New oral anticoagulants in atrial fibrillation

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Atrial fibrillation (AF) is a major risk factor for stroke. Currently, acetylsalicylic acid (a platelet inhibitor) and vitamin K antagonists (VKAs; oral anticoagulants), including warfarin, are the only approved antithrombotic therapies for stroke prevention in patients with AF. Although effective, VKAs have unpredictable pharmacological effects, requiring regular coagulation monitoring and dose adjustment to maintain effects within the therapeutic range. The clinical development pathway for novel anticoagulants often involves evaluation of efficacy and safety in a short-term indication, such as the prevention of venous thrombo-embolism (VTE), followed by longer-term VTE treatment studies, and finally chronic indications, including stroke prevention studies in patients with AF. The coagulation pathway provides many targets for novel anticoagulants, including Factor Xa (FXa) and Factor IIa (thrombin). Numerous oral, direct FXa inhibitors are in various stages of clinical development, including rivaroxaban, LY517717, YM150, DU-176b, apixaban, and betrixaban, and are anticipated to overcome the limitations of VKAs. Dabigatran is the only oral direct thrombin inhibitor in late-stage development. Studies of these agents for stroke prevention in patients with AF are planned or ongoing. If approved, they may represent the next generation of anticoagulants, by providing new therapeutic options for stroke prevention in patients with AF.

Keywords
Anticoagulant • Atrial fibrillation • Factor Xa inhibitor • Direct thrombin inhibitor • Stroke

Introduction
Atrial fibrillation (AF) is the most common significant cardiac arrhythmia and causes considerable morbidity and mortality. It is estimated to affect 4.5 million people in the EU and up to 2.3 million people in the US.1–3 Because the prevalence of AF increases with age,3–5 it is estimated that the number of people with the disease will increase dramatically over the next 50 years. Thus, the projected number of persons with AF in the US will exceed 10 million by 2050 (Figure 1).6 AF is a chronic disorder, which promotes thrombus formation particularly in the left atrium. AF increases the overall risk of stroke five-fold,7 and is associated with particularly severe strokes.8,9 It is also a significant risk factor for stroke recurrence.10 One of the main objectives of treating patients with AF with long-term anticoagulants is to prevent thrombo-embolism and reduce the risk of stroke. The recent ACC/AHA/ESC guidelines recommend a risk-based approach to stroke prevention (Table 1),1 so that each individual’s stroke risk is calculated to identify those who are at higher risk, and who may benefit most from anticoagulant therapy. Acetylsalicylic acid (ASA), an antiplatelet agent, is recommended for patients with AF who have a low to intermediate risk of stroke,3 but only provides modest protection.11 Vitamin K antagonists (VKAs), such as warfarin, are the only oral anticoagulants currently recommended for the prevention of stroke in patients with a moderate to high risk of stroke, who account for 76% of patients with AF.12 VKAs produce their anticoagulant effect by preventing the γ-carboxylation of the vitamin K-dependent coagulation factors prothrombin and Factors VII, IX, and X.13 VKAs reduce the risk of AF-related stroke by about 70%.5,14 However, they have a narrow therapeutic window: insufficient anticoagulation may result in stroke, whereas over-anticoagulation increases the risk of bleeding (Figure 2).1,15 VKAs have unpredictable pharmacokinetics and pharmacodynamics, which are affected by genetic factors, drug–drug interactions, and consumption of foods containing vitamin K.13 Due to these factors, regular coagulation monitoring and dose adjustment of VKAs are needed to ensure that anticoagulant effects remain within the narrow therapeutic range.

Coagulation monitoring has formed the cornerstone to the effective management of patients receiving VKAs. Monitoring of the international normalized ratio (INR) levels is required to compensate for the complex pharmacokinetics of the VKAs, especially the high inter- and intrapatient variability and multiple food and drug interactions that leads to the need for dose adjustment.13 A predictable pharmacological profile that negates the need for
frequent monitoring is widely regarded as essential for any new agent. There are clinical and pharmacoeconomical advantages to fixed dose, unmonitored agents. For example, fewer hospital or clinic visits and a lower potential for dose-adjustment errors suggest that there are benefits for patients and healthcare professionals. However, coagulation monitoring is an important opportunity to assess patients and reassure them. Its absence from routine clinical care will need to be addressed; it is important to note that low molecular weight heparins (LMWHs) are widely accepted anticoagulants administered parenterally that do not require coagulation monitoring.

The limitations of VKAs highlight the unmet need for new anticoagulants in the prevention of stroke in patients with AF. Therefore, the characteristics of an ideal anticoagulant for long-term use in a chronic condition such as AF would include: oral administration, predictable pharmacokinetics and pharmacodynamics, a low propensity for food and drug interactions, administration of fixed doses, a wide therapeutic window, and no requirement for regular monitoring.

This paper reviews the most recent data published and presented on the new oral anticoagulants and compares their clinical profiles relevant to their potential use in AF.

**New anticoagulants**

There are many targets for novel anticoagulants in the coagulation pathway (Figure 3). Drugs targeting the tissue factor/Factor VIIa complex, such as tissue factor pathway inhibitor, prevent the initiation of coagulation. The propagation of coagulation can be inhibited by drugs that block Factors IXa or Xa, or their respective coenzymes, Factors VIIIa and Va. These cofactors can be inactivated by activated protein C. Soluble thrombomodulin can also affect the protein C anticoagulant pathway by converting thrombin (Factor IIa) from a procoagulant enzyme into a potent activator of protein C. Factor Xa (FXa) inhibitors may block FXa indirectly or directly. Fondaparinux and idraparinux inhibit FXa indirectly requiring antithrombin as a cofactor. In contrast, direct FXa inhibitors bind to the active site of FXa and block the interaction with its substrates. There are several orally active, direct FXa inhibitors in clinical development for stroke prevention in patients with AF, including LY517717, YM150, DU-176b, apixaban, betrixaban, and rivaroxaban (BAY 59-7939).

In the final step of the coagulation pathway, thrombin converts fibrinogen to fibrin. Oral, direct thrombin inhibitors include ximelagatran (now withdrawn) and dabigatran. They bind directly to thrombin, blocking its interaction with substrates and thereby preventing fibrin formation, thrombin-mediated activation of Factors V, VIII,
XI, and XII, and thrombin-induced platelet-aggregation. Heparin-based anticoagulants, such as unfractionated heparin or LMWH, are parenterally administered and act by binding to antithrombin and inhibiting both thrombin and FXa.

**Development of novel anticoagulants**

Although there is a great need for new anticoagulants for the prevention of stroke in patients with AF, some novel anticoagulants have been evaluated initially in short-term indications, such as the prevention of venous thrombo-embolism (VTE) after total hip or knee replacement surgery. This approach is ideal for anticoagulant drug development, because studies with well-defined efficacy and safety endpoints can be carried out in a population in which there is a relatively high rate of VTE events, and bleeding can be monitored and controlled in a hospital environment. These types of surgery are performed under elective circumstances in patients who are fit enough to undergo the procedure. In addition, there is a large number of patients who undergo this procedure on a year-by-year basis. Studies that are successful in phase II lead to the initiation of phase III VTE prevention studies. Drugs may then be investigated in the longer-term setting, such as phase II VTE treatment studies, which have a duration of 3 months or longer. VTE treatment studies can be used as dose-finding studies for stroke prevention studies in patients with AF—meaning these drugs can go straight into phase III development in this indication without having specific phase II stroke prevention studies in patients with AF. Phase III studies in this indication require long-term therapy of a year or more, and large numbers of patients are required to evaluate the effects of new agents compared with VKAs.

Phase II VTE treatment studies can be used to guide anticoagulant dose selection in phase III stroke prevention studies in patients with AF for several reasons: VTE treatment studies provide an indication of the long-term safety profile and anticoagulant effects of the study drug in patients with chronic disease and similar comorbidities to patients with AF. Also, there are similarities between VTE and AF and their recommended treatments. For example, haemodynamic conditions and the pathophysiology of thrombus formation are similar in the systemic venous system and the left atrium in patients with VTE and AF, respectively. Thus, new anticoagulants that have the ability to prevent and treat VTE may also be effective for stroke prevention in patients with AF. Furthermore, guidelines recommend the same target INR of warfarin, the current standard of care, for both the treatment of VTE and stroke prevention in AF. Therefore, new anticoagulants that can demonstrate efficacy and safety against dose-adjusted warfarin should theoretically be effective in both indications.

**Direct thrombin inhibitors**

Several oral, direct thrombin inhibitors have undergone clinical development or are being tested for stroke prevention in patients with AF, including ximelagatran and dabigatran.

Ximelagatran underwent an extensive clinical trial programme. It was evaluated for VTE prevention after orthopaedic surgery and for treatment of VTE before its efficacy in preventing stroke and systemic thrombo-embolism in patients with AF was demonstrated in two phase III trials. However, hepatotoxicity and major adverse cardiovascular events were observed in several studies, and ximelagatran was withdrawn from all markets and from further development in February 2006. Ximelagatran is a prodrug, and its active metabolite melagatran has been associated with rebound thrombin generation on termination in an in vitro study. This rebound phenomenon has also been observed in patients with unstable angina, and after termination of treatment with argatroban (a direct thrombin inhibitor), dalteparin (a LMWH), and unfractionated heparins, respectively.

Three large-scale, non-inferiority phase III studies have now been reported on dabigatran. All three studies compared two doses of dabigatran (150 and 220 mg once daily) with the approved enoxaparin regimen for that region; in all three studies the first dose of dabigatran was given as a half dose on the day of surgery. Two studies showed dabigatran 150 and 220 mg once daily to be non-inferior to enoxaparin (40 mg once daily) for the prevention of the composite of total VTE and all-cause mortality after total knee replacement (TKR) or total hip replacement (THR). The rates of major bleeding were low and similar between the treatment groups in both studies. However, in a third study of over 2600 patients, which compared 12–15 days of dabigatran or enoxaparin 30 mg twice daily, both doses of dabigatran were shown to be inferior to enoxaparin for the prevention of the composite of total VTE and all-cause mortality after major knee replacement surgery. No significant differences in the incidence of liver enzyme elevation and acute coronary events were observed across this phase III programme.

Results from a dose-finding study in patients with AF suggested that dabigatran (150 mg twice daily) had similar efficacy and safety to warfarin. Subsequently, blinded doses of dabigatran 110 and 150 mg twice daily were chosen for the ongoing phase III study (RE-LY) for the prevention of stroke in patients with AF, vs. warfarin. This study has a target enrolment of 15 000 patients and results are expected in 2010.
Factor Xa inhibitors

An attractive alternative to direct thrombin inhibition is selective inhibition of FXa. Indeed, FXa may be a better target than thrombin because it has fewer functions outside coagulation; thus, inhibition of FXa may cause fewer side-effects.\(^{19,34}\) Numerous studies have shown that FXa inhibitors have anti-thrombotic efficacy at doses that are not associated with excessive bleeding.\(^{35}\) Moreover, unlike thrombin inhibitors, direct FXa inhibitors such as DU-176b have not been associated with rebound thrombin generation.\(^{27,35,36}\) Finally, numerous large-scale, randomized trials have shown that the efficacy of heparin-based anticoagulants improves as the selectivity for FXa increases.\(^{37-40}\) For example, the selective FXa inhibitor fondaparinux has superior efficacy over LMWHs, which inhibit FXa and thrombin in ratios of 4:1 to 1:5:1, respectively, depending on the LMWH, and in turn have greater efficacy than unfractionated heparin, which has a FXa:IIa ratio of 1:1.\(^{19,41,42}\) Therefore, FXa may be a better target than Factor IIa for an effective and safe anticoagulant.

Factor Xa inhibitors in development

Numerous direct and indirect FXa inhibitors are currently at various stages of clinical development, including idraparinux, biotinylated idraparinux, LY517717, YM150, DU-176b, apixaban, betrixaban, and rivaroxaban (Table 2). Pivotal phase III studies of stroke prevention in patients with AF are yet to be completed for these agents; however, phase II studies have been reported in some cases, which establish the efficacy and safety of these FXa inhibitors for the prevention of VTE after orthopaedic surgery and/or for the treatment of VTE. These findings suggest that these drugs may have the potential to be useful for stroke prevention in patients with AF.

Indirect Factor Xa inhibitors

Idraparinux is a subcutaneous, indirect FXa inhibitor. It is a hypermethylated, long-acting pentasaccharide, allowing once-weekly administration.

### Table 2  Factor Xa inhibitors in clinical development\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>VTE prevention(^b)</th>
<th>VTE treatment</th>
<th>Stroke prevention in patients with AF</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect FXa inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Idraparinux</td>
<td>—</td>
<td>Phase III VAN GOGH study completed(^28) (NCT00062803)</td>
<td>Phase III AMADEUS study halted (NCT0070655)</td>
<td>—</td>
</tr>
<tr>
<td>Biotinylated idraparinux</td>
<td>Phase III EQUINOX bioequipotency study completed (NCT00311090)</td>
<td>Phase III CASSIOPEA study recruiting in patients with PE (NCT00345618)</td>
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<tr>
<td>Oral, direct FXa inhibitors</td>
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<td></td>
</tr>
<tr>
<td>LYS17717</td>
<td>Phase Ib completed</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>YM150</td>
<td>Phase Ib ONYX-2 study ongoing (NCT0033678)</td>
<td>—</td>
<td>Phase II ongoing (NCT00448214)</td>
<td>—</td>
</tr>
<tr>
<td>DU-176b</td>
<td>Phase IIa completed</td>
<td>—</td>
<td>—</td>
<td>ACS planned</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Phase IIb completed; ongoing in cancer patients (NCT00320255)</td>
<td>Phase II Botticelli-DVT study completed(^15)</td>
<td>Phase III ARISTOTLE study ongoing (NCT00412984)</td>
<td>Post-ACS, Phase II ongoing (NCT00313300)</td>
</tr>
<tr>
<td></td>
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<td>Phase III ADVANCE-1 study ongoing (NCT00371683)</td>
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<td></td>
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<td>Phase III ADOPT study ongoing (NCT00457002)</td>
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<td></td>
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<td>Phase III EXPERT study ongoing (NCT00275069)</td>
<td>—</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Planned</td>
<td></td>
<td>Planned</td>
<td>Secondary prevention of stroke and MI planned</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Phase III RECORD studies (NCT00329628, completed; NCT00332020, completed; NCT00361894, reported; NCT00362232, ongoing)</td>
<td>Phase III EINSTEIN studies ongoing (NCT00440193, NCT00439777, NCT00439725)</td>
<td>Phase III ROCKET AF study ongoing (NCT00403767)</td>
<td>Phase II post-ACS ATLAS ACS TIMI 46 study ongoing (NCT00402597)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; AF, atrial fibrillation; FXa, Factor Xa; MI, myocardial infarction; PE, pulmonary embolism; VTE, venous thromboembolism.

\(^a\)ClinicalTrials.gov identifier given in parentheses where available.

\(^b\)Prevention of VTE after major orthopaedic surgery, unless indicated otherwise.
dosing. In a randomized VTE treatment study, idraparinux (2.5–10 mg once weekly) had similar efficacy (composite of VTE and all-cause mortality, and change in thrombotic burden) to warfarin and demonstrated dose-dependent increases in major bleeding. The lowest dose of idraparinux (2.5 mg once weekly) was compared with standard therapy in the phase III VAN GOGH study, which was conducted in patients (n=2904) with deep vein thrombosis (DVT) or pulmonary embolism (PE) who received treatment for 3 or 6 months. Idraparinux had similar efficacy to standard therapy for the treatment of DVT, but failed to demonstrate non-inferiority for the treatment of PE.

The phase II VTE treatment study of idraparinux was also used to define the dose for the phase III AMADEUS study. This was an open-label, non-inferiority trial comparing idraparinux with dose-adjusted warfarin for the prevention of thrombo-embolic events in patients with AF and at least one additional risk factor for stroke. It was stopped prematurely because there was a lower incidence of events than expected in all groups, and a very large number of patients would be required to show a significant difference between the therapies. There was also a trend for more bleeding.

Because idraparinux has a very long duration of action, a biotinylated version of this drug (SSR 126517) is also in clinical development. The addition of the biotin moiety would allow the rapid removal of the drug upon the addition of avidin. A bioequi potency study of biotinylated idraparinux vs. idraparinux for the treatment of DVT is currently ongoing, and patients are being recruited into the phase III CASSIOPEA study of biotinylated idraparinux vs. warfarin for the treatment of PE.

**Oral, direct Factor Xa inhibitors**

**LY517717**

LY517717 (Lilly) is an oral, direct FXa inhibitor with an inhibitory rate constant (Kᵢ) for FXa of 4.6–6.6 nM and an elimination half-life of ~25 h in healthy subjects; it is eliminated mainly by the faecal route. LY517717 has not yet been studied for stroke prevention in patients with AF, and only VTE prevention data are currently available. In a randomized, double-blind, dose-escalation study in patients undergoing THR, LY517717 demonstrated dose-dependent efficacy with a similar incidence of bleeding to enoxaparin for the prevention of VTE (DVT/PE). No information is currently available regarding future studies with LY517717 (Table 3).

**YM150**

YM150 (Astellas) is an oral, direct FXa inhibitor, with a Kᵢ for FXa of 31 nM, which inhibits prothrombin activation induced by free and clot-associated FXa and prothrombinase. In preclinical studies, YM150 demonstrated potent antithrombotic effects in venous and arterial thrombosis animal models with a lower bleeding time prolongation than warfarin. In a phase IIa, randomized, open-label, dose-escalation study for the prevention of VTE in patients undergoing THR, YM150 (3, 10, 30, or 60 mg once daily, starting 6–10 h after surgery) demonstrated a significant dose–response relationship for the primary efficacy endpoint (venographically determined DVT or symptomatic DVT/PE) and no major bleeding was reported. Further investigation of YM150 will continue in the ongoing ONYX-2 study, a randomized, double-blind, phase II, dose-ranging study of YM150 for VTE prevention in patients undergoing THR. It has also been reported that YM150 is in phase II of development for stroke prevention in patients with AF.

**DU-176b**

DU-176b (Daiichi Sankyo) is an oral, direct FXa inhibitor that inhibits FXa with a Kᵢ of 0.6 nM, and is 10 000-fold more selective for FXa than thrombin. At present, only preclinical and phase I clinical data on DU-176b have been published. In rat models, DU-176b inhibited both arterial and venous thrombosis in the same concentration range, whereas a 100-fold higher dose of fondaparinux was required to inhibit arterial thrombosis than venous thrombosis. In a phase I study in healthy male subjects (n = 12), a single 60 mg dose of DU-176b inhibited FXa activity, prolonged clotting parameters (prothrombin time and activated partial thromboplastin time), and reduced thrombus formation (venous and arterial) in a Badimon chamber for up to 5 h after administration of the dose. A phase IIa study of DU-176b administered once or twice daily for VTE prevention after THR demonstrated proof of principle, but the results have yet to be published. Phase IIb studies with DU-176b in VTE prevention, stroke prevention in patients with AF, and prevention of thrombo-embolic events in patients with acute coronary syndrome (ACS) are planned or have been initiated.

**Apixaban**

Apixaban (Bristol-Myers Squibb) is an oral, direct FXa inhibitor that is a highly selective and potent inhibitor of free FXa (Kᵢ = 0.8 nM) and prothrombinase activity. Preclinical studies of apixaban demonstrated its high oral bioavailability, low metabolic clearance, and multiple pathways of elimination—including renal and intestinal excretion. The randomized, double-blind, phase II APROPOS study of apixaban (total daily dose 5–20 mg) vs. enoxaparin or warfarin for VTE prevention after TKR in 1217 patients has been completed recently. Combined results from the apixaban groups demonstrated similar efficacy compared with enoxaparin and warfarin for reducing the incidence of the primary efficacy endpoint (the composite of DVT, PE, and all-cause mortality; P < 0.02 and P < 0.01 vs. enoxaparin and warfarin, respectively). The incidence of alanine aminotransferase (ALT) elevation (ALT >3× upper limit of normal) was lower in the apixaban treatment groups than the enoxaparin group. However, the incidence of major bleeding ranged from 0.0–3.3% for the apixaban doses, compared with an unexpectedly low rate of 0.0% in the enoxaparin and warfarin groups. Following these results, a phase III apixaban programme for VTE prevention after orthopaedic surgery has been initiated. The three ADVANCE studies will determine the efficacy and safety of apixaban 2.5 mg twice daily compared with enoxaparin in patients who have undergone major orthopaedic surgery. Two additional phase II studies are ongoing, which will evaluate apixaban for VTE prevention in patients with advanced metastatic cancer, and secondary prevention in patients with recent ACS. Recruitment for the Botticelli-DVT study of apixaban for the treatment of acute symptomatic DVT has also been completed. This randomized, double-blind, placebo-controlled phase II
Table 3 Pharmacokinetics and pharmacodynamic comparison of oral anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>LY517717</th>
<th>YM150</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Direct Factor Xa inhibitor</td>
<td>Direct thrombin inhibitor</td>
<td>Direct Factor Xa inhibitor</td>
<td>Direct Factor Xa inhibitor</td>
<td>Direct Factor Xa inhibitor</td>
<td>Direct Factor Xa inhibitor</td>
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<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Oral bioavailability</td>
<td>Relative oral bioavailability: ~80% in humans</td>
<td>Average absolute bioavailability is 6.5% in humans</td>
<td>Chimps (51%); dogs (88%); rats (43%)</td>
<td>Not available</td>
<td>~25–82%</td>
<td>Not available</td>
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<tr>
<td>47%56</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2–4 h59</td>
<td>2 h80</td>
<td></td>
<td>3 h80</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>K&lt;sub&gt;on&lt;/sub&gt;/K&lt;sub&gt;off&lt;/sub&gt;</td>
<td>K&lt;sub&gt;on&lt;/sub&gt; 1.7 × 10&lt;sup&gt;-7&lt;/sup&gt; s (very fast); K&lt;sub&gt;off&lt;/sub&gt; 5 × 10&lt;sup&gt;-3&lt;/sup&gt; s&lt;sup&gt;−1&lt;/sup&gt;</td>
<td>K&lt;sub&gt;on&lt;/sub&gt;=4.5 nM&lt;sup&gt;83,84&lt;/sup&gt;</td>
<td>K&lt;sub&gt;off&lt;/sub&gt;=0.8 nM&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Not available</td>
<td>K&lt;sub&gt;off&lt;/sub&gt;=6.6 nM&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Not available</td>
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<tr>
<td>Reversible</td>
<td>Yes58</td>
<td>Yes&lt;sup&gt;83,85&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;86&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Not reported</td>
<td>K&lt;sub&gt;off&lt;/sub&gt;=0.1 nM&lt;sup&gt;56&lt;/sup&gt;</td>
</tr>
<tr>
<td>Half-life</td>
<td>~9 h in healthy subjects; ~12 h in elderly subjects (&gt;75 years)59</td>
<td>17 h with multiple doses; 7–9 h with single doses&lt;sup&gt;81&lt;/sup&gt;</td>
<td>~12 h; terminal half-life 8–15 h&lt;sup&gt;87&lt;/sup&gt;</td>
<td>Elimination ζ ~25 h&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Not reported</td>
<td>19 h&lt;sup&gt;56&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mode of excretion</td>
<td>Dual mode of elimination with no major or active circulating metabolites: one-third of the administered dose is excreted renally as unchanged active drug, the remaining two-thirds being metabolized by the liver&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Renal (80%)&lt;sup&gt;83&lt;/sup&gt;</td>
<td>~70% in faeces and 25% renal—not detailed&lt;sup&gt;92&lt;/sup&gt;</td>
<td>Mainly faecal route&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Unchanged in bile&lt;sup&gt;56&lt;/sup&gt;</td>
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<tr>
<td>Accumulation</td>
<td>None&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Concentration-dependent accumulation with higher trough levels with bid regimens&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Not reported</td>
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<tr>
<td>Food</td>
<td>No dietary restrictions</td>
<td>Delayed absorption with food&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Not reported</td>
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<td>Age effect</td>
<td>No</td>
<td>Affects pharmacokinetic parameters, particularly elimination&lt;sup&gt;95&lt;/sup&gt;</td>
<td>Not reported</td>
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<td>Weight effect</td>
<td>No</td>
<td>Not reported, pharmacokinetics not significantly altered&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
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<tr>
<td>Gender effect</td>
<td>No</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
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<tr>
<td>Drug–drug interactions</td>
<td>No interactions reported with ASA&lt;sup&gt;67&lt;/sup&gt;, digoxin&lt;sup&gt;68&lt;/sup&gt;, NSAIDs&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Interaction with ASA with higher dabigatran doses&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
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</table>

ASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drug; bid, twice daily.
study examined the efficacy and safety of apixaban (5 mg twice daily, 10 mg twice daily and 20 mg once daily) compared with a LMWH or fondaparinux and a VKA for the treatment of subjects with acute, symptomatic DVT. All three doses of apixaban were considered similar to standard of care and led to the initiation of the phase III ARISTOTLE study of apixaban for stroke prevention in patients with AF. This randomized, double-blind study aims to evaluate the efficacy and safety of apixaban 5 mg twice daily vs. warfarin in 15,000 patients.

**Betrixaban**

Betrixaban [PRT-054021: Portola; licensed from Millennium Pharmaceuticals (MLN-1021)] is an orally available, small-molecule, direct FXa inhibitor that specifically and reversibly inhibits FXa with a Kᵢ of 0.1 nM. It has a bioavailability of 47%, a half-life of 19 h and is excreted almost unchanged in bile. Betrixaban has demonstrated antithrombotic activity in animal models of thrombosis, and inhibited thrombin generation in human blood at similar concentrations. Therefore, these concentrations of betrixaban may be sufficient to prevent venous thrombosis in humans. A phase I, randomized, placebo-controlled, single-dose-escalation study in 64 healthy subjects demonstrated that betrixaban was well tolerated across a wide range of doses. The completed phase II, randomized, open-label VTE prevention trial in patients undergoing TKR provided proof of principle for the efficacy and safety of betrixaban (15 or 40 mg twice daily) compared with enoxaparin (30 mg twice daily) in 215 patients. There are also plans to develop betrixaban for VTE prevention and treatment, stroke prevention in patients with AF, and for secondary prevention of stroke and myocardial infarction.

**Rivaroxaban**

Rivaroxaban (Bayer HealthCare AG and Johnson & Johnson/Ortho-McNeil) is an oral, direct FXa inhibitor with a Kᵢ of 0.4 nM. It has a half-life of up to 12 h in elderly subjects, and up to 9 h at steady state in healthy young subjects. The compound has no direct effect on platelet aggregation and it potently inhibits prothrombinase activity, as well as free and clot-associated FXa activity in human plasma. Preclinical studies have demonstrated the antithrombotic effects of rivaroxaban in various animal models of thrombosis.

Rivaroxaban was well tolerated in healthy human subjects, with a rapid onset of action and dose-proportional pharmacokinetics and pharmacodynamics. Rivaroxaban has no major or active circulating metabolites. It undergoes a dual mode of elimination with one-third of the unchanged active drug being eliminated renally; the remaining two-thirds of the drug are metabolized by the liver. A low propensity for clinically relevant drug–drug interactions has been observed with rivaroxaban and it has no effect on the QTc interval. Phase III studies of rivaroxaban for the prevention of VTE after major orthopaedic surgery, the treatment of VTE, and the prevention of stroke in patients with AF are ongoing. Furthermore, a large, dose-finding, randomized, double-blind, placebo-controlled phase II study (ATLAS ACS TIMI 46) is underway, which will investigate the efficacy and safety of rivaroxaban alone, or in combination with ASA, or ASA and thienopyridine in patients with recent ACS.

The first results of the extensive phase III clinical development programme for rivaroxaban in VTE prevention after major orthopaedic surgery have been reported. RECORD3 was a multinational, randomized, double-blind trial that compared the efficacy and safety of oral rivaroxaban 10 mg once daily with subcutaneous enoxaparin 40 mg once daily for the prevention of VTE in patients undergoing TKR surgery. Rivaroxaban showed significantly better efficacy than enoxaparin for the prevention of both asymptomatic and clinically relevant, symptomatic venous thrombo-embolic events. Rivaroxaban and enoxaparin had similar safety profiles. Three additional studies in this indication are ongoing. These studies are underpinned by the findings of the extensive phase II programme that investigated rivaroxaban for the prevention of VTE after major orthopaedic surgery.

Two phase Ib studies, with a treatment duration of 12 weeks, have investigated rivaroxaban for the treatment of VTE. In the ODIIXa-DVT dose-ranging study, patients with acute, symptomatic DVT were treated with rivaroxaban or enoxaparin and an oral VKA. In the EINSTEIN-DVT study, patients with acute, symptomatic, proximal DVT were randomized to receive double-blind rivaroxaban or open-label enoxaparin, tinzaparin or unfractionated heparin, and an oral VKA. Taken together, the results in over 1,150 patients with DVT suggested that all rivaroxaban doses were effective for the treatment of proximal DVT with similar efficacy to standard therapy and a low incidence of recurrent VTE. Furthermore, all rivaroxaban doses (10–30 mg twice daily and 20–40 mg once daily) had a low rate of bleeding or adverse events, similar to standard therapy, and there was no signal for compromised liver safety with rivaroxaban. Phase III studies with rivaroxaban for both the initial treatment and long-term secondary prevention of VTE (with 20 mg once daily) have been initiated.

The rivaroxaban VTE treatment studies also served as dose-finding for phase III studies of rivaroxaban for stroke prevention in patients with AF, and suggested that a fixed rivaroxaban dose of 20 mg once daily would be suitable for investigation in the ROCKET-AF study. This is a randomized, double-blind study that will compare the efficacy and safety of rivaroxaban 20 mg once daily with warfarin for the prevention of stroke in approximately 14,000 patients with AF. In this study, patients with moderate renal impairment, defined as a creatinine clearance between 30 and 49 mL/min, will receive a fixed dose of rivaroxaban 15 mg once daily. Previously, two pilot phase Ib studies have been conducted in Japanese patients with AF to determine whether there were any ethnic differences in the safety and pharmacology of rivaroxaban; however, the results are not yet available. The results of the large-scale phase III study of rivaroxaban for stroke prevention in patients with AF will determine whether rivaroxaban 20 mg once daily can be used in this indication.

**Conclusions**

VKAs, including warfarin, are currently the only oral anticoagulants available for stroke prevention in patients with AF. New anticoagulants with a favourable safety profile that do not require frequent coagulation monitoring or dose adjustment are needed. Drugs that inhibit FIIa and FXa are attractive options and numerous oral, direct FXa inhibitors are in clinical development; they may
eventually replace VKAs. Rivaroxaban has already shown promising efficacy and safety in VTE prevention and treatment studies, relative to standard therapy, and a large-scale phase III study of rivaroxaban aims to determine the efficacy and safety of rivaroxaban for stroke prevention in patients with AF. Proof of principle for VTE prevention in patients undergoing major orthopaedic surgery has also been shown for other oral, direct FXa inhibitors in clinical development, including LY517717, YM150, and apixaban. The results of VTE prevention studies are awaited for DU-176b and betrixaban but early findings are promising. Dabigatran is currently the only direct thrombin inhibitor being tested in this indication. If any of these novel anticoagulants are approved for stroke prevention in patients with AF, we could potentially see a change in therapeutic strategies for preventing thromboembolic events in patients with AF.

Conflict of interest: A.G.G.T. is a consultant to Astellas, Bayer HealthCare AG and Scios, Inc., GlaxoSmithKline, Portola, and sanofi-aventis.

References


