Oral Direct Factor Xa Inhibitors in Development for the Prevention and Treatment of Thromboembolic Diseases

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Abstract—Anticoagulants are recommended for the prevention and treatment of a wide variety of thromboembolic events. Although existing anticoagulants are effective, their use is limited by parenteral administration or the requirement for frequent monitoring and subsequent dose adjustment. Therefore, there is an urgent need for novel oral agents with a predictable anticoagulant action. Because of its key position in the coagulation cascade and its limited roles outside of coagulation, Factor Xa has emerged as an attractive target for novel anticoagulants. As a result, the past decade has witnessed an explosion of research into small-molecule, oral, direct Factor Xa inhibitors, and several are now in clinical development. Rivaroxaban, LY517717, YM150, apixaban, PRT054021, and DU-176b, among others, have shown considerable promise; rivaroxaban is currently furthest ahead in its developmental program, having entered phase III in 3 indications. It is hoped that before long, these anticoagulants will allow us to enter an era of convenient oral anticoagulation without the need for regular monitoring or dose adjustment. (Arterioscler Thromb Vasc Biol. 2007;27:000-000.)

Key Words: anticoagulant ■ atrial fibrillation ■ Factor Xa inhibitor ■ stroke ■ venous thromboembolism

Since the discovery of heparin in 1914, the use of anticoagulants has greatly advanced the prevention and treatment of life-threatening thromboembolic events. Current guidelines now recommend the short-term or long-term use of these drugs in a wide variety of indications, including the prevention of venous thromboembolism (VTE), manifesting as deep vein thrombosis (DVT), or pulmonary embolism (PE), in patients with acute medical illness or those undergoing major orthopaedic or general surgery, and for the immediate treatment and longer-term secondary prevention of acute DVT and PE.1,2 Anticoagulant therapy is also recommended for the long-term prevention of ischemic stroke in patients with atrial fibrillation (AF) and the prevention of recurrent myocardial infarction in patients with acute coronary syndromes, such as unstable angina or non-ST–elevated myocardial infarction.3,4 Currently, available options for anticoagulation include treatment with unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonists (VKAs) including warfarin), and, more recently, the synthetic pentasaccharide fondaparinux (Arixtra). Although these drugs have proved effective in treating and reducing the risk of thromboembolic disease,5 they are associated with significant drawbacks that limit their use and acceptability in the clinical setting. UFH, LMWH, and fondaparinux are administered parenterally, making them inconvenient and costly for long-term use, particularly outside of the hospital setting where visits to or from a health care professional may be required if patients are unwilling or unable to self-administer.6 VKAs are the only available oral anticoagulants; however, their narrow therapeutic window, unpredictable pharmacology, and numerous food and drug interactions necessitate frequent, inconvenient, and costly monitoring and dose adjustment to ensure that anticoagulant effects remain within the therapeutic range. As a result, VKAs are difficult to manage, studies show that <50% of patients using the VKA warfarin are within the therapeutic range in the community setting; therefore, the remaining patients are under- or over-anticoagulated, which places them at increased risk for experiencing thromboembolic events or bleeding, respectively.7 In a recent qualitative study, it was not surprising to find that levels of patient dissatisfaction with warfarin treatment were high.8 Another study revealed a sense of resignation among long-term warfarin users with AF, these patients had adapted their lifestyles to accommodate the inconveniences associated with treatment, because they recognized that warfarin is a life-sustaining therapy that has been shown to be effective.9

Thus there is a real unmet clinical need for novel oral anticoagulants without the requirement for frequent monitoring and dose adjustment.6 This is a need made more urgent by the increasing number of people presenting with risk factors for thromboembolic events (as a result of the rapidly ageing population) and by the trend for shorter hospital stays and early patient discharge after many procedures.10–12

Several drugs are currently in development in an attempt to meet this need.13–16 Unlike the more traditional anticoagu-
The coagulation cascade. Ovals denote potential targets for an anticoagulant; rectangles denote components of the cascade whose inhibition would provide the most effective anticoagulation.

Direct Factor Xa Inhibition as a Mechanism for Novel Anticoagulants

Inhibition of any one enzyme in the coagulation cascade (Figure) should reduce the formation of fibrin polymers from fibrinogen, thus decreasing clot formation. Therefore, in theory, any single enzyme in the cascade would be a suitable target for a novel anticoagulant. For example, Factor IXa (FXa), a crucial component of the coagulation cascade, and summarizes the preclinical and clinical findings of the oral FXa inhibitors currently in development, all of which are direct FXa inhibitors.

The coagulation cascade, Inflammation or Tissue Injury, and Thrombin, which is a promoter of inflammation and cellular proliferation. In addition to its procoagulant role, thrombin, however, also plays an important role in anticoagulation and anti-inflammation through thrombin–thrombomodulin-mediated activation of protein C. Thrombin is also a promoter of inflammation and cellular proliferation. Through disruption of these additional functions, inhibition of thrombin may be more likely to have effects outside coagulation than inhibition of FXa. Although FXa inhibitors would inhibit thrombin generation via the pro-thrombinase complex, they may allow the vital functions of existing thrombin to continue, thus potentially maintaining hemostasis at sites of hemostatic challenge.

FXa has also been shown to activate clotting over a much wider concentration range than thrombin in model systems and in vitro assays, suggesting that FXa inhibitors may have a wider therapeutic window than thrombin inhibitors. Therefore, it may be easier to maintain a patient’s blood level of FXa inhibitor within the therapeutic range. In support of this, a recent clinical dose-finding study of the direct thrombin inhibitor dabigatran etexilate (Rendix) for stroke prevention in patients with AF demonstrated that only 1 of the 5 regimens tested had adequate efficacy without an unacceptably increased incidence of major bleeding.

Furthermore, rebound thrombin generation has been reported after withdrawal of drugs that inhibit thrombin (eg, UFH and LMWHs), leading to thrombin levels that are significantly greater than before or during treatment. This exaggerated reactivation of the coagulation system can rapidly result in thrombus growth and subsequent ischemic events. Rebound thrombin generation after withdrawal of UFH and LMWH may be caused by the pool of active fibrin-associated thrombin, which UFH and LMWH are unable to inhibit. It may also be caused by depletion of the natural anticoagulant tissue factor pathway inhibitor (tissue factor pathology inhibitor); LMWH and UFH stimulate release of tissue factor pathology inhibitor from endothelial cells (which contributes to the antithrombotic effect of both drugs), but their prolonged use may result in depletion of tissue factor pathology inhibitor. These 2 possible causes of rebound thrombin generation may only be applicable to heparin use, and not thrombin inhibition in general, because a possible rebound phenomenon was associated with the direct thrombin inhibitor ximelagatran, which does not stimulate release of tissue factor pathology inhibitor and is able to inhibit fibrin-associated thrombin. Low levels of the natural anticoagulant activated protein C, a third possible cause of rebound thrombin generation, are a result of thrombin inhibition in general. Therefore, low levels of activated protein C could account for rebound thrombin generation after withdrawal of both heparins and direct thrombin inhibitors. In theory, low levels of activated protein C should not be an issue with a direct FXa inhibitor.

Finally, the possible superiority of FXa over thrombin as a potential target for novel anticoagulants may also be inferred from the observed increase in efficacy of heparin-based anticoagulants as their selectivity for FXa increases. LMWHs have a higher ratio of FXa-to-thrombin inhibition (the actual ratio is specific to each LMWH) than UFH. Fondaparinux, a synthetic pentasaccharide corresponding to the heparin sequence that bridges antithrombin (AT) to FXa, inhibits FXa and not thrombin. The superior efficacy of LMWHs over UFH for the prevention of VTE after orthopedic surgery, and of fondaparinux over LMWHs, has been demonstrated in numerous large-scale randomized studies. However, another possible explanation for this observation may be provided by nonspecific binding of heparin-based anticoagulants to plasma proteins, which occurs to a lesser extent with LMWH than UFH, and not at all with fondaparinux.
Therefore, clinical evidence and theoretical arguments point toward FXa as a very promising target for anticoagulant therapy. Also, there is reason to believe that direct FXa inhibition may be superior to indirect AT-mediated inhibition. At therapeutic doses, AT-bound indirect FXa inhibitors, such as UFH, LMWH, and fondaparinux, are unable to inhibit FXa within the prothrombinase complex, the physiologically relevant form of FXa responsible for activation of prothrombin to thrombin in the coagulation cascade.\textsuperscript{34–36} This may be because AT is unable to compete effectively with the substrate prothrombin for the catalytic center of FXa in the prothrombinase complex.\textsuperscript{34} UFH and LMWH may also be prevented from inhibiting clot-associated FXa,\textsuperscript{15} possibly as a result of competition between AT and fibrin(ogen) for FXa binding. However, small-molecule direct FXa inhibitors are able to inhibit both free and prothrombinase-bound FXa, and may also be able to inhibit clot-associated FXa.\textsuperscript{37,38} This would prevent clot-associated FXa from activating prothrombin and thereby contributing to the procoagulant activity of thrombi, and therefore to the propagation of thrombosis.\textsuperscript{39} Furthermore, the indirect FXa inhibitors UFH and LMWH bind the platelet factor 4, rendering it antigenic. This can lead to heparin-induced thrombocytopenia, characterized by a low platelet count and high risk of thrombosis.\textsuperscript{40} Direct FXa inhibitors have not been found to interact with platelet factor 4.\textsuperscript{41}

Based on these reasons, the past decade has witnessed extensive research into small-molecule, orally active, direct FXa inhibitors.

**Rivaroxaban**

Rivaroxaban (BAY 59 to 7939; Bayer HealthCare AG and Scios, Inc.; Table 3) is an oral direct FXa inhibitor in clinical development for the prevention and treatment of thromboembolic disorders. This compound potently inhibits FXa (K\textsubscript{i} 0.4 nM) with a >10 000-fold greater selectivity for FXa than for other related serine proteases, and effectively inhibits not only free FXa activity but also prothrombinase activity and clot-associated FXa activity.\textsuperscript{37,38}

Rivaroxaban demonstrated potent antithrombotic effects in a variety of animal arterial and venous thrombosis models, and did not significantly prolong bleeding times at antithrombotic doses.\textsuperscript{37,42,43}

These encouraging preclinical findings were supported by the results of phase I single- and multiple-dose studies. Rivaroxaban, administered in single doses of up to 80 mg or multiple doses of up to 30 mg twice daily (bid), was well-tolerated in healthy males, with predictable dose-proportional pharmacokinetics (PK) and pharmacodynamics (PD).\textsuperscript{44,45} Maximum rivaroxaban plasma concentrations were achieved rapidly (only 2.5 to 4 hours after oral administration), with a terminal half-life of 5 to 9 hours, and there was no evidence of relevant accumulation beyond steady state.\textsuperscript{45} The relative oral bioavailability of rivaroxaban was \approx 80%.\textsuperscript{44} Furthermore, there was a good correlation between plasma levels of rivaroxaban and inhibition of FXa activity or prolongation of prothrombin time (PT) at all doses tested.\textsuperscript{44,45} It is likely that the half-life of 5 to 9 hours determined in healthy subjects may be prolonged further in the clinical setting, particularly in elderly patients (whose renal clearance of rivaroxaban may be delayed) and in those undergoing surgery.

Rivaroxaban was rapidly excreted in healthy human subjects after oral administration.\textsuperscript{46} Excretion was dual-mode, via the biliary/renal (28%) and renal (66%) routes, with 36% of rivaroxaban excreted as unchanged drug in the urine. Unchanged rivaroxaban was identified as the main compound in human plasma at all time points investigated (up to 12 hours), and no major active circulating metabolites were detected.

Results of further phase I studies demonstrated that gender and body weight had no clinically relevant influence on the PK and PD of rivaroxaban in healthy subjects, suggesting that rivaroxaban could be administered at a fixed dose, regardless of patients’ gender or weight.\textsuperscript{47} The absorption of rivaroxaban was moderately increased by coadministration with food (increased C\textsubscript{max} and AUC), irrespective of food type, and coadministration with food was found to reduce interpatient variability, thereby increasing the predictability of rivaroxaban.\textsuperscript{48}

Rivaroxaban also demonstrated a low propensity for clinically relevant drug–drug interactions with aspirin, the nonsteroidal anti-inflammatory drug naproxen, and the cardiac glycoside digoxin.\textsuperscript{49–53} These are potential concomitant medications in patients receiving anticoagulants for the prevention and treatment of thromboembolic disorders. There was no PK interaction with the combination of rivaroxaban and enoxaparin; however, though moderate additive effects on anti-FXa activity (increases of 48% and 43% compared with rivaroxaban and enoxaparin, respectively) and PT (increase of 38% compared with enoxaparin) were observed, these were not considered clinically important. This suggests that

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>K\textsubscript{i} for FXa (nM)</th>
<th>Half-life (hours)</th>
<th>Time to C\textsubscript{max} (hours)</th>
<th>Bioavailability (%)</th>
<th>Mode of Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Bayer HealthCare AG and Scios, Inc.</td>
<td>0.4</td>
<td>5–9* (11–13 in elderly subjects)</td>
<td>2.5–4*</td>
<td>60–86†</td>
<td>Biliary/fecal (28%); renal (66%)</td>
</tr>
<tr>
<td>LYS17717</td>
<td>Lilly</td>
<td>4.6–6.6</td>
<td>~25*</td>
<td>—</td>
<td>25–82†</td>
<td>Primarily gastrointestinal</td>
</tr>
<tr>
<td>YM150</td>
<td>Astellas</td>
<td>31</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Bristol Myers-Squibb</td>
<td>0.8</td>
<td>&gt;10†</td>
<td>—</td>
<td>34–88†</td>
<td>Multiple, including renal and fecal</td>
</tr>
</tbody>
</table>

C\textsubscript{max} indicates maximum plasma concentration.

* Determined in healthy subjects.

† Determined in animal models.
rivaroxaban and enoxaparin could be given concomitantly or sequentially, eg, for bridging therapy.52

Overall, rivaroxaban was well-tolerated in phase I studies. In addition, rivaroxaban did not prolong the QTc interval in elderly patients, who represent a significant proportion of the potential target patient population.53

One phase IIA and three phase IIb clinical studies of rivaroxaban for the prevention of VTE in patients undergoing major orthopaedic surgery were performed. In all 4 studies, the primary efficacy end point was the composite of the incidence of any DVT, objectively confirmed, nonfatal PE, and all-cause mortality in the per-protocol population. The primary safety end point was major bleeding. Results of the three phase IIb studies are shown in Table 1.

Proof of principle for rivaroxaban for the prevention of VTE was demonstrated in a phase IIA open-label study conducted in patients undergoing elective primary total hip replacement (THR).44

Two phase IIb, double-blind, dose-finding studies with twice-daily rivaroxaban were then conducted; one in 706 patients undergoing elective THR and one in 613 patients undergoing elective total knee replacement (TKR).54

In both the hip and knee phase IIb bid studies, observed incidences of the primary efficacy end point with all doses of rivaroxaban tested were similar to, or lower than, those with enoxaparin (Table 1).55,56 Significant dose–response relationships between rivaroxaban and the primary efficacy end point were not observed in either study, which could be attributable to the efficacy of the lower rivaroxaban doses. Although trends for increasing incidences of major, postoperative bleeding with increasing rivaroxaban dose were reported (P = 0.0007 and P = 0.045 for the knee and hip replacement studies, respectively; Table 1), no rivaroxaban dose group had a significantly higher incidence of major bleeding than the enoxaparin dose groups. However, the studies were not powered to detect differences between treatment groups. The observed incidences of major postoperative bleeding with the lower doses of rivaroxaban (total daily doses of 5 to 20 mg) were similar to those with enoxaparin. Overall, these studies suggested that oral rivaroxaban at total daily doses of 5 to 20 mg had similar efficacy and safety to enoxaparin for the prevention of VTE after orthopaedic surgery.55,56

As in healthy subjects, rivaroxaban had predictable PK and PD in patients who have undergone major orthopedic surgery.54,55,57 Good correlations were observed between rivaroxaban plasma concentration and inhibition of FXa activity and prolongation of PT. Age, renal function, and body weight had only small effects on the PK parameters of rivaroxaban, suggesting that rivaroxaban could be administered at a fixed dose, regardless of patients’ age, renal function, or body weight.

A fourth phase II study of rivaroxaban, a further phase IIb, randomized, double-blind study, investigated a more convenient od dosing regimen for the prevention of VTE in patients undergoing elective THR, compared with enoxaparin.49 Patients (n = 873) were randomized to receive oral rivaroxaban 5, 10, 20, 30, or 40 mg od (initiated 6 to 8 hours after surgery), or subcutaneous enoxaparin 40 mg od (initiated the

### Table 1. Incidences of the Efficacy End Points and Primary Safety End Point in 3 Phase IIb, Double-Blind, Randomized Studies of Rivaroxaban for the Prevention of VTE After Major Orthopedic Surgery55,56,58

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Rivaroxaban (Total Daily Dose)</th>
<th>Enoxaparin*</th>
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<tbody>
<tr>
<td></td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>TKR bid study</td>
<td>20/63 (31.7)</td>
<td>23/57 (40.4)</td>
</tr>
<tr>
<td>THR bid study</td>
<td>16/104 (15.4)</td>
<td>15/109 (13.8)</td>
</tr>
<tr>
<td>THR od study</td>
<td>14/94 (14.9)</td>
<td>12/113 (10.6)</td>
</tr>
<tr>
<td>Major VTE n/N (%)§</td>
<td>2/63 (3.2)</td>
<td>3/57 (5.3)</td>
</tr>
<tr>
<td>THR bid study</td>
<td>3/104 (2.9)</td>
<td>1/109 (0.9)</td>
</tr>
<tr>
<td>THR od study</td>
<td>8/94 (8.5)</td>
<td>3/113 (2.7)</td>
</tr>
<tr>
<td>Safety</td>
<td>TKR bid study</td>
<td>1/100 (1.0)</td>
</tr>
<tr>
<td>THR bid study</td>
<td>1/132 (0.8)</td>
<td>3/136 (2.2)</td>
</tr>
<tr>
<td>THR od study</td>
<td>3/128 (2.3)</td>
<td>1/142 (0.7)</td>
</tr>
</tbody>
</table>

*30 mg bid beginning postoperatively in the TKR bid study, 40 mg od beginning preoperatively in the THR bid study and the THR od study.
†DVT; symptomatic, confirmed, nonfatal PE; and all-cause mortality (no reports).
‡Dose arm suspended because of regulatory request.
§Composite of proximal DVT; symptomatic, confirmed, nonfatal PE; and VTE-related death (no reports).
evening before surgery). Treatment continued for a further 5 to 9 days and mandatory bilateral venography was performed the next day.

Incidence of the primary efficacy end point were lower in patients receiving rivaroxaban at any of the doses tested, compared with patients receiving enoxaparin (Table 1). There was no dose–response relationship between rivaroxaban and the primary efficacy end point \((P=0.0852)\); however, there was a significant decrease in the incidence of major VTE \((P<0.001)\); therefore should be investigated further.

This 10-mg od dosing regimen is currently being investigated in the phase III studies of rivaroxaban for the prevention of VTE after major orthopedic surgery. Initiated in December 2005, these studies \(\text{RECO} \text{foundland in major Orthopaedic surgery reducing the Risk of DVT and PE}\) (www.clinicaltrials.gov; NCT00329682, NCT00332020, NCT00361894, NCT00362232). Across the phase Ib VTE prevention studies, elevated levels of the liver enzymes alanine aminotransferase or aspartate aminotransferase were low. There did not appear to be any dose dependency between rivaroxaban and increased liver enzymes.50,51

In addition to VTE prevention, rivaroxaban was also evaluated for the initial treatment (and secondary prevention) of acute, symptomatic, proximal DVT in 2 phase Ib dose-ranging studies.59,60 The studies, which enrolled 1156 patients, investigated the efficacy and safety of 3 months of double-blind rivaroxaban (od or bid) at total daily doses of 20 to 60 mg. Rivaroxaban was compared with a standard therapy of parenterally administered heparin or LMWH followed by an oral VKA (eg, warfarin).

The results after 3 months of treatment suggest that rivaroxaban, given once or twice daily, effectively reduced the incidence of recurrent DVT, PE, and all-cause mortality to a similar degree as standard therapy.59,60 The rates of recurrent DVT were low across all rivaroxaban treatment groups, and similar to those with standard therapy. Rivaroxaban also reduced thrombus size (a surrogate efficacy end point) to a similar extent as standard therapy. In the od study, symptomatic VTE events \(\text{VTE-related death, PE, and recurrent DVT}\) were lower with all rivaroxaban doses tested than with the comparator.60 The incidence of major bleeding was low in both studies \((1.7\% \text{ and } 3.3\%)\) with rivaroxaban versus an unexpectedly low \(0.0\%\) with standard therapy in the bid study, and \(0.0\% \text{ to } 1.5\%\) with rivaroxaban versus \(1.5\%\) with standard therapy in the od study). Overall, the studies suggested that rivaroxaban, given once or twice daily, has a similar efficacy and safety to standard therapy for the treatment of proximal DVT. Based on these promising findings, a phase III program with long-term od rivaroxaban for the treatment of VTE has been initiated. The program comprises two open-label studies (one in patients with DVT, and the other in patients with PE) comparing rivaroxaban treatment of up to 12 months with standard therapy, and a third, double-blind, placebo-controlled study investigating prolonged rivaroxaban treatment \(\text{in patients with DVT or PE}\). A main rivaroxaban dose of \(20 \text{ mg od}\) is being investigated in all 3 studies.

These phase Ib DVT treatment studies contributed to the choice of dose for a phase III program of rivaroxaban for the long-term prevention of stroke in patients with AF, which has been initiated. As in the phase III VTE treatment program, a main rivaroxaban dose of \(20 \text{ mg od}\) is being investigated (www.clinicaltrials.gov; NCT00403767). Furthermore, a phase II, double-blind, randomized, placebo-controlled, dose-finding study is planned in patients with recent acute coronary syndromes (www.clinicaltrials.gov; NCT00402597).

In summary, rivaroxaban has completed extensive phase II studies in 2 indications and has entered large-scale phase III studies in 3 indications \(\text{VTE prevention, VTE treatment, and stroke prevention in patients with AF}\). Rivaroxaban holds promising clinical potential for acute and long-term predictable anticoagulant care.

**LY517717**

LY517717 \((\text{Lilly; Table 3})\) is an oral direct FXa inhibitor in clinical development for the prevention of VTE after THR or THR. In preclinical studies, LY517717 was shown to have a Ki of \(4.6 \text{ to } 6.6 \text{ nM}\), an oral bioavailability of \(25\% \text{ to } 82\%\), and a 1000-fold greater selectivity for FXa than related serine proteases.61 It also demonstrated antithrombotic effects both in vitro and in vivo in a rat arteriovenous shunt model, and studies in dogs suggested that the compound did not have associated bleeding issues.61

LY517717 was well-tolerated in healthy subjects and, with a half-life of \(\approx 25 \text{ hours}\), would be suitable for an od dosing regimen. Elimination of LY517717 appeared to be primarily via the gastrointestinal route.62

Based on these findings, a phase II, double-blind, double-dummy, dose-ranging study was initiated to determine the efficacy and safety of LY517717, compared with enoxaparin, for the prevention of VTE in patients undergoing THR or THR.62 Patients \((N=511)\) were randomized to receive 1 of 6 oral doses of LY517717 \((25, 50, 75, 100, 125, \text{ or } 150 \text{ mg od})\) initiated postoperatively, or enoxaparin \(40 \text{ mg od}\) initiated the evening before surgery. Treatment was continued for a total of 6 to 10 doses; patients underwent mandatory bilateral venography within 12 hours of the last dose and were assessed for symptomatic DVT, PE, and bleeding events until day 30 \((\pm 7)\) after treatment initiation. The primary efficacy end point of the study was the incidence of VTE in the per-protocol population at the end of treatment, and safety end points were the incidences of major and minor bleeding up to 30 days after treatment initiation.
Because of lack of efficacy, the 3 lowest LY517717 dose arms were stopped early and the study was completed with the 3 highest doses only. The 100-, 125-, and 150-mg od doses of LY517717 were not inferior to enoxaparin, with similar incidences of the efficacy end point (17.1% to 24.0% versus 22.2% with enoxaparin) and lower incidences of major bleeding (0.0% to 0.9% versus 1.1% with enoxaparin) and minor bleeding (0.0% to 1.0% versus 2.2% with enoxaparin). Dose–response relationships were observed between LY517717 and prolongation of PT, and exposure (measured by the area under the plasma concentration–time curve). Gender and creatinine clearance were found to affect LY517717 exposure and were thus partly responsible for the reported intra-subject variability of 35%.

No information is currently available regarding the future plans for LY517717.

YM150

YM150 (Astellas; Table 3) is in development for the prevention of DVT and thromboembolic complications in patients with AF. The compound has a Ki for FXa of 31 nM, and inhibits prothrombin activation induced by free FXa, prothrombinase, and whole-blood clots. YM150 demonstrated a 10 000-fold higher selectivity for FXa than for thrombin.66 YM150 was found to interfere with the absorption of YM150.63 PK effects correlated with PD effects, and a dose–response relationship between YM150 and PD was observed. Furthermore, these studies showed low variability in YM150 plasma concentration after oral single and multiple doses.

A randomized, open-label, proof-of-principle phase IIa study was performed in 174 patients to assess the safety and efficacy of 7 to 10 days of treatment with oral YM150 (3, 10, 30, or 60 mg od) for the prevention of VTE after THR, relative to enoxaparin 40 mg od.65 A significant dose–response relationship between YM150 and PD was observed (P=0.006). No major bleeding events were reported in any study arm and no significant dose–response relationship was observed between YM150 10 to 60 mg and the incidence of minor bleeding. Overall, oral YM150 at doses of 10 to 60 mg od was shown to be well-tolerated and effective. A large-scale, double-blind, dose-finding phase IIb study (ONYX-2) has now been initiated to confirm the efficacy and safety of YM150 in patients undergoing THR (www.clinicaltrials.gov; NCT00353678).

DU-176b

DU-176b (Daiichi Sankyo) has a Ki for FXa of 0.56 nM and a 10 000-fold higher selectivity for FXa than for thrombin.66 DU-176b dose-dependently prolonged PT and activated partial thromboplastin time in human plasma. The compound exhibited high oral bioavailability in rats and monkeys and antithrombotic effects in both venous and arterial models of thrombosis in rats.66 Comparisons between DU-176b and other anticoagulants in rat models suggested that the therapeutic dose range of DU-176b might be wider than that of UFH, LMWHs, and warfarin, because of a lower risk of bleeding;67 furthermore, a much higher dose of the indirect FXa inhibitor fondaparinux was required to inhibit arterial compared with venous thrombosis, whereas DU-176b prevented arterial and venous thrombosis within the same dose range.68 DU-176b was also found to potentiate the effects of the antiplatelet agent ticlopidine and tissue plasminogen activator in rat thrombosis models, suggesting that combination therapy of DU-176b with either of these agents may be clinically beneficial.69 As expected, AT deficiency did not affect the antithrombotic potency of DU-176b, suggesting that this compound could be used in patients with low plasma AT concentrations.70

DU-176b significantly reduced thrombus formation in both venous and arterial conditions in a phase I study in 12 healthy adults, as assessed ex vivo using a Badimon chamber.71 Inhibition of FXa activity peaked 1.5 hours after dosing and returned to baseline 12 hours after dose, with antithrombotic effects persisting for up to 5 hours after dose. Pharmacological analyses showed that DU-176b was scarcely metabolized and suggested the potential for convenient od dosing.72 Based on the wealth of available preclinical data and promising phase I results, a phase IIa, open-label, dose-finding study of DU-176b for the prevention of VTE after THR was initiated (www.clinicaltrials.gov; NCT00107900), involving ~600 patients. Results of this trial are not currently available.

Phase IIb studies with DU-176b for the prevention of VTE and the prevention of stroke in patients with AF are in the planning stages. Studies in patients with acute coronary syndromes are also planned.

Apixaban

Apixaban (Bristol Myers-Squibb; Table 3) is a follow-up compound to the oral direct FXa inhibitor razaxaban and is believed to have a superior risk-to-benefit ratio with respect to bleeding. Apixaban is a highly selective and potent (Ki =0.8 nM) inhibitor of both free and prothrombinase-bound FXa.73 In animal models, the compound was found to have a high oral bioavailability (51%, 88%, and 34% in chimpanzees, dogs, and rats, respectively), multiple pathways of elimination, including renal and fecal excretion, and minimal potential for drug–drug interactions and the formation of reactive metabolites.74 Furthermore, it demonstrated potent antithrombotic effects in a rabbit model of venous thrombosis, at doses that preserved hemostasis.75 A phase IIb study of apixaban for the prevention of VTE in patients undergoing TKR has recently been completed. The randomized study compared 6 doses of oral double-blind apixaban (5, 10, or 20 mg given as a single or twice-daily divided dose) with open-label enoxaparin or warfarin for 10 to 14 days in 1217 patients. The incidence of the primary efficacy end point (composite of DVT, PE, and all-cause mortality) in the apixaban groups combined was significantly lower than in the enoxaparin and warfarin groups (P<0.02 and P<0.01, respectively). Moreover, there was a low inci-
TABLE 2. Oral, Direct FXa Inhibitors in Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indications and Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Bayer HealthCare AG and Scios, Inc.</td>
<td>Phase III for VTE prevention after orthopedic surgery, prevention of stroke in patients with AF, and treatment of acute DVT phase II for ACS</td>
</tr>
<tr>
<td>LY517717</td>
<td>Lilly</td>
<td>Phase II for VTE prevention after orthopedic surgery</td>
</tr>
<tr>
<td>YM150</td>
<td>Astellas</td>
<td>Phase II for VTE prevention after orthopedic surgery</td>
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<td>DU-176b</td>
<td>Daiichi Sankyo</td>
<td>Phase II for VTE prevention after orthopedic surgery</td>
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<tr>
<td>Apixaban</td>
<td>Bristol Myers-Squibb</td>
<td>Phase II for VTE prevention after orthopedic surgery, treatment of acute DVT, VTE prevention in patients with unstable angina or heart attack, and prevention of thromboembolic events in patients with advanced metastatic cancer</td>
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<tr>
<td>813893</td>
<td>GlaxoSmithKline</td>
<td>Phase I</td>
</tr>
<tr>
<td>PRT-054021</td>
<td>Portola</td>
<td>Phase II for VTE prevention after orthopedic surgery</td>
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The direct FXa inhibitor 813893 (GlaxoSmithKline) is in phase II for the prevention of VTE after orthopedic surgery and in phase I for the prevention of stroke in patients with AF. Preclinical data showed that this compound had a Ki of 7 nM for FXa, a bioavailability of 91% in rats and >55% in dogs, and no cytochrome P450 interactions.77 Phase I studies demonstrated that 813893 was well-tolerated with linear PK.

PRT054021

Formerly known as MLN-1021, the oral direct FXa inhibitor PRT054021 (Portola) has a Ki for FXa of 0.117 nM, bioavailability of 47%, and a half-life of 19 hours. PRT054021 demonstrated antithrombotic activity in animal models of thrombosis at doses that were found to inhibit thrombin generation in human blood.78

PRT054021 was well-tolerated at a wide range of doses in a phase I dose-escalation study involving 64 patients. The compound displayed a long half-life, suggesting a potential for od dosing, and had predictable PK and PD effects, as well as minimal interactions with food. PRT054021 was excreted almost unchanged in bile.

A multicenter randomized phase II study has recently been initiated to evaluate the safety and efficacy of PRT054021 40 mg bid and 15 mg bid compared with enoxaparin 30 mg for the prevention of VTE in ~200 patients undergoing THR (www.clinicaltrials.gov; NCT00375609). There are also plans to develop PRT054021 for the prevention and treatment of DVT, the prevention of stroke in patients with AF, and the secondary prevention of stroke and myocardial infarction.

Conclusions and Future Perspectives

Convincing evidence suggests that FXa may be an optimal target for a safe and effective anticoagulant for the prevention and treatment of thromboembolic events.

Although effective, indirect FXa inhibitors, such as fondaparinux, require parenteral administration. Parenteral administration is not clinically suitable for long-term use, such as in the treatment of DVT and the prevention of stroke in patients with AF. With the advent of sophisticated chemical techniques, recent years have witnessed huge efforts to synthesize small-molecule direct FXa inhibitors. Not only do these drugs offer the convenience of oral dosing but also they are likely to have predictable PK and PD profiles. As a result, anticoagulant effects are more likely to remain within the therapeutic range, thereby decreasing the likelihood of bleeding, and potentially removing the need for dose adjustment or frequent monitoring. It is hoped that this would lead to improved patient satisfaction, compared with existing anticoagulants, particularly for those patients requiring long-term therapy.

Several oral direct FXa inhibitors in development have been discussed. Table 2 summarizes the stage of development for each, by indication. Rivaroxaban is currently the furthest ahead in its development program, having entered phase III in 3 indications: (1) the prevention of VTE after major ortho-
pedic surgery; (2) the treatment of VTE; and (3) the prevention of stroke in patients with AF. Rivaroxaban has also entered phase II in acute coronary syndromes. Apixaban, LY517717, and YM150 showed promise in phase II clinical studies. Phase III studies of apixaban for VTE prevention after major orthopedic surgery and the prevention of stroke in patients with AF have been initiated. The other compounds discussed in this review are also promising. Moreover, additional oral direct FXa inhibitors are believed to be in development, for example, AVE-3247, EMD-503982, and KFA-1982, although available information on these compounds is extremely limited. The oral direct FXa inhibitors in development have demonstrated differing effects on laboratory coagulation tests, such as PT, activated partial thromboplastin time, and International Normalized Ratio, but there is no evidence to suggest a correlation between these effects and global outcomes.

Ultimately, only large-scale phase III studies will determine which compounds successfully balance efficacy with safety. The direct thrombin inhibitor dabigatran etexilate is also in advanced clinical development for the prevention and treatment of thromboembolic disorders. In addition, there are other oral direct thrombin inhibitors in various stages of development, as well as at least one oral, direct Factor IXa inhibitor.

Whatever the mechanism of action of the first new generation anticoagulant to reach the market, it is clear that the established methods of anticoagulant therapy will soon change. There is a wealth of promising oral direct FXa inhibitors in development that will likely become available to the clinician in the not-too-distant future. As a result, patients should be able to experience convenient oral anticoagulation without the need for frequent monitoring or dose adjustment.

Disclosures

A.G.G.T. is a consultant to Astellas, Bayer HealthCare AG and Scios, Inc., GlaxoSmithKline, Portola, and Sanofi-Aventis.

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Oral Direct Factor Xa Inhibitors in Development for the Prevention and Treatment of Thromboembolic Diseases

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Arterioscler Thromb Vasc Biol. published online March 22, 2007; Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2007 American Heart Association, Inc. All rights reserved. Print ISSN: 1079-5642. Online ISSN: 1524-4636

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