaban, apixaban, and dabigatran etexilate have been completed, and phase III trials with all three agents are some finished and some ongoing.

Idraparinux

Idraparinux has been evaluated in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), the extended secondary prophylaxis of VTE, and the long-term prevention of stroke in patients with atrial fibrillation. The phase III Van Gogh trials compared subcutaneous idraparinux at a dose of 2.5 mg once-weekly with LMWH or UFH followed by 3 or 6 months of a VKA for the treatment of patients with DVT or PE¹⁸. In the DVT patients, the primary efficacy outcome, the rate of recurrent VTE at 3 months, was similar in the idraparinux and conventionally-treated groups (2.9% and 3.0%, respectively). At 3 months, clinically relevant bleeds were less common with idraparinux than with conventional treatment (4.5% and 7.0%, respectively; $p=0.004$). In the PE patients, idraparinux was less effective than conventional anticoagulant therapy at 3 months. Thus, the rate of recurrent VTE was 3.4% in those treated with idraparinux and 1.6% in those given conventional therapy. Rates of clinically relevant bleeding at 3 months in patients treated with idraparinux or conventional anticoagulant therapy were 5.8% and 8.2%, respectively¹⁸. The discordant efficacy results in the DVT and PE trials highlight the importance of adequate levels of anticoagulation for initial treatment of PE because the majority of recurrences occurred early in idraparinux-treated patients. These findings suggest that PE patients require higher initial doses of idraparinux than DVT patients; however, the safety of higher dose treatment remains to be established. The efficacy of long-term idraparinux therapy was evaluated in the Van Gogh extension trial, which enrolled patients from the DVT or PE trials who had received 6 months of treatment with either idraparinux or a VKA¹⁹. Patients were randomized to an additional 6 months of treatment with either subcutaneous idraparinux at a dose of 2.5 mg once-weekly or placebo. Compared with placebo, idraparinux was effective in reducing the rate of recurrent VTE (from 3.7% to 1.0%; $p=0.002$), but was associated with an increased risk of major bleeding (1.9% in the idraparinux group, including 3 fatal intracranial bleeds, vs none in the placebo group; $p<0.001$)¹⁹. The Amadeus trial in patients with atrial fibrillation was stopped after randomization of 4576 patients because of a significantly increased number of clinically relevant bleeds and intracranial bleeds with idraparinux in comparison with

VKAs (19.7% vs. 11.3% and 1.1% vs. 0.4%, respectively)²⁰. Consequently, SSR 126517 has been developed. It is unclear, however, whether rendering idraparinux reversible through biotinylation will improve the benefit-to-risk profile of the drug. The bioequipotency of SSR 126517 in comparison with an equimolar dose of idraparinux has been evaluated in a clinical trial addressing the treatment of symptomatic DVT without symptomatic PE (EQUINOX trial). Currently, SSR 126517 is also under investigation in patients with symptomatic PE who are administered an initial treatment with enoxaparin (CASSIOPEA trial). Finally, a SSR 126517 dose regimen adjusted to patient characteristics (age and renal function), which might preserve efficacy without an increased haemorrhagic risk, is presently being evaluated in patients with atrial fibrillation (BOREALIS-AF trial).

Rivaroxaban

To date, the efficacy and safety of rivaroxaban for the prophylaxis and treatment of VTE has been evaluated in phase II and phase III trials involving over 24,000 patients. Additionally, rivaroxaban is being evaluated for the treatment of PE, secondary prevention after acute coronary syndromes and the prevention of stroke and non-central nervous system embolism in patients with atrial fibrillation. Four phase III clinical trials, the RECORD 1-4 studies, were designed to evaluate the effectiveness of rivaroxaban administered at a dose of 10 mg once-daily starting 6-8 h postoperatively in the prevention of VTE in patients undergoing major orthopaedic surgery²¹⁻²⁴. The RECORD 1 and 2 trials, which studied patients undergoing total hip replacement, compared rivaroxaban administered for 5 weeks with enoxaparin 40 mg administered once-daily starting the evening before surgery for 5 weeks (RECORD 1)²¹ or for 10-14 days followed by placebo (RECORD 2)²². In the RECORD 3 and 4 trials, patients undergoing total knee replacement were randomized to receive prophylaxis for 10-14 days with postoperative rivaroxaban or with enoxaparin 40 mg once-daily starting the evening before surgery (RECORD 3)²³, or enoxaparin 30 mg twice-daily starting 12-24 h after surgery (RECORD 4)²⁴. All four studies demonstrated that rivaroxaban was significantly more effective than enoxaparin in VTE prophylaxis following total hip or knee replacement. The incidence of major and non-major bleeding events was similar between the two comparator groups in each of the four trials. A pooled analysis was performed on all randomized patients who received at least one dose of double-blind study medication to evaluate the effect of rivaroxaban on the composite of symptomatic VTE (comprising DVT or PE) and death, and bleeding²⁵. These primary outcomes were analyzed at day 12±2 in the active treatment pool (i.e. during the enoxaparin-controlled period common to all studies, to allow for unbiased comparison of rivaroxaban with enoxaparin),

and for the total study duration pool (planned treatment period and 30-35 days follow-up). This analysis demonstrated that in the regimens tested, rivaroxaban reduced the composite of major clinical outcomes compared with enoxaparin regimens, with no significant increase in the risk of major bleeding in patients undergoing major orthopaedic surgery²⁵. The utility of rivaroxaban for VTE treatment was assessed in two phase II studies. The ODIXa-DVT study randomized 613 patients with symptomatic proximal DVT without PE to a 3-month course of rivaroxaban (at doses of 10, 20, or 30 mg once-daily or 40 mg twice-daily) or to LMWH followed by warfarin²⁶. The primary efficacy outcome, a reduction in thrombus burden based on improvement in the results of repeated ultrasound evaluation at 21 days and no evidence of recurrent VTE, was achieved in 43.8% to 59.2% of those given rivaroxaban and in 45.9% of those given conventional anticoagulant therapy. The incidence of major and minor bleeding increased with escalating doses of rivaroxaban (range: 5.0%-11.6%) compared with patients treated with LMWH/warfarin (6.3%)²⁶. The Einstein-DVT study randomized 543 patients with symptomatic proximal DVT without PE to a 3-month course of once-daily rivaroxaban (at doses of 20, 30, or 40 mg) or to conventional anticoagulant therapy²⁷. The primary efficacy end point, a composite of symptomatic recurrent VTE plus an increase in thrombus burden (as detected by repeated ultrasound examination and perfusion lung scanning), occurred in 6% of those randomized to rivaroxaban and in 9.9% of those given conventional therapy. The incidence of clinical relevant bleeding occurred in 2.2%-6.0% of patients in rivaroxaban groups and in 8.8% of patients in LMWH/warfarin group, with no significant dose-response for bleeding²⁷. There was no apparent dose-response for efficacy with rivaroxaban in either trials. However, the dose-dependent increase in the risk of bleeding was reported in the ODIXa-DVT study indicating that twice-daily regimen for rivaroxaban might increase risk of bleeding. Based on the results of these trials, phase III trials evaluating rivaroxaban for initial and extended treatment of VTE and for the prevention of stroke in atrial fibrillation (ROCKET-AF) are using the 20 mg once-daily dose.

Apixaban

At present, the efficacy and safety of apixaban for the prophylaxis and treatment of VTE is being evaluated in phase II and phase III trials involving nearly 25,000 patients. Trials are also underway involving over 20,000 patients for secondary prevention after acute coronary syndromes and the prevention of stroke in patients with atrial fibrillation. In the phase II APROPOS trial, apixaban prevented more cases of DVT, PE and death after total knee replacement than enoxaparin, but the risk of bleeding correlated with drug dose²⁸. In the phase II Botticelli-DVT trial, 520 patient-

ts with proximal DVT were randomized to a 3-month course of treatment with apixaban (at doses of 5 or 10 mg twice-daily or 20 mg once-daily) or to conventional anticoagulant therapy with LMWH or fondaparinux followed by a VKA²⁹. The primary efficacy end point, a composite of recurrent VTE and increased thrombus burden (as detected by repeated ultrasound and perfusion lung scanning), occurred in 6.0%, 5.6%, and 2.6% of patients given apixaban at doses of 5 or 10 mg twice-daily or 20 mg once-daily, respectively, and in 4.2% of those treated with conventional therapy. Rates of major plus clinically relevant non-major bleeding were 8.6%, 4.5%, and 7.3% in the apixaban arms, respectively, and 7.9% in those given conventional treatment²⁹. Based on these results, phase III trials are evaluating both a 2.5 and a 5 mg twice-daily regimen of apixaban for initial and extended treatment of VTE. Apixaban was also tested as an additional treatment for patients with acute coronary syndromes in the phase II APPRAISE-1 safety study³⁰. Being administered in combination with currently recommended antiplatelet therapy, apixaban appeared to be safer in low dose (2.5 mg twice-daily), while the 10 mg twice-daily and 20 mg once-daily arms were stopped early due to increased total bleeding³⁰. On the basis of results of the phase II trials, other phase II and III trials are ongoing. The ADOPT study is investigating once-daily apixaban of 2.5 mg for one month compared to enoxaparin for the prevention of VTE in medically ill patients. The three ADVANCE studies are investigating the efficacy and safety of apixaban (2.5 mg twice-daily) compared with enoxaparin in patients undergoing major orthopaedic surgery. The preliminary results for ADVANCE-1 failed to show (statistical) non-inferiority when compared with enoxaparin. AVERROES and ARISTOTLE are both phase III trials on stroke prevention in atrial fibrillation patients. AVERROES is comparing apixaban against aspirin in a superiority trial of stroke prevention among patients with atrial fibrillation at moderate risk or in whom VKAs are contraindicated or refused, whereas ARISTOTLE is a phase III non-inferiority trial comparing apixaban with warfarin for stroke prevention in high-risk patients with atrial fibrillation.

Dabigatran etexilate

Phase II and III clinical trials assessing dosages, efficacy and tolerability in numerous indications including VTE prevention and treatment, stroke prevention in atrial fibrillation, and secondary prevention of cardiac events in patients with acute coronary syndromes have been conducted or are underway with dabigatran etexilate. To date, two phase II dose-ranging studies and three phase III clinical trials have been completed for the evaluation of dabigatran etexilate in VTE prevention in patients undergoing orthopaedics surgery³¹⁻³⁵. In the BISTRO I study, dabigatran etexilate demonstrated an acceptable safety therapeutic profile with

doses ranging from 12.5 to 300 mg twice-daily in patients undergoing elective total hip replacement³¹. There were bleeding events in two patients, who had a lower creatinine clearance (<50 ml/min) on the higher doses of 300 mg twice-daily³¹. Subsequently, in the BISTRO II study (dabigatran etexilate compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement) four different doses of dabigatran etexilate were compared with enoxaparin, with a significant reduction in VTE events in patients receiving 150 mg twice-daily, 300 mg once-daily and 225 mg twice-daily, with an increase in major bleeding observed in the 300 mg once-daily dose (4.7%)³². The RE-MODEL trial in patients undergoing total knee replacement compared 75 or 110 mg of dabigatran etexilate starting 1-4 h postoperatively followed by 150 or 220 mg once-daily, respectively, with enoxaparin 40 mg 12 h before surgery and then once-daily starting 12-24 h postoperatively³³. The primary efficacy outcome (the composite of total VTE, proximal and distal DVT demonstrated by mandatory bilateral venography, symptomatic VTE, and all-cause mortality during the treatment period of 6-10 days) occurred at similar rates in patients receiving the two doses of dabigatran etexilate (36.4% in the 220 mg group and 40.5% in the 150 mg group) or enoxaparin (37.7%); both doses of the oral agent met the pre-specified criterion for non-inferiority. The rates of the major safety endpoint and major bleeding were low and similar in the three groups, and no significant differences in liver enzyme elevations were observed³³. The RE-NOVATE trial demonstrated that the 150 or 220 mg doses of dabigatran etexilate were non-inferior to the 40 mg enoxaparin regimen for the extended prevention (28-35 days) of VTE following total hip replacement³⁴. Another phase III trial of dabigatran etexilate for DVT prophylaxis following total knee replacement, RE-MOBILIZE, used the same doses of drug as the RE-MODEL trial, but the initial half-dose was administered 6-12 h postoperatively and the comparator, enoxaparin at a dose of 30 mg twice-daily, was only administered postoperatively, which is the preferred schedule in North America³⁵. The primary endpoint was the same as in the RE-MODEL trial, but dabigatran etexilate at 150 and 220 mg doses had VTE rates of 33.7% and 31.1%, respectively, which were significantly higher than the enoxaparin regimen (25.3%)³⁵. Hence, in the RE-MOBILIZE trial dabigatran etexilate did not demonstrate non-inferiority as compared with the North American enoxaparin regimen. A meta-analysis of efficacy and safety data for the recommended dose of dabigatran etexilate, 220 mg once-daily, for VTE prophylaxis after major orthopaedic surgery was performed combining RE-MODEL and RE-NOVATE, and also including RE-MOBILIZE³⁶. No significant differences were detected between dabigatran etexilate and enoxaparin in any of the end-points analyzed, either in the two trial analysis

(all $p > 0.15$), or when all three trials were combined (all $p > 0.30$). Risk ratios analyses for the composite end-point total VTE and all-cause mortality were 0.95 [95% CI 0.82–1.10] and 1.05 [95% CI 0.87–1.26] in the two and three trial analyses, respectively. Meta-analysis of RE-MODEL and RE-NOVATE supported the conclusions of the individual trials that dabigatran etexilate is non-inferior to enoxaparin 40 mg once-daily, with a similar safety profile. Meta-analysis of all three trials found no significant differences between treatments in any of the end-points analyzed³⁶. Phase III trials evaluating dabigatran etexilate for the treatment and secondary prevention of symptomatic VTE (RE-COVER, RE-MEDY, and RE-SONATE) are ongoing. For stroke prevention in atrial fibrillation, the phase II dose-ranging PETRO study was conducted in 502 participants randomized to receive different doses of dabigatran alone or in combination with aspirin (81 or 325 mg) or open-label warfarin³⁷. This clinical study found no serious liver toxicity with only a small fraction of patients (0.9%) observed to have raised aminotransferase levels and also justified dose selection for subsequent trials³⁷. The ongoing RE-LY study (randomized evaluation of long-term anticoagulant therapy comparing 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) compares warfarin with two doses (150 or 110 mg twice-daily) of dabigatran in moderate to high-risk patients with atrial fibrillation.

In March 2008 the European Union approved the use of dabigatran etexilate for DVT prevention post-elective total hip or knee replacement surgery. Dabigatran etexilate has been marketed in Italy since December 2008. It is available in capsules formulation of 75 and 110 mg. The recommended daily doses for DVT prevention is 220 mg daily (two capsules of 110 mg) and treatment should be initiated within 1–4 h of completed surgery as soon as haemostasis is achieved. The duration of treatment is 10 days for knee replacement and 28–35 days for hip replacement. The initial dose post-surgery is 110 mg followed by 220 mg. Patients with moderate renal impairment (creatinine clearance 30–50 ml/min) require reduced dosages.

New anticoagulants: potential advantages and challenges in anticoagulation management

Selective inhibitors of factor Xa and thrombin have the potential to be more effective, safer and easier to use than the currently available anticoagulant drugs. The greatest unmet need in anticoagulation therapy is replacement of VKAs with an orally active agent that can be given in fixed doses without routine coagulation monitoring. Consequently, most of the current attention is focused on new oral anticoagulants. All of

the new oral inhibitors of factor Xa or thrombin have a rapid onset of action with peak plasma levels achieved within 2 to 4 h. Thus, these new agents have the potential to avoid the need for parenteral anticoagulants in the initial phase of treatment. With a predictable pharmacological profile that allows fixed dosing, low propensity for food and drug interactions and no need for coagulation monitoring, new oral anticoagulants may also offer advantages over VKAs for extended VTE therapy of for long-term use in a chronic condition such as atrial fibrillation. While formal cost-effectiveness analyses are not yet available, avoidance of the intensive, costly, and frequent coagulation monitoring required with VKAs as well as a lower potential for dose-adjustment errors with consequent potential reduction in adverse vascular events precipitated by the narrow therapeutic window of VKAs should result in a significant improvement in quality of life and cost-savings.

As regards new parenteral anticoagulants, idraparinix or its biotinylated counterpart, SSR 126517, have the advantage of once-weekly administration. If higher dose SSR 126517 proves as effective and safe as conventional anticoagulation for treatment of PE, the drug could be used as an alternative to LMWH or fondaparinux for initial VTE treatment. Thus, a single subcutaneous injection of SSR 126517 could provide anticoagulation coverage while waiting for a therapeutic response with VKAs, simplifying the management of patients incapable of self injection. With once-weekly subcutaneous injection and no need for coagulation monitoring, SSR 126517 may also have a place in the long-term management of VTE provided that its efficacy and safety are confirmed in the phase III trials. However, the availability of shorter-acting oral factor Xa or thrombin inhibitors may limit the need for a long-acting parenteral agent.

The lack of safe rapidly-acting specific antidotes to reverse the anticoagulant effect remains a main challenge for the new anticoagulants. This is particularly problematic for drugs with a long half-life, such as idraparinix. Development of a biotinylated version of idraparinix may overcome this limitation provided that avidin, the antidote, is readily available and its safety established. Although not well studied, dialysis is likely to clear the direct factor Xa or thrombin inhibitors, all of which are small molecules.

In addition to assessing the antithrombotic efficacy and the haemorrhagic potential of these new agents, the experience with ximelagatran, an oral direct thrombin inhibitor that did not receive FDA approval because of hepatic toxicity, mandates careful attention to off-target side-effects. At present, it is unclear whether hepatic toxicity is unique to ximelagatran, or whether it represents a class effect. Ongoing studies with dabigatran etexilate and the oral factor Xa inhibitors will clarify this issue.

Although the new anticoagulants have been designed

to be administered without coagulation monitoring, there are conditions where monitoring may be helpful to make appropriate dose adjustments. For example, monitoring may be needed in patients with hepatic or renal impairment or in those taking concomitant medications that may affect anticoagulant metabolism. How best to monitor the new anticoagulants is uncertain. SSR 126517 can be monitored using anti-factor Xa assays, but the tests must be performed using this drug as a standard. Specific kits have been studied and are ready to be commercialized, but data on usefulness and reliability of these measures are not available. Monitoring is at the moment more complicated for the oral factor Xa and thrombin inhibitors. These agents have variable effects on routine tests of coagulation, and none of these tests provide a good indication of drug levels. Factor Xa inhibition assays may prove useful to monitor oral factor Xa inhibitors. However, these assays have not been standardized and the therapeutic level is likely to vary among the different agents. Although the ecarin clotting time can be used to monitor dabigatran etexilate, the test is not available in all laboratories and has not been yet standardized. These issues will need to be addressed as the development of new anticoagulants moves forward.

Compliance with new anticoagulants may also be a critical issue because for some drugs and/or indications a twice-daily administration is required; moreover, compliance may be difficult to assess in the absence of routine coagulation monitoring.

Finally, the cost of new anticoagulants may also be a potential obstacle on their usage, particularly if these drugs prove only to be as effective and safe as existing agents. Even with the added expense of coagulation monitoring, warfarin is relatively inexpensive³⁸; therefore, unless the cost of the new anticoagulants is relatively low, these drugs are likely to be reserved for patients who cannot be adequately controlled on warfarin, or for those without ready access to a laboratory. However, formal cost-effectiveness analyses are needed.

Even if the new drugs appears to be easier to use, anticoagulation clinics could still have a place in the management of anticoagulated patients for assessment of compliance, monitoring disease progress and determining the duration of anticoagulation; moreover, they could play an important role in monitoring off-target side-effects of the new drugs.

Conclusions

Current data suggest that both factor Xa and thrombin are good targets for new anticoagulants. Direct head-to-head comparison trials are needed to evaluate the relative benefit-to-risk ratios of the two classes of agents, but such studies are unlikely to be conducted in the near future. In the meantime, parallel clinical trial programs are ongoing to assess their efficacy and safety for the prevention and treatment of venous and

arterial thromboembolism. Because of their pharmacologic properties, new anticoagulants represent an attractive alternative to the currently available drugs, and approval of one or more of these agents will lead to an improved drug armamentarium for the management of thromboembolic disorders. However, potential challenges of bringing new anticoagulants to the clinic should be taken into account.

References

1. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133:141S-159S.
2. Weitz JI, Hirsh J, Samama MM. New antithrombotic drugs. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133:234S-256S.
3. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133:160S-198S.
4. Lee A, Agnelli G, Büller H, Ginsberg J, Heit J, Rote W, et al. Dose-response study of recombinant factor VIIa/tissue factor inhibitor recombinant nematode anticoagulant protein c2 in prevention of postoperative venous thromboembolism in patients undergoing total knee replacement. *Circulation* 2001; 104:74-8.
5. Eriksson BI, Dahl OE, Lassen MR, Ward DP, Rothlein R, Davis G, et al, Fixit Study Group. Partial factor IXa inhibition with TTP889 for prevention of venous thromboembolism: an exploratory study. *J Thromb Haemost* 2008; 6:457-63.
6. Walenga JM, Jeske WP, Fareed J. Short- and long-acting synthetic pentasaccharides as antithrombotic agents. *Expert Opin Investig Drugs* 2005; 14:847-58.
7. Veyrat-Follet C, Vivier N, Trelu M, Dubruc C, Sanderink GJ. The pharmacokinetics of idraparinux, a long-acting indirect factor Xa inhibitor: population pharmacokinetic analysis from Phase III clinical trials. *J Thromb Haemost* 2009; 7:559-65.
8. Spyropoulos AC. Investigational treatments of venous thromboembolism. *Expert Opin Investig Drugs* 2007; 16:431-40.
9. Roehrig S, Straub A, Pohlmann J, Lampe T, Pernerstorfer J, Schlemmer KH, et al. Discovery of the novel antithrombotic agent 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (BAY 59-7939): an oral, direct factor Xa inhibitor. *J Med Chem* 2005; 48:5900-8.
10. Perzborn E, Strassburger J, Wilmen A, Pohlmann J, Roehrig S, Schlemmer KH, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939 – an oral, direct factor Xa inhibitor. *J Thromb Haemost* 2005; 3:514-21.
11. Kubitzka D, Becka M, Wensing G, Voith B, Zuehisdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct factor Xa inhibitor – after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005; 61:873-80.

12. Mueck W, Becka M, Kubitzka D, Voith B, Zuehisdorf M. Population model of the pharmacokinetics and pharmacodynamics of rivaroxaban – an oral, direct factor Xa inhibitor – in healthy subjects. *Int J Clin Pharmacol Ther* 2007; 45:335-44.
13. Pinto DJ, Orwat MJ, Koch S, Rossi KA, Alexander RS, Smallwood A, et al. Discovery of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (apixaban, BMS-562247), a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor Xa. *J Med Chem* 2007; 50:5339-56.
14. Huel NH, Nar H, Pripke H, Ries U, Stassen JM, Wiene W. Structure-based design of novel potent nonpeptide thrombin inhibitors. *J Med Chem* 2002; 45:1757-66.
15. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 2008; 36:386-99.
16. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol* 2007; 64: 292-303.
17. Stangier J, Stahle H, Rathgen K, Fuhr R. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clin Pharmacokinet* 2008; 47:47-59.
18. Buller HR, Cohen AT, Davidson B, Decousus H, Gallus AS, Gent M, et al., van Gogh Investigators. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007; 357:1094-104.
19. Buller HR, Cohen AT, Davidson B, Decousus H, Gallus AS, Gent M, et al., van Gogh Investigators. Extended prophylaxis of venous thromboembolism with idraparinux. *N Engl J Med* 2007; 357:1105-12.
20. Boussier MG, Bouthier J, Buller HR, Cohen AT, Crijns H, Davidson BL, et al., the Amadeus Investigators. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomized, open-label, non-inferiority trial. *Lancet* 2008; 371:315-21.
21. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al., RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; 358:2765-75.
22. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al., RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled study. *Lancet* 2008; 371:31-9.
23. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al., RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; 358:2776-86.
24. Turpie AG, Bauer KA, Davidson B, Gent M, Kwong L, Lassen MR, et al. Once-daily oral rivaroxaban compared with subcutaneous enoxaparin every 12 hours for thromboprophylaxis after total knee replacement: RECORD4. *Blood (ASH Annual Meeting Abstracts)* 2008; 112:35.
25. Turpie AG, Lassen MR, Kakkar AK, Eriksson B, Miselwitz F, Bandel TJ, et al. A pooled analysis of four pivotal studies of rivaroxaban for the prevention of venous thromboembolism after orthopaedic surgery: effect on symptomatic venous thromboembolism, death, and bleeding. *Blood (ASH Annual Meeting Abstracts)* 2008; 112:36.
26. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, et al., ODIXa-DVT Study Investigators. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in patients with Acute Symptomatic Deep-Vein Thrombosis) study. *Circulation* 2007; 116:180-7.
27. Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS, et al., Einstein-DVT Dose-Ranging Study investigators. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. *Blood* 2008; 112:2242-7.
28. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost* 2007; 5:2368-75.
29. Buller H, Deitchman D, Prins M, Segers A, Botticelli Investigators Writing Committee. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. *J Thromb Haemost* 2008; 6:1313-8.
30. Alexander JH, Wallentin L. Safety of the factor Xa inhibitor, apixaban, in combination with antiplatelet therapy after acute coronary syndromes: results from the APPRAISE-1 dose guiding trial. Presented at the European Society of Cardiology Congress 2008 in Munich, 30 August-3 September, 2008. <http://www.americanheart.org/downloadable/heart/1220306467486APPRAISE%20LBCT%20ESC08%20090208.pdf> (date of consultation: 04-04-2009).
31. Eriksson BI, Dahl OE, Ahnfelt L, Kälebo P, Stangier J, Nehmiz G, et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. *J Thromb Haemost* 2004; 2:1573-80.
32. Eriksson BI, Dahl OE, Buller HR, Hettiarachchi R, Rosencher N, Bravo ML, et al., BISTRO II Study Group. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost* 2005; 3:103-11.
33. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al., RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007; 5:217-85.
34. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al., RE-NOVATE Study Group. Dabigatran etexilate vs. enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial. *Lancet* 2007;

- 370:949-56.
35. Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, et al. RE-MOBILIZE Writing Committee. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009; 24:1-9.
 36. Wolowacz SE, Roskell NS, Plumb JM, Caprini JA, Eriksson BI. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. *Thromb Haemost* 2009; 101:77-85.
 37. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol* 2007; 100:1419-26.
 38. Hull RD, Raskob GE, Pineo GF, Feldstein W, Rosenbloom D, Gafni A, et al. Subcutaneous low molecular-weight heparin vs warfarin for prophylaxis of deep vein thrombosis after hip or knee implantation. An economic perspective. *Arch Intern Med* 1997; 157:298-303.