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New Anticoagulants

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Traditional anticoagulant drugs, including unfractionated heparin and warfarin, have several limitations. New anticoagulants have been developed that target a single coagulation factor and have predictable dose-response relationships. These include direct thrombin inhibitors and factor Xa inhibitors. Two parenteral direct thrombin inhibitors, lepirudin and argatroban, have FDA approval for the management of heparin-induced thrombocytopenia (HIT). Bivalirudin is a parenteral direct thrombin inhibitor that is licensed for patients undergoing percutaneous coronary interventions and for those with HIT who require percutaneous coronary interventions. Ximelagatran, an oral prodrug of the direct thrombin inhibitor melagatran, showed efficacy in the prevention and treatment of venous thromboembolism as well as stroke prevention in patients with atrial fibrillation. However, due to nonhematologic safety concerns, it did not receive FDA approval in the US. Fondaparinux is a synthetic pentasaccharide, which binds to antithrombin, thereby indirectly selectively inhibiting factor Xa. Fondaparinux demonstrated efficacy compared to low-molecular-weight heparin in randomized clinical trials and is FDA approved for the prevention and treatment of venous thromboembolism. The OASIS 5 trial in non-ST-segment elevation acute coronary syndromes recently demonstrated that the fondaparinux dose approved for prophylaxis of deep venous thrombosis is as efficacious with respect to ischemic outcomes as therapeutic doses of enoxaparin; fondaparinux, however, was associated with a substantial reduction in major bleeding at 9 days and mortality at 1 and 6 months. A number of oral direct factor Xa inhibitors as well as other oral direct thrombin inhibitors are in clinical development for the prevention and treatment of thrombosis; the current status of these anticoagulants is reviewed along with the challenges faced in designing pivotal clinical trials of these agents in comparison to existing anticoagulants.

The coagulation pathway is centrally involved in the formation of both arterial and venous thrombi and the development of molecules that inhibit its function is a major strategy for the design of new antithrombotic drugs. Until very recently, pharmacologic prophylaxis of venous thromboembolism was based on three types of anticoagulants: vitamin K antagonists (e.g., warfarin), unfractionated heparin, and low-molecular-weight heparins. Whereas these antithrombotic agents are multi-targeted, i.e., act on a number of coagulation factors, new antithrombotic drugs have been developed that are selective for one specific coagulation factor. The vitamin K antagonists, the only oral anticoagulants currently approved for use, have a number of limitations; these are shown along with their respective consequences in **Table 1**. An "improved" oral anticoagulant that is at least as effective as warfarin in preventing thrombus formation and at least as safe with respect to bleeding risk would be highly desirable. The desired properties of such an agent are shown in **Table 2**.

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Direct Thrombin Inhibition

Thrombin plays a central role as a procoagulant by converting fibrinogen to fibrin as well as by activating its other substrates including factor V, factor VIII, factor XI, factor XIII, and the platelet protease-activated receptors (PAR-1

Table 1. Limitations of vitamin K antagonists.

Limitation	Consequence
Slow onset of action	Overlap with a parenteral anticoagulant
Genetic variation in metabolism	Variable dose requirements
Multiple food and drug interactions	Frequent coagulation monitoring (INR)
Narrow therapeutic index	Frequent coagulation monitoring (INR)

Table 2. Characteristics of an "improved" oral anticoagulant.

- Good bioavailability
- No food or drug interactions
- Rapid onset of action
- Wide therapeutic window
- Predictable anticoagulant response (no monitoring required)
- Availability of an antidote
- No unexpected toxicities
- Reasonable cost
- Mechanism(s) to ensure compliance with therapy

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and PAR-4). The substrate specificity of thrombin derives from specific surface binding sites (e.g., exosite 1 for fibrin) for its substrates. Direct thrombin inhibition is therefore an attractive antithrombotic strategy.

Direct thrombin inhibitors (DTIs) inhibit thrombin by directly binding to exosite 1 and/or the active site of thrombin. Recombinant hirudins (e.g., lepirudin) bind with very high affinity to thrombin to form a 1:1 stoichiometric complex that is essentially irreversible. Lepirudin is administered intravenously and its plasma half-life is ~1 hour; the drug is eliminated via the kidneys and dose adjustment is required for patients with impaired renal function. Lepirudin has a narrow therapeutic window. Therefore, dosing of its anticoagulant effect must be monitored to maintain the activated partial thromboplastin time (aPTT) at 1.5-2.0 times baseline. Argatroban, a synthetic L-arginine derivative, is a reversible direct thrombin inhibitor. Argatroban is administered intravenously and has a plasma half-life of ~45 minutes. The anticoagulant activity of argatroban is monitored using the aPTT, and the dose is adjusted to achieve an aPTT ratio of 1.5-3.0 times baseline. Argatroban is metabolized in the liver and is relatively contraindicated in patients with severe hepatic dysfunction; it is the drug of choice for patients with heparin-induced thrombocytopenia (HIT) with severe renal impairment. Lepirudin and argatroban are US Food and Drug Administration (FDA) approved for anticoagulation in patients with HIT.

Bivalirudin is a synthetic 20–amino acid polypeptide with an NH_2-terminal domain that interacts with the thrombin active site and a carboxy-terminus, homologous to that of hirudin, that binds to exosite 1 on thrombin. After binding to bivalirudin, thrombin cleaves a Pro-Arg bond at the NH_2-terminal end of the molecule, making it a reversible thrombin inhibitor. Bivalirudin is administered intravenously and has a plasma half-life of ~25 minutes. It is licensed for patients undergoing percutaneous coronary interventions as an alternative to heparin and for those with HIT who require percutaneous coronary interventions.

Ximelagatran: Development and Regulatory Agency Reviews

Melagatran is a dipeptide mimetic of the region of fibrinopeptide A that interacts with thrombin's active site. Melagatran has poor oral bioavailability and must be given subcutaneously. Ximelagatran, a prodrug of melagatran, exhibits 20% bioavailability after oral administration. Once absorbed, ximelagatran is rapidly transformed to melagatran, which has a half-life of about 4–5 hours. About 80% of melagatran is excreted via the kidneys. Ximelagatran produced a predictable anticoagulant response and little in the way of food or drug interactions and went through an extensive clinical development program, some of which is excerpted below.

In patients undergoing total knee replacement, ximelagatran was compared with adjusted-dose warfarin for the prevention of venous thromboembolism (VTE) in a series of trials performed in North America. In the first EXULT trial, 2301 patients undergoing total knee replacement were randomly assigned to ximelagatran (24 mg or 36 mg twice daily started the morning after surgery) or warfarin (target INR 2.5 started the evening of surgery).[1] The rates of overall VTE and death were significantly lower in the ximelagatran 36 mg group than in the warfarin group (p = 0.003). Rates for proximal deep venous thrombosis (DVT) and major and minor bleeding were not significantly different. The second phase of the EXULT trial randomized an additional 2300 patients and showed superior efficacy of ximelagatran (36 mg bid) as compared to adjusted-dose warfarin.[2]

The THRIVE treatment trial evaluated ximelagatran as initial treatment for acute VTE. Ximelagatran was administered as a fixed oral dose and without laboratory monitoring or dose adjustment. In the trial, 2489 patients with acute DVT (~35% with associated pulmonary embolism) were randomly assigned to either ximelagatran 36 mg twice daily or enoxaparin 1 mg/kg subcutaneously twice daily (5-20 days) followed by warfarin (INR 2.0-3.0).[3] After 6 months of therapy, the cumulative incidence of recurrent VTE was 2.0% in the enoxaparin/warfarin group and 2.1% in the ximelagatran group. Major bleeding and all-cause mortality were 2.2% and 3.4%, respectively, in the enoxaparin/warfarin group, and 1.3% and 2.3% in the ximelagatran group. In the THRIVE III trial, 1233 VTE patients who had completed 6 months of conventional anticoagulation therapy were randomized to ximelagatran (24 mg twice daily) or placebo for an additional 18 months.[4] Among the 612 patients receiving ximelagatran, 12 developed recurrent VTE. In contrast, 71 of the 611 patients receiving placebo developed recurrent VTE (hazard ratio 0.16; $p < 0.001$). All-cause mortality, and major and minor bleeding rates did not differ significantly between the two groups.

The SPORTIF trials were designed as non-inferiority trials comparing ximelagatran (36 mg bid) with adjusted-dose warfarin (INR 2-3) for the prevention of stroke in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. In the open-label SPORTIF III, which included 3467 patients, the intention-to-treat event rate was not significantly different between the two groups (1.6% per year with ximelagatran and 2.3% per year with warfarin).[5] In the double-blind SPORTIF V trial, the incidence of stroke and systemic embolism were also similar (1.6% per year with ximelagatran and 1.2% per year with warfarin).[6] The rates of major bleeding in the ximelagatran and warfarin arms were not significantly different in the two trials.

A New Drug Application (NDA) was filed in the US for ximelagatran for the indications of DVT prophylaxis following total knee replacement, secondary prophylaxis of VTE after intial anticoagulant therapy, and stroke prevention in atrial fibrillation. It had been recognized that approximately 6% of patients treated with ximelagatran for more than 2 months in the clinical trials developed a tran-

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sient increase in alanine aminotransferase (ALT).[7] While this was usually asymptomatic and reversible whether or not ximelagatran was continued, a small number of patients exhibited a concomitant increase in bilirubin and there was at least 1 case of definite hepatotoxicity. Because of concerns about hepatotoxicity, the FDA denied approval of ximelagatran in 2004; the review also raised other issues related to the design and interpretation of the results of several of the studies and the potential for an increased risk of coronary events following the discontinuation of ximelagatran after major orthopedic surgery (**Table 3**). In the atrial fibrillation trials, the relatively low frequency of thromboembolic events in the warfarin comparator arm coupled with the need to choose an appropriate non-inferiority margin will mandate the inclusion of considerably larger number of patients with atrial fibrillation in trials of other new oral anticoagulants for this indication. While a regimen of ximelagatran along with subcutaneous melagatran in the perioperative period had previously been approved in Europe for the short-term prophylaxis of DVT following major orthopedic surgery, the drugs were removed from the market in 2006. The ximelagatran program nevertheless provided an important "proof of principle" in demonstrating that fixed doses of an oral anticoagulant without routine coagulation monitoring can be as efficacious in preventing thrombosis and as safe with respect to major bleeding as warfarin in adults with satisfactory renal function. This strategy is being used in clinical trials of other oral direct thrombin and factor Xa inhibitors, which have high oral bioavailability and a wide therapeutic window.

Dabigatran Etexilate

Dabigatran etexilate is an oral prodrug that is converted to dabigatran, an oral thrombin inhibitor that is most advanced in clinical development. The plasma half-life of dabigatran is 14-17 hours, allowing for once-daily dosing, and elimination is primarily via renal excretion. The bioavailability of dabigatran etexilate following oral administration is only ~4-5%. The efficacy and safety of dabigatran etexilate have been evaluated in a phase II study in patients undergoing total hip and knee replacement.[8] Dabigatran etexilate is currently being evaluated in large phase III clinical trials for the prevention and treatment of VTE and for stroke prevention in atrial fibrillation. The RE-MOBILIZE (2600 patients) and RE-MODEL (2000 patients) trials are DVT prophylaxis trials following total knee replacement, while the RE-NOVATE trial (3415 patients) has been carried out in patients undergoing total hip replacement. The comparator in these trials, which were powered for noninferiority, is enoxaparin, and enrollment has been completed. About 4500 patients are currently being entered into the double-blind RE-COVER (2550 patients) and RE-MEDY (2000 patients) trials, which are comparing dabigatran versus warfarin for the treatment and secondary prevention of symptomatic VTE, respectively. The Re-LY trial is investigating dabigatran versus warfarin for preventing stroke and systemic embolic events in patients with atrial fibrillation and plans to enroll 15,000 patients.

Table 3. US Food and Drug Administration (FDA) Action Letter on Ximelagatran.

Safety Concerns	Efficacy Concerns
Elevated hepatic enzymes	Clinical significance of endpoints (orthopedic surgery)
Increased risk for coronary events (orthopedic surgery)	Choice of comparator (EXULT orthopedic surgery trials, THRIVE IIII secondary VTE prevention trial)
	Choice of non-inferiority margin (SPORTIF program in atrial fibrillation)
	Validity of SPORTIF III results in atrial fibrillation (open label trial)

Factor Xa Inhibition

Factor Xa is an attractive target for the design of new anticoagulants as factor Xa is positioned at the start of the common pathway of coagulation. As the amount of serine protease is amplified at each step of the cascade, it has been hypothesized that the selective inhibition of coagulation factors above thrombin might be a highly effective antithrombotic strategy. Furthermore, by not inhibiting thrombin activity directly, such agents might allow traces of thrombin to escape neutralization, thereby facilitating hemostasis and leading to a favorable safety profile with respect to bleeding.

Synthetic Pentasaccharides

Fondaparinux is the first selective factor Xa inhibitor to receive FDA approval for the prevention and treatment of VTE. Fondaparinux is a single entity (1728 daltons) that is obtained by chemical synthesis. It is a pentasaccharide, which rapidly binds only to antithrombin in the blood. Fondaparinux induces a critical conformational change in antithrombin that increases the affinity of antithrombin for factor Xa, potentiating the natural inhibitory effect of antithrombin against factor Xa by a factor of about 300.[9] Once antithrombin binds to factor Xa, a further conformational change releases fondaparinux unchanged from its binding site. Once fondaparinux is released, it can catalyze the binding of further antithrombin molecules to factor Xa. Each molecule of fondaparinux can therefore bind consecutively to several molecules of antithrombin. Once the covalent complex between factor Xa and antithrombin has been formed, the enzyme-inhibitor complex is then cleared from the circulation.

The selective action of fondaparinux toward factor Xa contrasts with the action of unfractionated heparin and low-molecular-weight heparin, which act on a number of coagulation factors; a comparison of the properties of unfractionated heparin, low-molecular-weight heparin, and

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fondaparinux is shown in **Table 4**. Unfractionated heparin has equipotent activity against factors IIa and Xa, but also acts on factors IXa, XIa and XIIa in an antithrombin-dependent manner. Low molecular weight heparins, which are prepared by chemical or enzymatic depolymerization of unfractionated heparin, have relatively more anti-factor Xa than anti-factor IIa activity.

Idraparinux is a hypermethylated analogue of fondaparinux that binds to antithrombin with very high affinity such that the half-life of the drug is prolonged to ~80 hours. Idraparinux has been evaluated using once-weekly subcutaneous doses of 2.5 mg in the treatment of acute VTE[10] and the long-term prevention of stroke in patients with atrial fibrillation. There is no specific antidote for idraparinux, but a biotinylated form of the drug, which has a specific antidote, is currently in clinical trials.

Fondaparinux in the Prevention and Treatment of Venous Thromboembolism

The thromboprophylactic efficacy and safety of fondaparinux were studied in four multicenter prospective, randomized, double-blind, comparative studies.[11-14] Two studies, EPHESUS[11] and PENTATHLON 2000,[12] were conducted in elective hip replacement surgery patients, one (PENTAMAKS)[13] in elective major knee surgery patients and one (PENTHIFRA)[14] in patients undergoing surgery for hip fracture. In all these trials, fondaparinux was administered subcutaneously at the dose of 2.5 mg, once daily, starting 6 hours postoperatively. In the PENTATHLON 2000 and PENTAMAKS trials, fondaparinux was compared to the 30 mg twice-daily regimen of enoxaparin (starting 12 to 24 hours postoperatively) and in the two other studies, fondaparinux was compared to the 40 mg once-daily regimen of enoxaparin (starting 12 hours before surgery and followed by an injection 12 to 24 hours postoperatively). The primary efficacy outcome in all four studies was VTE up to day 11 after surgery.

The EPHESUS study enrolled 2309 patients undergoing hip replacement surgery.[11] Fondaparinux reduced the incidence of venous thromboembolism from 9.2% with enoxaparin to 4.1%, a relative risk reduction of 55.9% ($p < 0.001$). A total of 2275 hip replacement surgery patients was recruited in the PENTATHLON 2000 study.[12] Among the patients evaluable for primary efficacy, 6.1% in the fondaparinux group and 8.3% in the enoxaparin group developed VTE, a relative risk reduction of 26.3% ($p = 0.099$). In the PENTHIFRA study, 1711 patients undergoing surgery for fracture of the upper third of the femur were recruited.[14] The incidence of VTE by day 11 was 8.3% in the fondaparinux group and 19.1% in the enoxaparin group, a relative risk reduction of 56.4% ($p < 0.001$). In the EPHESUS, PENTATHLON 2000, and PENTHIFRA trials, there was no difference between the groups receiving fondaparinux or enoxaparin in the incidence of major bleeding or death.

The PENTAMAKS trial,[13] performed in patients undergoing knee replacement surgery, involved 1049 patients. The incidence of venous thromboembolism was 12.5% and 27.8% in the fondaparinux and enoxaparin groups, respectively. Fondaparinux significantly reduced the incidence of VTE compared with enoxaparin, with a relative risk reduction of 55.2% ($p < 0.001$). There were 11 major bleeding episodes in the fondaparinux group (including 9 episodes of overt bleeding with a bleeding index of two or more) and 1 in the enoxaparin group ($p = 0.006$), but there were no significant differences between the two groups in the incidence of bleeding leading to death or reoperation or occurring in a critical organ.

A meta-analysis of the four studies was performed.[15] Overall, 7344 patients undergoing major orthopedic surgery of the lower limbs were randomized into the four phase III studies. Their ages ranged from 18 to 101 years and their body weight varied from 30 to 226 kg. Fondaparinux reduced the incidence of VTE by day 11 from 13.7% in the

Table 4. Comparative properties of unfractionated heparin, low molecular weight heparins (LMWH), and fondaparinux.

	Unfractionated Heparin	LMWH	Fondaparinux
Source	Animal	Animal	Synthetic
Structure	Heterogeneous	Heterogeneous	Homogeneous
Targets	Multiple	Multiple	Single (factor Xa)
Pharmacologic Effect	Activity expressed as IU (anti-Xa = anti-IIa)	Activity expressed as IU (anti-Xa > anti-IIa)	Activity expressed gravimetrically as μg or μmol
Administration	Intravenously or two to three times daily, subcutaneously	One to two times daily subcutaneously	Once daily subcutaneously
HIT Response	—	~80% crossreactivity with heparin-induced thrombocytopenia (HIT) antibodies	No crossreactivity with HIT antibodies
Bioavailability	Variable	High	High
Half-life	Dose-dependent ~1-1.5 hours (IV)	~4 hours	~17 hours
Mode of Excretion	Reticuloendothelial, urinary	Urinary	Urinary
Antidote	Protamine sulfate	Protamine sulfate (partial neutralization)	None

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enoxaparin-treated group to 6.8%, an odds reduction of 55.2%; for proximal DVT, fondaparinux led to an odds reduction of 57.4%. The incidences of fatal and non-fatal pulmonary embolism up to day 49 were low (< 1%) and did not differ between the two groups. However, the incidence of symptomatic events during follow-up in these studies and other DVT prophylaxis studies should be interpreted with caution because most patients who had a positive venogram will usually be treated with therapeutic doses of anticoagulants. In addition, about 40% of the patients who were free of VTE in the trials at day 11 received extended prophylaxis with low-molecular-weight heparins or vitamin K antagonists during extended follow-up. Safety analysis showed that there were more adjudicated episodes of major bleeding in the fondaparinux group (2.7%) than in the enoxaparin group (1.7%). In both treatment groups, major bleeding occurred mostly within the first 5 days after surgery. The difference in major bleeding between the two treatment groups was mainly accounted for by an excess of bleeding with a bleeding index of two or more. Minor bleeding events occurred in 3.0% of patients in the fondaparinux group and in 2.7% in the enoxaparin group.

In the phase III trials of fondaparinux in major orthopedic surgery, fondaparinux was to be initiated 6 ± 2 hours postoperatively. A *post-hoc* analysis of the phase III trials showed that in patients who received the first injection of fondaparinux at 6 hours or more after skin closure, the incidence of VTE was comparable to that observed in patients who received this injection less than 6 hours after skin closure ($p = 0.57$). In contrast, the incidence of major bleeding was significantly lower when the first injection was given at 6 hours or more after skin closure (2.1%) rather than earlier (3.2%). Based on these observations, the FDA-approved product label recommends initiating fondaparinux treatment at least 6 hours after orthopedic surgery. Fondaparinux is cleared by the kidneys and is contraindicated in patients with creatinine clearance less than 30 mL/min.

In patients undergoing total hip replacement, the efficacy of thromboprophylaxis with low-molecular-weight heparin for up to 4 weeks after surgery has been well established. In the PENTHIFRA-Plus trial, after an initial one-week prophylaxis with fondaparinux, 656 hip fracture surgery patients were assigned to an additional 3 weeks of treatment with a once-daily subcutaneous injection of either 2.5 mg of fondaparinux or placebo.[16] Fondaparinux reduced the incidence of VTE from 35.0% in the placebo group to 1.4% (3/208 patients), a relative risk reduction of 95.9% ($p < 0.001$). The incidence of symptomatic VTE was also significantly lower with fondaparinux (0.3%) than with placebo (2.7%). Although there was a trend toward more major bleeding in the fondaparinux group (2.4%, 8 patients) compared with placebo (0.6%), no fatal bleeding or bleeding in a critical organ occurred in either treatment group.

The PEGASUS Trial compared prophylaxis with dalteparin 5000 units once daily (2500 units started preoperatively and 6 hours postoperatively) to fondaparinux 2.5 mg once daily (started 6 hours postoperatively) in high-risk patients undergoing abdominal surgery.[17] The two regimens had comparable efficacy and safety; in a subgroup of patients with malignancy, fondaparinux was significantly more efficacious in preventing venous thrombosis.

In patients presenting with acute DVT or pulmonary embolism, the MATISSE-DVT[18] and MATISSE-PE[19] trials showed that initial therapy with fondaparinux once daily was at least as efficacious and safe as low molecular weight heparin or intravenous unfractionated heparin. In these studies, the fondaparinux dose was 7.5 mg for patients weighing 50-100 kg, 5 mg for those weighing less than 50 kg, and 10 mg for those weighing more than 100 kg.

Fondaparinux is FDA approved for the prevention of VTE following hip fracture surgery, total hip replacement, total knee replacement, and major abdominal surgery. It is also approved for the initial treatment of patients with DVT and pulmonary embolism.

Fondaparinux in Acute Coronary Syndromes

Phase II trials of adequate size were performed to determine the optimal dose of fondaparinux for the prophylaxis of VTE following major orthopedic surgery[20] and the treatment of DVT.[21] A phase II trial of fondaparinux in unstable angina (PENTUA) showed that the dose used for prophylaxis following major surgery was as efficacious as the higher doses used to treat VTE.[22] This study provided the fondaparinux dose that was used in the Organization to Assess Strategies for Ischaemic Syndromes (OASIS) 5 and 6 trials.

The OASIS 5 study evaluated the efficacy of fondaparinux versus enoxaparin in the acute treatment of patients with unstable angina/non-ST-segment elevation myocardial infarction, with regard to the incidence of death, myocardial infarction, and refractory ischemia as well as safety as defined by the incidence of major bleeds.[23] Fondaparinux (2.5 mg once daily) was as effective as enoxaparin (1 mg/kg bid) for the primary composite efficacy endpoint at 9 days (5.8% and 5.7%, respectively), but was associated with a 48% reduction in major bleeding at 9 days ($p < 0.001$). This reduction in bleeding is due to the dose and/or properties (i.e., absence of anti-factor IIa activity) of fondaparinux as compared to low-molecular-weight heparin. At 30 days, there was a significant reduction in mortality in the fondaparinux arm (2.9% vs 3.5%, $p = 0.02$), which was maintained at 6 months. The OASIS 6 study evaluated the efficacy of fondaparinux versus standard therapy (unfractionated heparin or placebo) in patients with ST-segment elevation myocardial infarction.[24] Treatment with fondaparinux (2.5 mg once daily) reduced the risk of death or recurrent myocardial infarction by 14% at day 30 (9.7% versus 11.2%, $p = 0.0008$). The incidence of major bleeding was similar in the fondaparinux and standard therapy arms.

The results of the OASIS 5 and 6 clearly demonstrate the efficacy and safety of "prophylactic" doses as com-

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pared to therapeutic doses of enoxaparin or unfractionated heparin in a broad group of patients with ACS. The data from OASIS 5 suggest that anticoagulant-related bleeding can lead to a subsequent increase in recurrent coronary ischemic events and death. It was, however, noted that there was an increased incidence of catheter thrombosis in fondparinux-treated patients undergoing percutaneous coronary interventions. This will likely impact on the use of fondaparinux in acute coronary syndrome patients requiring urgent revascularization procedures.

Oral Factor Xa Inhibition

The clinical studies using fondaparinux demonstrated that selective inhibition of factor Xa is a highly effective approach to the prevention and treatment of venous thromboembolism as well as the management of acute coronary syndromes. This has given impetus to developing oral direct factor Xa inhibitors for the prevention and treatment of patients of thrombosis. It should, however, be noted that these agents inhibit factor Xa within the assembled prothrombinase complex as well as free factor Xa, while fondaparinux is only able to inhibit the pool of free factor Xa in the blood.

The oral direct factor Xa inhibitors that are in clinical development include rivaroxaban (BAY 59-7939), apixaban (BMS), YM150 (Astellas), DU-176b (Daiichi), LY517717 (Lilly), and PRT054021 (Portola). Rivaroxaban (Bay 59-7939) is a non-peptidic, orally bioavailable, small molecule that directly inhibits factor Xa. It has a rapid onset of action and a half-life of 5-9 hours. The ODIXa-KNEE and ODIXA-HIP were phase II multicenter, parallel group, double-blind dose-ranging studies in patients undergoing total hip and total knee replacement, respectively.[25,26] These studies investigated a 12-fold dose range of rivaroxaban (total daily dose 5-60 mg) given twice daily in patients undergoing total hip (N = 722) and total knee (N = 621) replacement; an additional phase II study in patients undergoing total hip replacement investigated an 8-fold dose range of rivaroxaban given once daily (N= 873). Total rivaroxaban daily doses of 5-20 mg had similar safety and efficacy to enoxaparin for the prevention of VTE following major orthopedic surgery. A dose of 10 mg administered once daily starting 6 hours after surgery is the dose undergoing evaluation in the large phase III RECORD program, which includes two double-blind studies in total hip replacement and two in total knee replacement. The trials will include over 10,000 patients, and the comparator anticoagulant in all four studies is enoxaparin. One of the studies in patients undergoing total hip replacement will evaluate the efficacy of 5 weeks of rivaroxaban prophylaxis versus 10-14 days of enoxaparin. Phase II trials of rivaroxaban in the treatment of VTE have been completed; phase III studies for this indication and stroke prevention in atrial fibrillation have been initiated.

Summary

Selective inhibitors of specific coagulation factors represent a new class of antithrombotic agents. As compared to conventional drugs, they have the potential to be more effective, safer and easier to use. Clinical studies with the parenteral factor Xa inhibitor fondaparinux indicate that selective inhibition of factor Xa is a highly effective approach for the prevention and treatment of VTE. Other selective inhibitors of factor Xa and thrombin including a number of oral agents are currently in development. Approval of one or more of these agents will lead to an improved drug armamentarium for the prevention and treatment of thrombosis.

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