

Indirect and direct anticoagulants predominantly inhibiting factor Xa

Job Harenberg

University of Heidelberg,
Institute of Experimental and
Clinical Pharmacology,
Faculty of Medicine, Ruprecht
Karls University Heidelberg,
Theodor Kutzer Ufer 1-3,
D-68167 Mannheim,
Germany
Tel.: +49 621 383 3378
Fax: +49 621 383 3808
E-mail: job.harenberg@
med.ma.uni-heidelberg.de

Synthetic or natural indirect and synthetic direct factor Xa inhibitors with specific actions on only factor Xa are currently in clinical development. The aim of these compounds is to improve the antithrombotic therapy when compared with heparins and vitamin K antagonists, which are characterized by multiple and partially unpredictable actions. The indirect factor inhibitors have to be administered parenterally, which is in contrast to the direct inhibitors of factor Xa, which may be given orally. This review describes the results of recent dose studies of these two classes of inhibitors of blood coagulation, for the prevention and treatment of arterial and venous thromboembolism.

Thromboembolic diseases are treated using immediate-acting unfractionated heparins (UFH), low-molecular-weight heparins (LMWH) and fondaparinux, followed by slowly acting oral vitamin K antagonists if long-term prophylaxis is indicated. Although these drugs have been proven to be effective in reducing the risk of thromboembolic disease, they are associated with limitations for clinical use. UFH, LMWH and fondaparinux are administered parenterally, making them inconvenient for long-term administration. UFH, lepirudin and argatroban require dose adjustment according to the therapeutic range of the activated partial thromboplastin time (aPTT). LMWH, fondaparinux and danaparoid have to be controlled by their antifactor Xa activity in renal impairment. Platelet count has to be determined in patients treated with these saccharide-derived anticoagulants. Vitamin K antagonists are characterized by a slow onset and offset of action, a narrow therapeutic window, a genetic variation of the metabolism and by food and drug interactions necessitating dose adjustment to ensure a therapeutic range of the international normalized ratio (INR) of 2–3 [1]. Thus, there is a real unmet clinical need for novel oral anticoagulants with rapid onset and offset of action, lack of routine monitoring and dose adjustment, lack of or infrequent food and drug interactions, and better efficacy and safety when compared with the conventional anticoagulants. The rapid onset and offset of action may avoid switching off and on with subcutaneous heparins, as is required during anticoagulation with vitamin K antagonists [2,3].

The development of new anticoagulants has therefore focused on synthetic small molecules to avoid the side effects or dose adjustment of the conventional anticoagulants [4]. Factor Xa inhibitors

act more upstream in the coagulation cascade compared with thrombin inhibitors. Small, indirect antithrombin-dependent inhibitors inhibit factor Xa in plasma, but not factor Xa in the prothrombinase complex or bound to the fibrin clot. Small direct synthetic molecules directed towards factor Xa and IIa can neutralize their respective targets irrespective of whether the targets are free in plasma, clot or prothrombinase-bound, an advantage over the indirect inhibitors, which require antithrombin to mediate their effect [5,6]. The advantage or disadvantage of this difference is not clear at present. This review focuses on the new synthetic and specific factor Xa inhibitors (Figure 1).

Indirect factor Xa inhibitors

Idraparinux

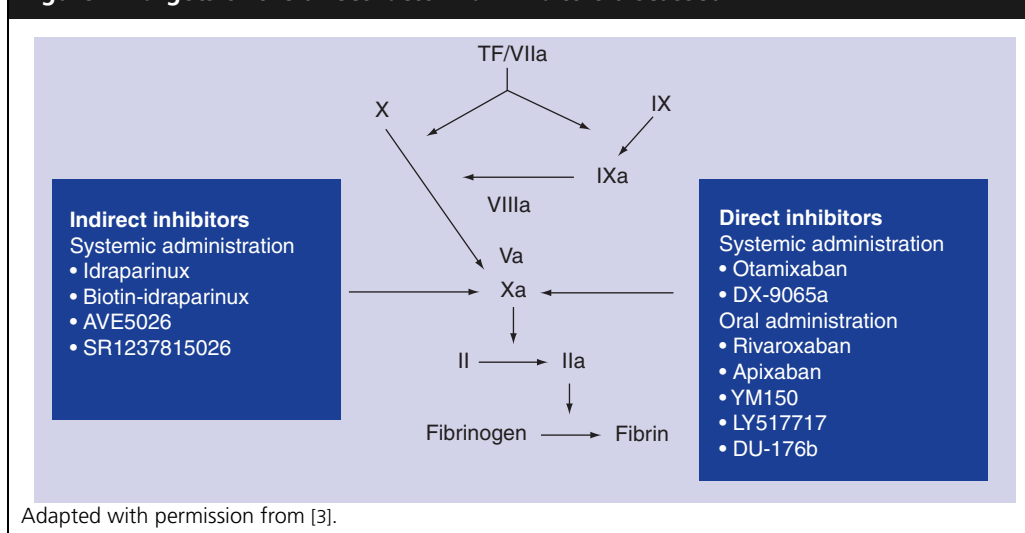
Idraparinux is a hypermethylated derivative of fondaparinux that binds antithrombin with high affinity and results in an increasing elimination half-life of up to 60 days after a 6-month treatment period. After the first injection, the elimination half-life was calculated at 1 week, after 12 injections once-weekly at 25 days, and after 24–56 injections at 60 days [7]. Idraparinux may not require routine monitoring of anticoagulant intensity, except in patients with renal impairment, children or bleeding complications [8]. It does not interact with protamine, the antidote for heparin. Thus, if uncontrolled bleeding occurs, a procoagulant, such as recombinant factor VIIa, may be beneficial [9]. Due to the long half-life, idraparinux was not investigated in postoperative medicine.

Treatment of acute venous thromboembolism

Four doses of once-weekly subcutaneous idraparinux were compared with initial enoxaparin

Keywords: apixaban, DU-176d, factor Xa inhibitors, idraparinux, LY517717, pulmonary embolism, rivaroxaban, thromboembolism, thrombolysis, YM150

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Figure 1. Targets of the direct factor Xa inhibitors discussed.

followed by warfarin in a Phase II dose-finding trial including more than 600 patients with proximal deep-vein thrombosis (DVT) for 12 weeks. The primary efficacy outcome was similar in all groups ($p = 0.4$) and did not differ from the warfarin group. There was a clear dose-response for major bleeding among patients treated with idraparinux ($p = 0.003$). Patients receiving 2.5 mg idraparinux had less bleeding than did warfarin recipients ($p = 0.03$). Gender, age, creatinine clearance, body weight and pharmacokinetic parameters were not associated with differences in the frequency of deterioration [10].

Phase III trials were conducted using 2.5 mg idraparinux subcutaneously once-weekly in patients without renal impairment, and 1.5 mg from the second injection in patients with renal impairment. Two randomized, open-label non-inferiority trials were conducted in patients with DVT (approximately 2900 patients) and pulmonary embolism (PE; approximately 3500 patients) to compare the efficacy and safety of idraparinux versus initial tinzaparin, enoxaparin or intravenous heparin, followed by INR-adjusted warfarin or acenocoumarol. The primary efficacy outcome was symptomatic recurrent venous thromboembolism (VTE) or death attributed to PE at 3 months.

For the DVT study, the incidence of recurrent VTE was 2.9% in the idraparinux group and 3.0% in the standard-therapy group (noninferior, $p < 0.001$). The incidence of clinically relevant bleeding after 3 months was 4.5% in the idraparinux group and 7.0% in the standard-therapy group ($p = 0.004$). After 6 months, the incidences of recurrent VTE and of clinically relevant bleeding did not differ compared with 6 months of

treatment. The rates of major bleeding were 0.8 and 1.2%, respectively, at 3 months ($p = 0.35$) and 1.9 and 1.5%, respectively, at 6 months ($p = 0.50$). The rate of death at 3 months was 2.3% in the idraparinux group and 2.0% in the standard-therapy group ($p = 0.61$), and after 6 months was 4.9% in the idraparinux and 3.9% in the standard-therapy group ($p = 0.25$).

In the PE study, the incidence of recurrent VTE was 3.4% in the idraparinux group and 1.6% in the standard-therapy group. The non-inferiority criterion was not met ($p = 0.59$). The incidence of clinically relevant bleeding was 5.8% in the idraparinux group and 8.2% in the standard-therapy group. At 6 months, the absolute difference of recurrent VTE or clinically relevant bleeding was similar between the groups compared with month 3. The rates of major bleeding were 1.1 and 2.1% at month 3 and 1.4 and 2.8% at month 6. The death rates were 5.1% in the idraparinux group and 2.9% in the standard-therapy group (month 3; $p = 0.006$). At 6 months, the death rate was 6.4% in the idraparinux group and 4.4% in the standard-therapy group ($p = 0.04$). The excess of deaths from PE reinforced concern about a decreased efficacy of idraparinux in patients with PE, the dose of idraparinux probably being too low [11].

The prolonged secondary prophylaxis of VTE using idraparinux has been investigated in the van Gogh Extension trial. Patients were randomly allocated to idraparinux (same dose regimen as in the DVT and PE trial) or to placebo for 6 months followed by an observation period for another 6 months. End points were the same as in the van Gogh DVT and PE trial.

Six of 594 patients in the idraparinix group (1.0%) and 23 of 621 patients in the placebo group (3.7%) had VTE (relative risk reduction 72.7%; $p = 0.002$). Major bleeding occurred in 11 of 594 patients in the idraparinix group (1.9%) and in none of the 621 patients in the placebo group ($p < 0.001$). The highest incidence of major bleeding was observed in patients who had received idraparinix in comparison with those who had received a vitamin K antagonist before randomization (3.1 vs 0.9%; $p = 0.06$). The intracranial bleeds during therapy with idraparinix are uncommon for antithrombin-dependent anticoagulants and may raise concerns about the safety of this compound.

After termination of the study, seven patients in the idraparinix group (1.2%) and 13 patients in the placebo group (2.1%) had recurrent venous thromboembolism ($p = 0.21$). The events started to reoccur at 3 months in patients initially randomized to placebo. At that time, they had received the last injection of idraparinix 9 months ago at the end of the DVT or PE study. The 60 days half-life may explain these findings [11].

Of 11 patients in the idraparinix group who had a major hemorrhage, eight had received idraparinix in the DVT/PE trial for a total of 12 months in both studies. These observations suggest a higher risk of hemorrhage in patients treated with idraparinix for 12 compared with 6 months. [12]. Pharmacokinetic analysis of the aXa assay and Heptest showed higher concentrations of idraparinix after 12 months than after 6 months of therapy ($p < 0.0001$). Due to the long half-life, idraparinix takes approximately 240 days to reach steady-state levels, which falls between 6 and 12 months of treatment. This may explain the higher bleeding rate during long-term treatment [13]. Caution is therefore warranted if anticoagulants have to be used in patients treated within the past 3 or even 12 months with idraparinix [14]. The elimination of the anticoagulant activity of the new biotinylated idraparinix by avidin may offer an option for further improvement of anticoagulant treatment [15].

Atrial fibrillation

The Phase III AMADEUS study was a randomized, open-label trial designed to compare the efficacy and safety of once-a-week 2.5 mg subcutaneous idraparinix versus INR-adjusted warfarin for the prevention of thromboembolic events in patients with atrial fibrillation and at least one additional risk factor for stroke. A total

of 4576 patients were randomized to show noninferior efficacy of idraparinix versus warfarin over a maximum treatment period of 36 months. The event rate of the end point was 0.9% with idraparinix and 1.3% with warfarin ($p = 0.007$), meeting the criteria for noninferiority. The incidence of clinically relevant bleeding was significantly higher in the idraparinix group than in the comparator group (19.7 vs 11.3%; $p < 0.0001$). Therefore, the study was terminated prematurely. Bleeding was more pronounced in patients with impaired renal function and in the elderly. The mortality did not differ between the treatment groups [101]. These observations indicate the need to consider a dose reduction of idraparinix depending on these characteristics in patients with atrial fibrillation. This is addressed in the new BOREALIS-AF study.

Biotinylated idraparinix

Biotinylated idraparinix is structurally similar to idraparinix sodium with the addition of a biotin segment. It has the same anticoagulant activity as idraparinix *in vivo* and the same pharmacological activity. Biotin has a strong and specific affinity for avidin, an egg protein, which can be given intravenously to rapidly bind, neutralize and eliminate idraparinix and its anticoagulant activity. This is a new perspective for improving the shortcomings of idraparinix.

A bioequipotency study of biotinylated idraparinix and idraparinix includes 700 patients with DVT, with a substudy on the neutralizing effect of avidin on the biotin–idraparinix induced anti-Xa activity (EQUINOX study [101]; identifier: NCT00311090).

Patients with symptomatic PE were treated in a randomized, double-blind, double-dummy, parallel group study with biotinylated idraparinix (3.0 mg subcutaneously [sc.] once-weekly) versus oral INR-adjusted warfarin in the treatment ($n = 3200$) (CASSIOPEA [101]; identifier: NCT00345618).

The multicenter, randomized, double-blind, noninferiority BOREALIS-AF study compares the efficacy and safety of once-a-week subcutaneous biotinylated idraparinix with INR-adjusted warfarin in the prevention of stroke and systemic thromboembolic events in patients with atrial fibrillation for a treatment period of 6 months to 2 years. All patients start with biotinylated idraparinix 3 mg (equivalent to 2.5 mg idraparinix) once-a-week for 7 weeks, and then the dose is reduced depending on age and renal function ([101]; identifier: NCT00580216).

Other parenteral inhibitors mainly inhibiting indirect factor Xa

AVE5026

AVE5026 is an ultra-LMWH with a mean molecular weight of 2500 Dalton and an anti-factor Xa:antithrombin ratio of more than 30 (Sanofi Aventis, Paris, France). This compound is included in this overview as it inhibits thrombin to a very low extent. The antifactor Xa:antithrombin ratio of LMWH preparations ranges from 1.7 to approximately 4. The reduced inhibition of thrombin may improve the efficacy and safety when compared with LMWHs.

A dose-finding Phase IIb study was performed in patients undergoing total knee replacement for prevention of VTE using one subcutaneous injection daily compared with enoxaparin (TREK trial). According to the stratification of the patients, the first dose was administered 12 h before or 8 h after surgery. A total of 678 patients were randomized to subcutaneously receive 5, 10, 20, 40 or 60 mg of AVE5026 or enoxaparin 40 mg once a day for 10 days after surgery. The primary efficacy outcome consisted of a combination of objectively confirmed asymptomatic DVT, symptomatic VTE and VTE-related deaths. The end point rates were 40.0, 44.1, 15.6, 13.6 and 5.3% for increasing doses of AVE5026, respectively, demonstrating the dose-dependent effect ($p < 0.0001$), compared with 35.8% in the enoxaparin group. Major bleeding rates increased from 0 to 3.4% with increasing doses of AV5026 ($p = 0.02$), compared with 0% in the enoxaparin group (Figure 2) [16].

SR123781

SR123781 is a short-acting synthetic hexadecasaccharide, injected once-daily, which is an indirect antithrombin-dependent inhibitor of Xa coagulation factors. The DRIVE Phase IIb study evaluating the hexadecasaccharide in the prevention of venous thromboembolic events in patients undergoing total hip replacement (THR [101]; identifier: NCT00338897) demonstrating a correlation between dose and clinical response, with a comparable efficacy and safety to enoxaparin. The SHINE Phase IIb study, evaluating SR123781 in patients with non-ST elevated acute coronary syndrome ([101]; identifier: NCT00123565). The results of these studies are not yet published. Phase III trials in acute coronary syndrome are planned.

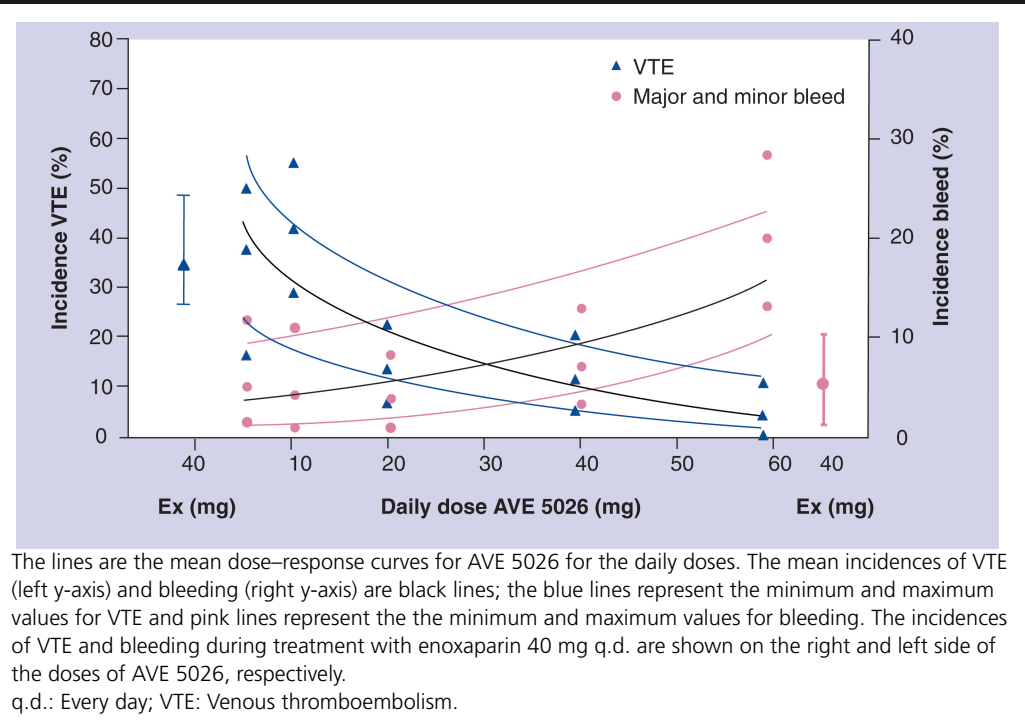
Direct factor Xa inhibitors

The direct factor Xa inhibitors consist of two classes of compounds: one requires systemic administration through a subcutaneous or intravenous route; the other, more important, class is characterized by oral absorption and good bioavailability. The compounds administered systemically are otamixaban (Sanofi Aventis) and LY517717 (Lilly, IN, USA). The orally administered compounds in clinical development include rivaroxaban (Bayer Healthcare, Leverkusen, Germany), apixaban (Bristol-Myers Squibb, NY, USA), YM150 (Astellas, Tokyo, Japan), DU-176b (Daiichi, Tokyo, Japan) and PRT054021 (Portola, CA, USA). It should be noted that these agents inhibit factor Xa within the assembled prothrombinase complex, as well as free factor Xa, while fondaparinux and idraparinux inhibit by binding to antithrombin the pool of free factor Xa in the blood [17].

Direct factor Xa inhibitors systemically active

Otamixaban

Otamixaban, or [2-(*R*)-(3-carbamoylimidoylbenzyl)-3-(*R*)-[4-(1-oxypyridin-4-yl)benzoylamino]-butyric acid methyl ester, hydrochloride salt], is a direct potent and selective inhibitor of factor Xa. It is administered intravenously. Otamixaban inhibited factor Xa in human plasma with a K_i of 0.52 nM towards this coagulation enzyme (0.25 ng/ml). The preclinical pharmacokinetics of otamixaban are characterized by a fast systemic clearance ($T_{1/2} = 0.5\text{--}1.5$ h). The renal excretion accounted for 13–32% of the total dose administered [18]. Otamixaban, a selective and direct inhibitor of factor Xa, was investigated in patients undergoing nonurgent percutaneous coronary intervention in a double-blind, double-dummy, parallel-group, dose-ranging trial, including more than 900 patients randomly assigned to either one of five weight-adjusted otamixaban regimens or weight-adjusted UFH. Otamixaban (or placebo) was given as a weight-adjusted intravenous bolus followed by a 3-h infusion (dose one = 0.025 mg/kg, followed by 0.035 mg/kg/h; dose two = 0.045 mg/kg, followed by 0.065 mg/kg/h; dose three = 0.080 mg/kg, followed by 0.120/kg/h; dose four = 0.120 mg/kg, followed by 0.160 mg/kg/h; and dose five = 0.140 mg/kg, followed by 0.200 mg/kg/h). UFH (or placebo) was also given as a weight-adjusted intravenous bolus (50–70 U/kg) just before percutaneous

Figure 2. Dose–response relationships between AVE 5026 and the incidences of venous thromboembolism and bleeding.

coronary intervention (PCI) to achieve an activated clotting time of 200–300 s with glycoprotein (GP) IIb/IIIa inhibitors, and 300–350 s without the planned use of GP IIb/IIIa inhibitors. The primary end points were change in prothrombin fragments 1 and 2 (F1+2), and anti-factor Xa activity. The main secondary end points were thrombolysis in myocardial infarction (TIMI) bleeding at day 3 or hospital discharge (whichever came first) and 30-day ischemic events. The median change in F1+2 from baseline to the end of infusion was greater with the highest otamixaban dose compared with UFH (-0.3 vs -0.2 ng/ml; $p = 0.008$). Antifactor Xa levels were 65, 155, 393, 571 and 691 ng/ml with otamixaban doses one to five, respectively. Significant TIMI bleeding (major or minor) occurred in 2.0, 1.9, 3.8, 3.9 and 2.6% of patients receiving otamixaban doses one to five, respectively, and in 3.8% of patients receiving UFH. Four TIMI major bleeds were observed. Ischemic events occurred in 5.8, 7.1, 3.8, 2.5 and 5.1% of patients receiving otamixaban doses 1 to 5, respectively, and in 5.6% of patients receiving UFH. Otamixaban reduced F1+2 significantly more than UFH at the highest dose regimen, whereas no significant difference in the incidence of TIMI bleeding was observed between the otamixaban and UFH groups [19].

DX-9065a

DX-9065a is a direct, small-molecule (571.07 Da), selective, reversible factor Xa inhibitor that, because of its small size, is able to inhibit both free factor Xa and factor Xa within the prothrombinase complex [20]. It has a three-compartment distribution, is cleared renally and, at therapeutic doses, has α -, β - and γ -half-lives of 0.23, 2.9 and 89.9 h, respectively [21]. This results in a functional half-life of between 30 min and 6 h, depending on the duration of infusion. XaNADU-ACS was a Phase II, multicenter, international, randomized, double-blinded, double-dummy, active-controlled study in patients with non-ST-elevation acute coronary syndrome (ACS). The composite end point of death, MI or urgent revascularization occurred in 19.5% of patients assigned to heparin, 19.3% of patients assigned to low-dose DX-9065a and 11.9% of patients assigned to high-dose DX-9065a (ns). Patients assigned to low-dose DX-9065a received a bolus (0.025 mg/kg⁻¹), a 3-h loading infusion (0.04 mg kg⁻¹/h⁻¹), and a maintenance infusion (0.012 mg kg⁻¹/h⁻¹) of DX-9065a. Those patients assigned to high-dose DX-9065a received a bolus (0.05 mg/kg⁻¹), a 3-h loading infusion (0.08 mg kg⁻¹/h⁻¹), and a maintenance infusion (0.024 mg kg⁻¹/h⁻¹) of DX-9065a. Patients assigned to either low- or high-dose DX-9065a tended to have less bleeding and required fewer

transfusions than those assigned to heparin. Rates of major or minor bleeding were similar among patients assigned to heparin (7.7%) and high-dose DX-9065a (7.0%), but tended to be lower (4.0%) in patients assigned to low-dose DX-9065a [22]. The benefit of DX-9065a compared with heparin is currently investigated in this indication ([101]; identifier: NCT00317395).

Direct factor Xa inhibitors orally active

Rivaroxaban

BAY 59-7939, or 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl)methyl}thiophene-2-carboxamide, with a molecular weight of 435.89 g/mol, now named rivaroxaban, is a highly potent, competitive, reversible, direct factor Xa inhibitor with a K_i of 0.4 nM for purified human factor Xa. After oral administration in man, it is absorbed in the stomach and small intestine with a bioavailability of 60–80%. Peak plasma levels are achieved in 3 h, and the drug circulates with a half-life of 9 h. In Phase I studies, the $t_{1/2}$ was between 5.8 and 9.2 h after oral administration in healthy volunteers and between 11 and 12 h in the elderly aged over 70 years as determined by the inhibition of factor Xa. Rivaroxaban has a dual mode of excretion, via the renal (66%) and fecal/biliary (28%) routes, and is mainly excreted as unchanged drug. Co-administration of rivaroxaban with food slightly increased the peak plasma concentrations. No additive effects on platelet aggregation were observed when rivaroxaban was co-administered with either aspirin or the NSAID naproxen, antacid drugs or digoxin. Due to the predominance of the renal pathway of excretion, the half-life of rivaroxaban is prolonged in the elderly and in patients with renal impairment [23].

Dose finding in postoperative prevention of venous thromboembolism

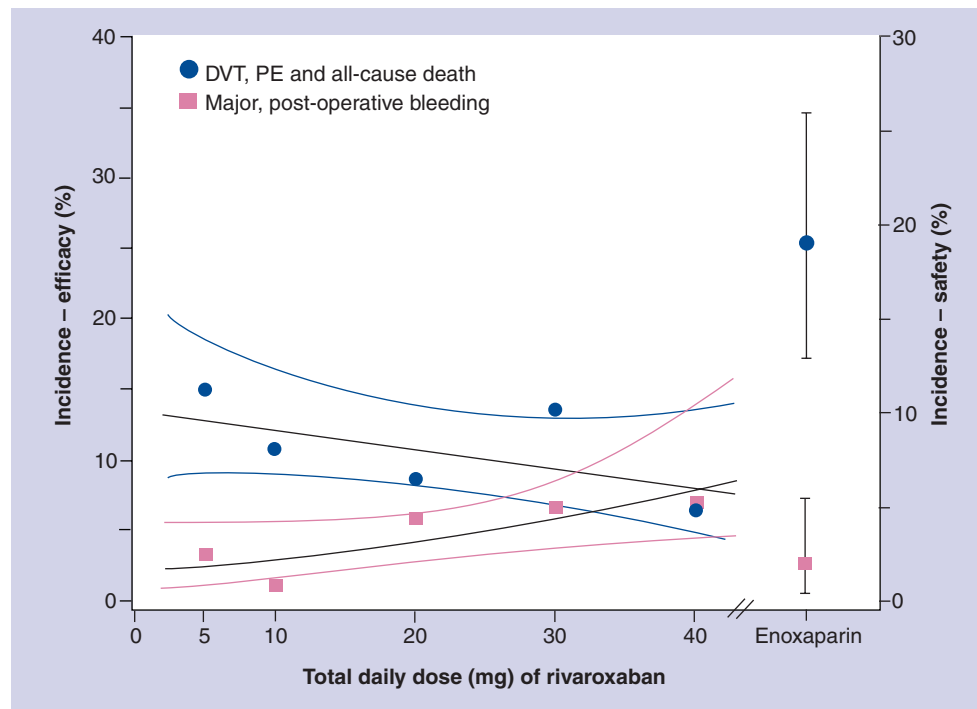
A Phase IIb trial investigated rivaroxaban in patients undergoing elective THR to assess the efficacy and safety compared with enoxaparin for prevention of VTE. Patients ($n = 873$) were randomized to once-daily 5, 10, 20, 30 or 40 mg rivaroxaban, initiated 6–8 h after surgery, or a once-daily subcutaneous enoxaparin dose of 40 mg starting the evening before surgery for 5–9 days. The primary end point (composite of any VTE and all-cause mortality) was observed in 14.9, 10.6, 8.5, 13.5 and 6.4%, with increasing doses of rivaroxaban, and in 25.2% of the 40 mg enoxaparin group, respectively ($p = 0.0852$).

Major postoperative bleeding was observed in 2.3, 0.7, 4.3, 4.9 and 5.1% of patients receiving increasing doses of rivaroxaban ($p = 0.0391$), and in 1.9% of patients receiving 40 mg enoxaparin. The dose–response relationships between rivaroxaban and the primary efficacy end point (DVT, non-fatal PE, all-cause death) and the primary safety end point (major postoperative bleeding events) is shown in Figure 3 [24].

In a Phase III trial, 2531 patients undergoing total knee arthroplasty (TKA) were randomized to rivaroxaban 10 mg once-daily or subcutaneous enoxaparin 40 mg once-daily. Enoxaparin was initiated 12 h before surgery, and rivaroxaban 6–8 h after surgery for 10–14 days. The primary efficacy end point was the composite of any DVT, non-fatal PE and all-cause mortality. This efficacy outcome occurred in 9.6% of patients receiving rivaroxaban compared with 18.9% of patients receiving enoxaparin (relative risk reduction 49%; $p < 0.001$). The incidences of major and non-major bleeding were similar in both the rivaroxaban and enoxaparin groups. During the treatment period, there were no deaths or PEs in the rivaroxaban group, and two deaths and four PEs occurred in the enoxaparin group. This study demonstrated an improved efficacy and safety of rivaroxaban compared with 40 mg enoxaparin after major orthopedic surgery (RECORD 3 study [25]).

RECORD 2 is a prospective, randomized, double-blind, clinical Phase III trial that compares short-term thromboprophylaxis using enoxaparin with extended thromboprophylaxis for up to 5 weeks with rivaroxaban in 2509 patients undergoing THR. Patients received 40 mg once-daily enoxaparin, beginning the evening before surgery and continuing for 10–14 days, followed by placebo until day 35, or rivaroxaban 10 mg once daily beginning 6–8 h after surgery for 35 days. The primary outcome was the composite of DVT, PE and all-cause mortality. The primary composite end point was 9.3% in the enoxaparin group and 2.0% in the rivaroxaban group (relative risk reduction: 79%; $p < 0.001$). The incidences of major and non-major bleeding were similar in both groups ($p = 0.246$). Thus, the extended therapy with rivaroxaban was more effective than short-term enoxaparin for the prevention of VTE in patients undergoing THA [26].

RECORD1 was a Phase III, multinational, randomized, double-blind, double-dummy trial to determine the efficacy and safety of 1 × 10 mg rivaroxaban, starting 6–8 h after surgery,

Figure 3. Dose–response relationships between rivaroxaban and the primary efficacy end point and the primary safety end point.

The black lines are the mean dose–response curves for rivaroxaban, estimated by logistic regression including total daily dose as a covariate. The pink lines represent the 95% confidence intervals for safety. The blue lines represent the 95% confidence intervals for efficacy. Reproduced with permission from [22].

compared with 1 × 40 mg enoxaparin initiated the evening before surgery, for 35 days in 4541 patients undergoing THR. The primary outcome was the composite of DVT, PE and all-cause mortality. This efficacy end point occurred in 1.1% of patients randomized to rivaroxaban and in 3.7% of patients randomized to enoxaparin (relative risk reduction: 70%, 95% confidence interval: 49–82%, $p < 0.001$). The incidence of major and non-major bleeding events was similar in both groups. Rivaroxaban was significantly more effective than enoxaparin for extended prophylaxis after THA, with a similar safety profile [27].

The pharmacokinetics/pharmacodynamics of rivaroxaban was analyzed from 870 patients during treatment of acute DVT using nonlinear, mixed-effect population modeling (NONMEM). Rivaroxaban C_{\max} and C_{trough} concentrations increased dose dependently. As expected, C_{\max} was higher and C_{trough} was lower after once-daily dosing, compared with twice-daily dosing, at equivalent total daily doses; however, 90% confidence intervals overlapped. Rivaroxaban plasma concentrations correlated linearly with pro-

thrombin time (PT). Co-medications (e.g. diuretics, NSAIDs and aspirin) had no relevant effects on the pharmacokinetics of rivaroxaban [28].

Treatment of acute venous thromboembolism

The randomized, parallel-group Phase II trial in patients with proximal DVT explored the efficacy and safety of rivaroxaban 10, 20, or 30 mg twice-daily or 40 mg once-daily, compared with enoxaparin 1 mg/kg twice-daily followed by vitamin K antagonist for 12 weeks. The primary efficacy outcome was an improvement in thrombotic burden at day 21 (defined as a ≥ 4 -point reduction in the thrombus score as measured by compression ultrasound examination, no name of thrombus score). The thrombus burden was less than 4 points in 53/100, 58/98, 62/109 and 49/112 patients receiving rivaroxaban 10, 20 or 30 mg twice-daily, or 40 mg once-daily, respectively, compared with 50/109 patients treated with enoxaparin/vitamin K antagonist. The primary efficacy end point was therefore achieved. There was no dose–response relationship between rivaroxaban and the primary efficacy end point ($p < 0.67$), and no difference to

patients randomized to enoxaparin/vitamin K antagonist. Major bleeding was observed in 1.7, 1.7, 3.3 and 1.7% of patients receiving rivaroxaban 10, 20 or 30 mg twice-daily or 40 mg once-daily and 0% of enoxaparin/vitamin K antagonist patients. There were no major bleeding events during the treatments [29].

The incidence of alanine aminotransferase (ALT) elevations of more than threefold the upper limit of normal (ULN) in the rivaroxaban groups ranged from 1.9 to 4.3% compared with 21.6% in the enoxaparin/vitamin K antagonist-treated group. This was not dose-dependent for rivaroxaban. Approximately half of the ALT elevations in the rivaroxaban-treated patients occurred during the first 3 weeks of treatment. In the enoxaparin/vitamin K antagonist-treated patients, the majority of ALT elevations occurred during the first 2 weeks of treatment. Beyond 21 days, the proportions of rivaroxaban- or vitamin K antagonist-treated patients with ALT elevations over threefold the ULN were similar (1.9% versus 0.9%). One patient on rivaroxaban had ALT of more than threefold the ULN in combination with bilirubin of more than twofold the ULN, and died of acute liver failure. Rivaroxaban was stopped prematurely in three patients because of elevated liver enzyme levels. In one, ALT and aspartate aminotransferase began to increase on the day after the initiation of treatment and returned to the normal range after termination of therapy. In the other, ALT and aspartate aminotransferase were elevated on day 1 of the study before first intake of study drug, when treatment was stopped immediately. This patient died 2.5 weeks later of carcinoma with liver metastases. In the third patient, rivaroxaban 40 mg once-daily was stopped after 23 days owing to a diagnosis of hepatitis B with raised liver aminotransferases; viral serology showed acute hepatitis B with seroconversion during the study period, and the patient died of acute liver failure 48 days after starting treatment [29].

The Einstein study is the second Phase II trial evaluating the efficacy and safety of rivaroxaban for the treatment of acute DVT of similar design, but compared once-daily rivaroxaban (20, 30 or 40 mg) with a heparin (either UFH or LMWH), followed by a vitamin K antagonist, in 543 patients with symptomatic DVT without symptomatic PE. The primary efficacy outcome (deterioration in thrombotic burden or symptomatic recurrent VTE) occurred in 5.4–6.6% of patients on rivaroxaban and 9.9% on heparin/vitamin K

antagonist. There was no evidence of a dose–efficacy relationship with rivaroxaban. During the first 3 weeks of treatment, the incidence of ALT elevations more than three-times the ULN was lower in patients on rivaroxaban [30]. On the basis of these trials, the 20 mg once-daily dose of rivaroxaban has been chosen for evaluation in Phase III randomized trials.

In a Phase III trial, rivaroxaban 1 × 20 mg is currently investigated in approximately 6200 patients with acute symptomatic DVT or PE and compared for prevention of recurrent VTE with initial anticoagulation with bodyweight-adjusted enoxaparin followed by INR-adjusted warfarin for 3–12 months ([101]; identifier: NCT00440193).

The prolonged prophylaxis of VTE is investigated in patients with an initial prophylaxis of VTE for 3–12 months and no indication for further anticoagulation. These patients are randomized to rivaroxaban 1 × 20 mg or placebo in a double-blind, prospective, randomized, clinical trial for 6 or 12 months, according to the decision of the physician (EINSTEIN EXTENSION [101]; identifier: NCT00439725).

Atrial fibrillation

In patients with nonvalvular atrial fibrillation rivaroxaban is compared with INR-adjusted dose oral warfarin for prevention of stroke in a double-blind, double-dummy, prospective, randomized trial in approximately 14,000 patients. Patients with a reduced creatinine clearance between 30 and 49 ml/min receive a reduced dose of 15 mg rivaroxaban once-daily. The primary composite outcome event consists of embolic and nonembolic stroke and non-cerebral nervous system systemic embolism. The secondary outcome end points are a composition of stroke, noncerebral nervous system systemic embolism and vascular death ([101]; identifier: NCT 004403767; Rocket trial).

The efficacy and safety of rivaroxaban for the prevention of stroke and embolism in 1200 subjects with nonvalvular atrial fibrillation are currently being investigated in a prospective randomized, double-blind, Phase III trial in Japan ([101]; identifier: NCT 00494871).

Acute coronary syndrome

In patients with acute coronary syndrome, a randomized, double-blind, placebo-controlled, multicenter, dose-escalating, Phase IIb study is being performed to evaluate the safety and efficacy of rivaroxaban in combination with aspirin alone or

with aspirin and clopidogrel in 1350 patients. Primary outcome measure is the combined incidence of fatal and major bleeding complications ([101]; identifier: NCT 00402597; the Atlas ACS TIMI 46 trial).

Apixaban

Apixaban is a follow-up compound to the oral, direct factor Xa inhibitor razaxaban and is a selective and potent ($K_i = 0.08$ nM) inhibitor of both free and prothrombinase-bound factor Xa in human plasma. In animal models, the compound had an oral bioavailability of 51, 88 and 34% in chimpanzees, dogs and rats, respectively, was eliminated by renal and fecal excretion, had minimal, if any, drug–drug interactions, and formed no active metabolites. Following oral administration in humans, the compound is absorbed to 80% within 3.5 h and is eliminated with a half-life ranging from 8 to 15 h. It is eliminated to approximately 25% by urinary excretion [31]. It demonstrated potent antithrombotic effects in a rabbit model of venous thrombosis. At present, drug–interaction studies have not been published.

Dose finding in postoperative prevention of VTE

A Phase IIb study for the prevention of VTE in patients undergoing total knee replacement compared 5, 10 or 20 mg apixaban once- or twice-daily with open-label enoxaparin or warfarin for 10–14 days in 1217 patients. The primary efficacy consisted of DVT confirmed by bilateral venogram, symptomatic DVT, nonfatal PE and death from any cause. The primary outcome rates for the doses of apixaban ranged from 5 to 12.5%, respectively, compared with 15.6% in the enoxaparin and 26.6% in the warfarin group, resulting in a relative risk reduction ranging from 21 to 69% when compared with enoxaparin, and from 53 to 82% when compared with warfarin (Figure 4). Total VTE rates were lower in the twice-daily than in the once daily apixaban groups. For the composite outcome of proximal DVT, PE and all-cause mortality, each apixaban group had an event rate ranging from 0 to 2.7%, compared with 4.6% for the enoxaparin group. The incidence of the primary efficacy end point in the apixaban groups combined was lower than in the enoxaparin and warfarin groups ($p = 0.02$ and 0.01 , respectively).

The incidence of major bleeding among apixaban-treated patients ranged from 0 (2.5 mg twice-daily) to 3.3% (20 mg once-daily). The overall incidences of minor bleeding during

apixaban, enoxaparin and warfarin treatment were 0.7, 7.2, 4.0 and 5.3%, respectively. A dose-related response was noted for the incidence of minor bleeding across the once-daily apixaban treatment groups ($p = 0.01$), but not for twice-daily groups ($p = 0.07$). There were no differences between once-daily and twice-daily dose groups. The data of the incidences of VTE and bleeding are depicted in Figure 4.

Three patients died due to fatal PE (2.5 mg twice-daily; after 8 days of study medication), myocardial infarction (2.5 mg twice-daily; diagnosis after 4 days of study medication, died 3 weeks later) and end-stage heart failure and cachexia (20 mg once-daily; died 6 weeks after 5 days of study medication).

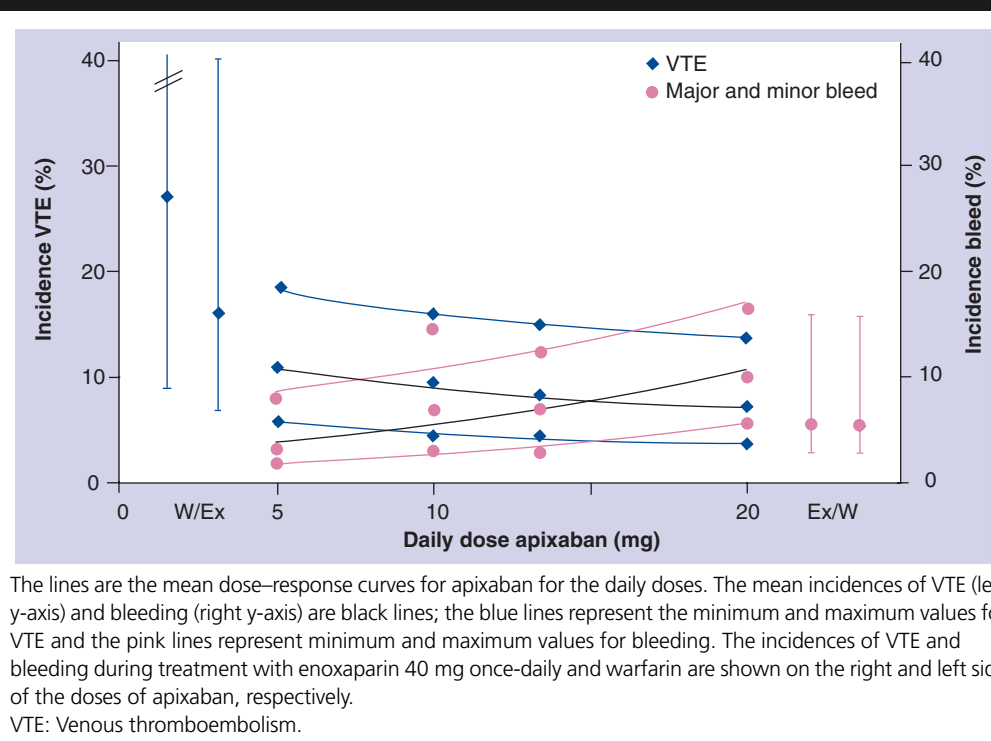
Two patients (apixaban 10 mg twice-daily and warfarin) had a single, concurrent elevation in ALT of more than threefold the ULN and total bilirubin of more than twofold the ULN on postoperative day 1, which returned to below these thresholds by the next evaluation and to within normal limits by the end of the treatment period (apixaban subject) or at the 30-day follow-up period (warfarin subject) with continued drug dosing [32].

A Phase III randomized, double-blind, multicenter study will evaluate the safety and efficacy of apixaban in more than 4000 patients undergoing elective THR surgery on the incidence of asymptomatic and symptomatic DVT, PE and all-cause mortality over 35 days. Secondary outcome measures are major and non-major bleeding events ([101]; identifier: NCT00423319).

Treatment of acute venous thromboembolism

In a Phase IIb dose-ranging study, the efficacy and safety of apixaban was evaluated in patients with confirmed, acute DVT. Patients were randomly allocated to one of three double-blind regimens of apixaban (5 mg twice daily, 10 mg twice-daily or 20 mg once-daily), or conventional treatment with LMWH or fondaparinux followed by open-label vitamin K antagonist adjusted to an INR of 2.0–3.0. A total of 520 patients were included and treated for 84–91 days. A bilateral venous compression ultrasound (CUS) of the legs and a perfusion lung scan (PLS) were performed within 36 h from randomization and at 12 weeks (Boticelli trial).

The primary efficacy outcome was the composite of symptomatic recurrent VTE and deterioration of the thrombotic burden as assessed by repeat bilateral CUS and PLS. The principal safety outcome was a composite of major and clinically relevant non-major bleeding.

Figure 4. Dose–response relationships between apixaban and the incidences of venous thromboembolism and bleeding.

For apixaban 5 mg twice-daily, 10 mg twice-daily, 20 mg once-daily, and for vitamin K antagonist, the primary efficacy outcome rates were 6.0, 5.6, 2.6 and 4.2%, respectively. The principal safety outcome rates were 8.6, 4.5, 7.3 and 7.9%, respectively. The rates of symptomatic VTE were 2.6, 3.2, 1.7 and 2.5%, respectively. The rates of major bleeding were 0.8% (5 mg twice-daily), 0 (10 mg twice-daily), 0.8 (20 mg once-daily) and 0% (enoxaparin/warfarin) (Figure 4). A fixed dose of apixaban seems to be as safe as enoxaparin/warfarin for treatment of acute VTE [33].

In a Phase III randomized, double-blind, double-dummy clinical noninferiority trial, 10 mg twice-daily apixaban is compared with initial bodyweight-adjusted enoxaparin, followed by INR-adjusted warfarin in approximately 5800 patients with acute DVT and PE. Primary objectives are the incidences of recurrent VTE or VTE-related death over 6 months.

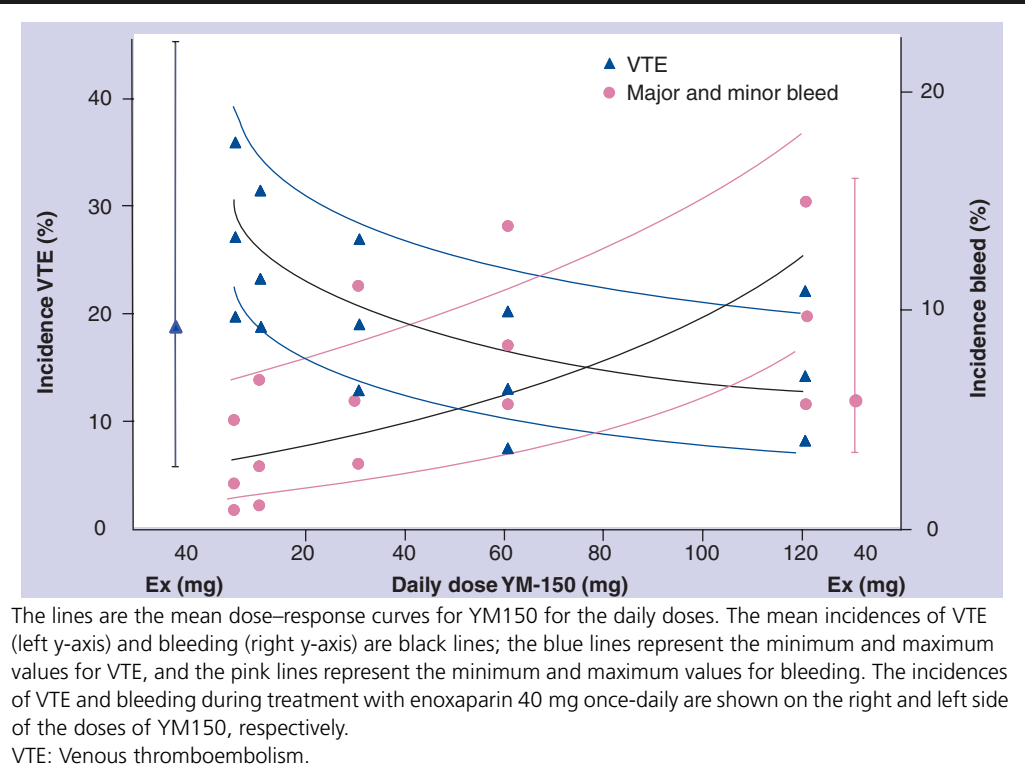
The prolonged prophylaxis after an acute episode of VTE is being investigated using apixaban versus placebo in those patients with no indication for a prolonged prophylaxis of VTE using vitamin K antagonist. A dose of 2.5 mg apixaban twice-daily is compared with 5 mg apixaban twice-daily and placebo twice-daily for 12 months. The primary end point of recurrent VTE is a determi-

nation of at least one of the apixaban dose regimen to be superior to placebo. The combined end point consists of symptomatic recurrent VTE and all-cause mortality in subjects who have completed a standard of 6–12 months of conventional anticoagulation for prevention of a symptomatic DVT or PE in approximately 650 patients per group.

Atrial fibrillation

A Phase III study has been initiated to evaluate the efficacy and safety of apixaban compared with warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Secondary outcome measures are confirmed ischemic stroke, hemorrhagic stroke, systemic embolism and all-cause death. This randomized, double-blind, parallel-arm study is expected to enroll 15,000 patients (Aristotle trial [101]; identifier: NCT00412984).

Another Phase III prospective, randomized, double-blind clinical trial investigates the prevention of stroke in patients with atrial fibrillation who have failed or are unsuitable for vitamin K antagonist treatment. Patients are randomized to 2 × 2.5 mg apixaban versus acetylsalicylic acid (81–324 mg once-daily) in a double-blind design and treated for up to 3 years. The study hypothesis is the superiority of apixaban to

Figure 5. Dose–response relationships between YM150 and the incidences of VTE and bleeding.

acetylsalicylic acid for preventing the competed outcome of stroke or systemic embolism in 5600 patients with atrial fibrillation with at least one additional risk factor for stroke (AVERROES [101]; identifier: NCT00496769).

Prevention of venous thromboembolism in hospitalized medical patients

In a Phase III randomized, double-blind, multi-center trial, the safety and efficacy of 2×2.5 mg apixaban for 35–45 days is compared with 1×40 mg enoxaparin for approximately 10–15 days during hospitalization, followed by placebo over 30 days in acutely ill medical subjects during and following hospitalization for prophylaxis of VTE. The end point is the combination of DVT detected by screening of patients at the end of the treatment period by CUS of both legs and confirmed DVT or PE during the study period. Approximately 6500 patients will be randomized to apixaban or enoxaparin/placebo (ADOPT [101]; identifier: NCT00457002).

Other indications

One study, potentially involving up to 1800 patients, has begun to assess the efficacy and safety of apixaban in patients who have

recently had unstable angina or a heart attack ([101]; identifier: NCT00313300). Another study currently underway is investigating apixaban for the prevention of thromboembolic events in patients with advanced metastatic cancer, and is expected to enroll 160 patients ([101]; identifier: NCT00320255).

YM150

The compound is an orally active direct factor Xa inhibitor and has a K_i for factor Xa of 31 nM, and inhibits prothrombin activation induced by free factor Xa, prothrombinase and whole-blood clots. YM150 demonstrated antithrombotic effects in animal models of venous and arterial thrombosis at doses that did not prolong bleeding time. In Phase I studies, the drug has been shown to be well tolerated in healthy volunteers. Food was not found to interfere with the absorption of YM150. Pharmacokinetic effects correlated with pharmacodynamic effects, and a dose–response relationship between YM150 and pharmacodynamics was observed but has not been published in detail so far [34].

YM150 was investigated in patients ($n = 174$) undergoing hip replacement surgery to assess the safety and efficacy of thromboprophylaxis in a

dose-escalation study (ONYX study). Patients were randomized per cohort to oral once-daily 3, 10, 30 and 60 mg YM150 or subcutaneous enoxaparin (40 mg daily) for 7–10 days treatment. The primary safety end point was major and clinically relevant non-major bleeding. No major and three clinically relevant non-major bleeds were reported, one in the 3-mg and two in the 10-mg groups. The VTE rate in the YM150 group ranged from 51.9% in the 3-mg group to 18.5% in the 60-mg group, and the VTE incidence in the pooled enoxaparin group was 38.7%, as demonstrated by venography. The efficacy analysis showed a dose-related trend in the reduced incidence of venographically demonstrated DVT with increasing dose of YM150 ($p = 0.006$) [35].

A double-blind, dose-finding, Phase IIb study (ONYX-2) was performed in patients undergoing elective hip replacement surgery versus open-label enoxaparin. A total of 1071 patients were treated in hospital and thereafter at home for up to 6 weeks with 5, 10, 30, 60 or 120 mg YM150 or 40 mg enoxaparin once-daily subcutaneously ([101]; identifier: NCT00353678). YM150 was initiated 6 h post-surgery and enoxaparin 12 h before surgery. The primary efficacy outcome was any DVT, symptomatic VTE and death up to 10 days. The safety outcome was major bleeding up to 10 days. The incidences of VTE were 27.4, 31.7, 19.3, 13.3 and 14.5% in patients receiving increasing doses of 5, 10, 30, 60 and 120 mg YM150 versus 19.8% in patients randomized to enoxaparin. The corresponding figures for bleeding complications were 2.5, 3.2, 6.5, 8.7 and 9.7% for the YM150 group, versus 5.4% for the enoxaparin group [36]. The mean values and standard deviations were used for depicting Figure 5.

LY517717

In preclinical studies, LY517717 was shown to have a K_i of 4.6–6.6 nM on factor Xa. Animal experiments demonstrated antithrombotic effects in a rat arteriovenous shunt model. In Phase I studies, the compound was well tolerated and had an oral bioavailability of 25–82% and a half-life of approximately 25 h, as published in part in an abstract [37].

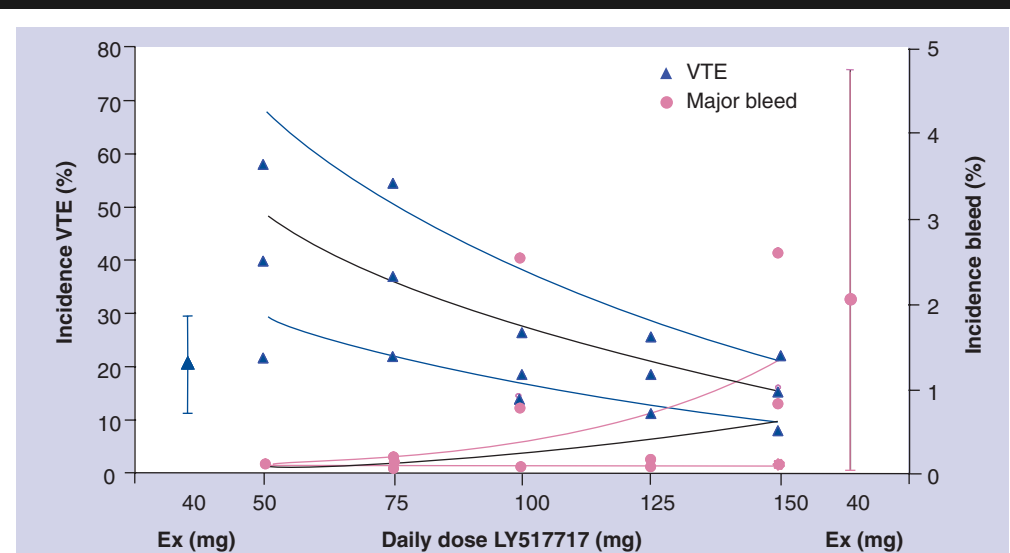
A Phase II, double-blind, double-dummy, dose-ranging study was initiated to determine the efficacy and safety of LY517717, compared with enoxaparin, for the prevention of VTE in patients undergoing TKR or THR. Patients ($n = 511$) were randomized to receive oral LY517717 (25, 50, 75, 100, 125 or 150 mg

once-daily) initiated 6–8 h postoperatively, or enoxaparin 40 mg once-daily initiated the evening before surgery. The primary efficacy end point of the study was the combined incidence of DVT in venography, which was performed in all patients on both legs and objectively confirmed suspicion of symptoms for DVT or PE. The safety end points were the incidences of major and minor bleeding up to 30 days after treatment initiation. Due to the lack of efficacy, the three lowest LY517717-dose arms were stopped early and the study was completed with the three highest doses only. The 100-, 125- and 150-mg once-daily doses of LY517717 were not inferior to enoxaparin, with similar incidences of the efficacy end point (17.1–24.0% vs 22.2% with enoxaparin) and lower incidences of major bleeding (0.0% to 0.9% vs 1.1% with enoxaparin) and minor bleeding (0.0–1.0% vs 2.2% with enoxaparin) [38]. The incidences of recurrent VTE and of bleeding are depicted in Figure 6.

DU-176b

The K_i of DU-176b for human factor Xa is approximately 10,000-times lower than the lowest K_i value for any other human serine proteases (thrombin). Its absorption takes 3–4 h, with a plasma half-life of 8.6–10.7 h, and it is cleared mainly through the kidneys. Anti-thrombotic effects were assessed comparing *ex vivo* thrombus inhibition in a Phase I trial using a perfusion chamber model. Under venous flow after 1.5 and 5 h, the thrombus was 28 and 21% smaller versus baseline, respectively ($p < 0.05$). Under arterial conditions, the reduction was 26 and 17% ($p < 0.05$). The quantification of thrombin generated during an observation time of 45 min was performed via the evaluation of the amidolytic activity by measurement of fluorescence, versus a thrombin activity titrated calibrator. The area under the curve was measured and is expressed as the endogenous thrombin potential. Thrombin generation decreased by 28% at 1.5 h and 10% at 5 h. Changes in PT and INR correlated well with plasma drug concentrations ($r = 0.79$ and 0.78) [39]. A Phase IIa, open-label, dose-finding study of DU-176b for the prevention of VTE after THR was initiated ([101]; identifier: NCT00107900), involving approximately 600 patients.

In patients with atrial fibrillation, four dose regimens of DU176b (1×30 mg, 2×30 mg, 1×60 mg and 2×60 mg daily taken orally) are

Figure 6. Dose–response relationships between LY157717 and the incidences of venous thromboembolism and bleeding.

The lines are the mean dose–response curves for LY157717 for the daily doses. The mean incidences of VTE (left y-axis) and bleeding (right y-axis) are black lines; the blue lines represent the 95% interval for VTE and the pink lines represent the 95% interval for bleeding. The incidences of VTE and bleeding during treatment with enoxaparin 40 mg once-daily are shown on the right and left side of the doses of LY157717, respectively. VTE: Venous thromboembolism.

compared with INR adjusted warfarin on the safety of treatment. Major and clinically relevant non-major bleedings are the safety outcomes. Approximately 2000 patients are planned to be included into the study ([101]; identifier: NCT00504556).

PRT054021

PRT054021 has a K_i for factor Xa of 0.117 nM and has demonstrated antithrombotic activity in animal models in rats. In healthy volunteers, the oral bioavailability was 47% and the half-life was 19 h. The compound was well tolerated at a wide range of doses in a Phase I dose-escalation study involving 64 patients. There were no relevant interactions with food. PRT054021 was excreted almost unchanged in bile. The data are on file or published in part as an abstract [40]. A multicenter, randomized, Phase II study has recently been initiated to evaluate the safety and efficacy of PRT054021 40 mg twice-daily and 15 mg twice-daily compared with enoxaparin 30 mg twice-daily for the prevention of VTE in approximately 200 patients undergoing TKR ([101]; identifier: NCT00375609).

Conclusion

Differences in the chemical structures of the compounds result in differences in the pharmacokinetic and pharmacodynamic parameters.

Hence, factor Xa inhibitors possess individual efficacy and safety profiles. The specific factor Xa inhibitors currently consist of two classes: indirect antithrombin-dependent compounds and direct factor Xa-binding compounds, which are administered systemically or orally. Idaraparinux is an indirect antithrombin-dependent compound and is presently on hold in clinical development due to bleeding complications during long-term treatment. This may be due to an accumulation and the 60 days half-life of the compound. Biotinylated idaraparinux is currently investigated in large clinical trials. Other antithrombin-dependent oligosaccharides (AVE5026, the hexasaccharide SR1237815026) show promising results, but are in the early stage of clinical development.

Otamixban and DX-9065a are systemic direct factor Xa-binding compounds developed for intravenous use for interventional indications in cardiology. They are in the early stages of clinical development. Several oral direct factor Xa inhibitors are in the late stages of clinical development. Rivaroxaban and apixaban are investigated in almost identical and very similar indications. At present, they do not encounter safety or efficacy problems. Data for rivaroxaban has been submitted to the regulatory bodies for approval in post-operative prophylaxis of VTE. Dabigatran etexilate, an oral direct thrombin inhibitor, has been submitted to regulatory agencies for approval

Executive summary

Indirect factor Xa inhibitor – idraparinux

- Idraparinux is an indirect antithrombin-dependent factor Xa inhibitor with a long half-life of 60 days and is given subcutaneously once a week.
- Idraparinux is effective for treatment of deep-vein thrombosis. In patients with pulmonary embolism, idraparinux is not as effective as enoxaparin/warfarin.
- Biotinylated idraparinux can be antagonized by intravenous avidin.
- The efficacy and safety of biotin idraparinux for treatment of acute deep-vein thrombosis and treatment of pulmonary embolism is currently being investigated.

Other parenteral inhibitors mainly inhibiting indirect factor Xa

- Subcutaneous new heparin-derived oligosaccharides inhibiting mainly factor Xa and, only to a small extent (if at all), thrombin (antifactor Xa:antithrombin ratio of more than 30), are in clinical development.

Direct factor Xa inhibitors systemically active

- The synthetic direct factor Xa inhibitors otamixaban and DX9065a are currently investigated in acute coronary syndrome. These compounds are given intravenously as a continuous infusion.
- These inhibitors may have an advantage over heparin and hirudin derivatives with regard to improved safety (no development of heparin-induced thrombocytopenia or hirudin antibodies).

Direct factor Xa inhibitors orally active – rivaroxaban

- Rivaroxaban is a synthetic oral direct factor Xa inhibitor with a half-life of approximately 9 h. It is given once-daily orally.
- Prophylaxis of venous thromboembolism in patients with elective joint replacement of the knee or of the hip less frequently develop venous thromboembolism and suffer from fewer bleeding complications compared with subcutaneous enoxaparin.
- The first results indicate the efficacy and safety of prolonged prophylaxis of venous thromboembolism in patients after elective total hip replacement.
- Dose-finding studies indicated that rivaroxaban is effective in the treatment of acute venous thromboembolism.
- Rivaroxaban is currently being investigated for prevention of systemic arterial embolism in patients with arterial fibrillation and for prevention of recurrent unstable angina in acute coronary syndrome.

Direct factor Xa inhibitors orally active – apixaban

- Apixaban is a synthetic oral direct factor Xa inhibitor with a half-life of approximately 10 h.
- Dose-finding studies have shown efficacy and safety of apixaban for prophylaxis of venous thromboembolism in patients undergoing elective knee replacement.
- A dose-finding study demonstrated the efficacy and safety of apixaban for treatment of acute venous thromboembolism.
- Apixaban is currently investigated in patients with arterial fibrillation for prevention of systemic embolism, as well as in other indications including acute coronary syndrome, prevention of thromboembolism in patients with metastatic cancer and for prolonged prevention of venous thromboembolism in patients hospitalized initially for acute medical illnesses.

Other oral direct factor Xa inhibitors in clinical development

- Other synthetic oral direct factor Xa inhibitors are in clinical development. Some of them have undergone first clinical trials in patients.
- At present, YM150, LY517717, DU-176b and PRT054021 are investigated in patients for prophylaxis of thromboembolism.

in postoperative prophylaxis of VTE. The potential advantages of one of the currently developed factor Xa inhibitors over the other factor Xa inhibitors, as well as over dabigatran etexilate, can not be identified at present. The non-anticoagulation actions of each compound may differ substantially, and thereby influence the clinical benefit.

Future perspective

It is suggested that one or more of the new synthetic, specific factor Xa inhibitors will be approved by the authorities for anticoagulation of patients within the next 2–5 years. Post-operative prophylaxis of VTE will be the first indication for the inhibitor(s). The oral direct

thrombin inhibitor dabigatran will also play an important role in this scenario. Within the next 3–6 years, one or more of these compounds or a thrombin inhibitor will successfully apply for treatment of acute VTE and atrial fibrillation. Others of the described inhibitors may be ready to submit their files for approval by the authorities. In the next 5–10 years, data from clinical studies in unstable angina and treatment of VTE in malignancy may be submitted to the health authorities for the described compounds. Other synthetic or recombinant inhibitors of specific coagulation proteases or antiproteases may be in or at the end of Phase III trials including new, non-anticoagulant indications.

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Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Hirsh J, O'Donnell M, Eikelboom JW. Beyond unfractionated heparin and warfarin: current and future advances. *Circulation* 116, 552–560 (2007).
- **Recent overview on new anticoagulants in cardiologic indications.**
2. Bates SM, Weitz JI: The status of new anticoagulants. *Br. J. Haematol.* 134, 3–19 (2006).
3. Eikelboom JW, Weitz JI: A replacement for warfarin: the search continues. *Circulation* 116, 131–133 (2007)
4. Saiah E, Soares C: Small molecule coagulation cascade inhibitors in the clinic. *Curr. Top. Med. Chem.* 5, 1677–1695 (2005).
5. Bauer KA: New anticoagulants. *Hematology Am. Soc. Hematol. Educ. Program* 450–456 (2006).
6. Turpie AGG: Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. *Arterioscler. Thromb. Vasc. Biol.* 27, 1238–1247 (2007).
- **Review of clinical studies for prevention of venous thromboembolism using oral factor Xa inhibitors.**
7. Ma Q, Fareed J: Idraparinux sodium. Sanofi-Aventis. *IDrugs* 7, 1028–1034 (2004).
8. Herbert JM, Hérault JP, Bernat A *et al.*: Biochemical and pharmacological properties of SANORG 34006, a potent and long-acting pentasaccharide. *Blood* 91, 4197–4205 (1998).
- **Pharmacology of the long-acting idraparinux.**
9. Bijsterveld NR, Vink R, Van Arken BE *et al.*: Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. *Br. J. Haematol.* 124, 653–658 (2004)
10. The PERSIST Investigators: A novel long-acting synthetic factor Xa inhibitor (SanOrg34006) to replace warfarin for secondary prevention in deep vein thrombosis: a Phase II evaluation. *J. Thromb. Haemost.* 2, 47–53 (2004).
- **Dose-finding study for idraparinux for treatment of patients with acute deep-vein thrombosis (DVT).**
11. The van Gogh Investigators: Idraparinux versus standard therapy for venous thromboembolic disease. *N. Engl. J. Med.* 357, 1094–1104 (2007).
- **Treatment of patients with acute DVT and pulmonary embolism using idraparinux.**
12. The van Gogh Investigators: Extended prophylaxis of venous thromboembolism with idraparinux. *N. Engl. J. Med.* 357, 1105–1112 (2007).
- **Prolonged secondary prophylaxis of patients suffering from acute venous thromboembolism with long-acting anticoagulant idraparinux.**
13. Harenberg J, Joerg I, Vukojevic Y, Weiss C, Mikus G: Anticoagulant effects of idraparinux after termination of therapy for prevention of recurrent venous thromboembolism: observations from the van Gogh trials. *Eur. J. Clin. Pharmacol.* (2008) (In press).
- **Idraparinux has a half-life of 60 days.**
14. Harenberg J, Weiss C, Mikus G, Joerg I, Vukojevic Y: Long elimination half-life of idraparinux after termination of therapy explains bleeding in the van Gogh trials. *J. Thromb. Haemost.* (2008) (In press).
15. Savi P, Hérault JP, Duchaussoy P *et al.*: Reversible biotinylated oligosaccharides, a new approach for a better management of the anticoagulant therapy. *J. Thromb. Haemost.* (Suppl.), Abstract P-W-645 (2007).
16. Lassen MR, Dahl OE, Mismetti P, Destrée D: AV5026, a new anticoagulant for prevention of venous thromboembolism in total knee replacement surgery – TREK: a dose ranging study. *Blood* 110, Abstract 311 (2007).
- **Dose-finding study for the very low-molecular-weight heparin AV5026.**
17. Ansell J: Factor Xa or thrombin: is factor Xa a better target? *J. Thromb. Haemost.* 5(Suppl. 1), 60–64 (2007).
18. Paccaly A, Frick A, Rohatagi S *et al.*: Pharmacokinetics of otamixaban, a direct factor Xa inhibitor, in healthy male subjects: pharmacokinetic model development for Phase 2/3 simulation of exposure. *J. Clin. Pharmacol.* 46, 37–44 (2006).
- **Pharmacology of the intravenous direct factor Xa inhibitor otamixaban.**
19. Cohen M, Deepak L, Bhatt DL *et al.*: on behalf of the SEPIA-PCI Trial Investigators: Randomized, double-blind, dose-ranging study of otamixaban, a novel, parenteral, short-acting direct factor Xa Inhibitor, in percutaneous coronary intervention: The SEPIA-PCI Trial. *Circulation* 115, 2642–2651 (2007).
- **Efficacy and safety of otamixaban in percutaneous coronary intervention.**
20. Rezaie AR: DX-9065a inhibition of factor Xa and the prothrombinase complex: mechanism of inhibition and comparison with therapeutic heparins. *Thromb. Haemost.* 89, 112–121 (2003).
21. Dyke CK, Becker RC, Kleiman NS *et al.*: First experience with direct factor Xa inhibition in patients with stable coronary disease: a pharmacokinetic and pharmacodynamic evaluation. *Circulation* 105, 2385–2391 (2002).
- **Antithrombotic effect of the oral direct factor Xa inhibitor DX-9065a in patients with stable coronary artery disease.**
22. Alexander JH, Yang H, Becker RC *et al.*: on behalf of the XANADU-ACS Investigators: First experience with direct, selective factor Xa inhibition in patients with non-ST-elevation acute coronary syndromes: results of the XANADU-ACS trial. *J. Thromb. Haemost.* 3, 439–447 (2005).
- **Clinical study with DX-9065a in patients with acute coronary syndrome.**
23. Kubitz D, Haas S: Novel factor Xa inhibitors for prevention and treatment of thromboembolic diseases. *Expert Opin. Invest. Drugs* 15, 843–855 (2006).
- **Overview on the pharmacological properties of rivaroxaban.**
24. Eriksson BI, Lars C, Borris LC *et al.*: for the ODIXa-HIP Study Investigators: A once-daily, oral, direct factor Xa inhibitor, rivaroxaban (BAY 59–7939), for thromboprophylaxis after total hip replacement. *Circulation* 114, 2374–2381 (2006).
- **Postoperative prophylaxis of venous thromboembolism with rivaroxaban.**
25. Lassen MR, Turpie AG, Rosenthal N *et al.*: Rivaroxaban – an oral, direct factor Xa inhibitor – for thromboprophylaxis

- after total knee arthroplasty: the RECORD3 trial. *Blood* 110, Abstract 308 (2007).
26. Kakkar AK, Brenner B, Dahl OE *et al.*: Extended thromboprophylaxis with rivaroxaban compared with short-term thromboprophylaxis with enoxaparin after total hip arthroplasty: the RECORD2. *Blood* 110, Abstract 307 (2007).
 27. Eriksson BI, Borris LC, Friedman RJ *et al.*: Oral rivaroxaban compared with subcutaneous enoxaparin for extended thromboprophylaxis after total hip arthroplasty: the RECORD1. *Blood* 110, Abstract 6 (2007).
 28. Mueck W, Agnelli G, Buller H: Rivaroxaban has predictable pharmacokinetics (PK) and pharmacodynamics (PD) when given once or twice daily for the treatment of acute, proximal deep vein thrombosis (DVT). *Blood* 110, Abstract 1880 (2007).
 29. Agnelli G, Gallus A, Goldhaber SZ *et al.*; for the ODIXa-DVT Study Investigators: Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939). The ODIXa-DVT Study. *Circulation* 116, 180–187 (2007).
 - **Treatment of acute DVT with rivaroxaban.**
 30. Buller HR: Once-daily treatment with an oral, direct factor Xa inhibitor – rivaroxaban (BAY 59-7939) – in patients with acute, symptomatic deep vein thrombosis: the EINSTEIN-DVT dose-finding study. *Eur. Heart J.* 27, 761 Abstract (2006).
 31. Pinto DJ, Orwat MJ, Koch S *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.* 50, 5339–5356 (2007).
 - **Pharmacology of apixaban and other oral direct factor Xa inhibitors.**
 32. 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.* 5, 2368–2375 (2007).
 - **Prophylaxis of venous thromboembolism in patients undergoing total knee replacement using apixaban.**
 33. Buller HR: A dose finding study of the oral direct factor Xa inhibitor apixaban in the treatment of patients with acute symptomatic deep vein thrombosis – the Botticelli investigators. *J. Thromb. Haemost.* (Suppl.), Abstract O-S-003 (2007).
 34. Iwatsuki Y, Shigenaga T, Moritani Y *et al.*: Biochemical and pharmacological profiles of YM150, an oral direct Factor Xa inhibitor. *Blood* 108, Abstract 911 (2006).
 35. Eriksson BI, Turpie AGG, Lassen MR *et al.*; for the Onyx Study Group: A dose escalation study of YM150, an oral direct factor Xa inhibitor, in the prevention of venous thromboembolism in elective primary hip replacement surgery. *J. Thromb. Haemost.* 5, 1660–1665 (2007).
 - **Dose-finding study of the oral direct factor Xa inhibitor YM150 for prophylaxis of venous thromboembolism in patients undergoing elective hip replacement.**
 36. Eriksson BI, Turpie AGG, Lassen MR *et al.*: Once daily YM150, an oral direct factor Xa inhibitor, for prevention of venous thromboembolism in patients undergoing elective primary hip replacement. *Blood* 110, Abstract 309 (2007).
 37. Norman P: Medicinal Chemistry – 12th RSC-SCI Symposium (Part I), Enzyme Inhibitors. IDdb Meeting Report, Cambridge, UK (2003).
 38. Agnelli G, Haas SK, Krueger KA, Ginsberg JS, Dmitrienko A, Brandt JT: A Phase II study of the safety and efficacy of a novel oral fXa inhibitor (LY517717) for the prevention of venous thromboembolism following TKR or THR. *J. Thromb. Haemost.* 5, 746–753 (2007).
 - **Dose-finding study for prophylaxis of venous thromboembolism in patients undergoing elective knee or hip replacement using the oral direct factor Xa inhibitor LY517717.**
 39. Zafar MU, Vorchheimer DA, Gaztanaga J *et al.*: Antithrombotic effects of factor Xa inhibition with DU-176b: Phase-I study of an oral, direct factor Xa inhibitor using an *ex-vivo* flow chamber. *Thromb. Haemost.* 98, 883–888 (2007).
 40. Abe K, Siu G, Edwards S *et al.*: Animal models of thrombosis help predict the human therapeutic concentration of PRT54021, a potent oral Factor Xa inhibitor. *Blood*. 108, Abstract 901 (2006).

Website

101. ClinicalTrials.gov website – a registry of federally and privately supported clinical trials
ClinicalTrials.gov