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Beyond heparin and warfarin: the new generation of anticoagulants

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Heparin and warfarin are widely used for the prevention and treatment of venous and arterial thromboembolism. Although effective, both agents have important limitations; for example, both drugs must be monitored, which is inconvenient for patients and for physicians. Heparin requires parenteral administration and can cause heparin-induced thrombocytopenia, an immune-mediated process that can lead to life-threatening thrombosis. Warfarin also has its limitations. Due to its slow onset of action, warfarin must be overlapped with heparin (or another rapidly acting anticoagulant) when treating patients with established thrombosis or who are at high risk for thrombosis. Warfarin dosing is variable because its activity is influenced by dietary intake of vitamin K, genetic polymorphisms in enzymes that are involved in its metabolism and numerous drug–drug interactions that promote or reduce its activity. New anticoagulants have been developed to overcome these problems. Building on a better understanding of coagulation pathways, advances in structure-based drug design and information derived from natural anticoagulants isolated from hematophagous organisms, most of the new anticoagulants target specific coagulation enzymes. Focussing on drugs that have at least completed Phase II evaluation, this article briefly reviews the coagulation pathways and its natural regulators; outlines the limitations of existing anticoagulants and identifies the opportunities for new ones; highlights the properties of selected new anticoagulants; describes the clinical trial results with these agents; and provides a perspective on their potential strengths and weaknesses.

Keywords: anticoagulants, arterial thromboembolism, direct thrombin inhibitors, Factor Xa inhibitors, pentasaccharides, venous thromboembolism

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1. The coagulation system

Coagulation occurs at sites of vascular injury in three overlapping stages; initiation, propagation and fibrin formation. Coagulation is initiated by tissue factor (TF), which is exposed at sites of vascular injury [1]. TF binds activated Factor VII (FVIIa) to form the TF–FVIIa complex, or extrinsic tenase, which activates FIX and FX. Activation of FX is more efficient and the resultant FXa generates small amounts of thrombin [1]. This low concentration of thrombin serves as an instigating factor to amplify coagulation by activating FVIII and FV: key cofactors for propagation of coagulation. Thrombin also activates platelets, thereby providing a negatively charged phospholipid surface onto which coagulation factors assemble and interact more efficiently. Coagulation is propagated by intrinsic tenase, the complex that forms when FIXa binds to FVIIIa on the surface of activated platelets. Intrinsic tenase amplifies FX activation and the resultant FXa then binds to FVa on the surface of activated platelets to form the prothrombinase complex. Once

incorporated into the prothrombinase complex, FXa efficiently activates prothrombin to generate a burst of thrombin [1].

In the final stage of coagulation, this burst of thrombin converts fibrinogen to fibrin. As a potent platelet agonist, thrombin also induces platelet aggregation at sites of vascular injury. Fibrin binds these platelet aggregates together to form a platelet–fibrin network. Thrombin then activates FXIII, which cross-links and stabilizes the fibrin.

2. Natural inhibitors of coagulation

Thrombosis occurs when procoagulant stimuli overwhelm natural anticoagulant and fibrinolytic systems [2]. Coagulation is regulated by the antithrombotic properties of the vessel wall, the protein C pathway, antithrombin and TF pathway inhibitor (TFPI). Endothelial cells lining the vessel wall actively resist thrombosis by generating prostacyclin and nitric oxide (NO), which are potent vasodilators and platelet inhibitors [3]. Endothelial cells also express ADPase, which degrades ADP and limits platelet recruitment at sites of injury [4]; and synthesize and release tissue plasminogen activator, which initiates fibrinolysis to degrade fibrin deposited on the endothelial cell surface [5].

The protein C pathway serves as an on-demand system for the regulation of thrombin generation. Thrombomodulin, a thrombin receptor on the vessel wall surface [6], binds thrombin and converts it from a procoagulant into a potent activator of protein C [7,8]. Along with its cofactor, protein S, activated protein C inhibits thrombin generation by inactivating FVa and FVIIIa [9]. The density of thrombomodulin is higher on small vessels than it is on larger ones. To overcome this, large vessels express more endothelial protein C receptor. This receptor promotes protein C activation by binding protein C and presenting it to the thrombin–thrombomodulin complex where it can be activated [10].

Antithrombin serves as an irreversible inhibitor of thrombin, FXa and other clotting enzymes. The activity of antithrombin is enhanced by heparan sulfate, a glycosaminoglycan found on the vessel wall [11]. Most of the heparan sulfate is located on the abluminal surface of the endothelium where it is poised to promote antithrombin activity when there is denuding injury. Glycosaminoglycans on the luminal surface of endothelial cells also bind TFPI, a bivalent inhibitor that blocks the initiation of coagulation by inhibiting TF-bound FVIIa in an FXa-dependent fashion [12]. TFPI is also found in the α -granules of platelets and is released when these cells are activated at sites of vascular injury.

Hereditary deficiencies of antithrombin, protein C or protein S are associated with venous thromboembolism (VTE), reflecting a loss of natural anticoagulant pathways. Decreased production, consumption or loss of these anticoagulant proteins in the urine can lead to acquired deficiency states. The most common cause of acquired

deficiency is consumption associated with excessive activation of coagulation. This often occurs in patients with severe sepsis. In these patients, consumption of natural anticoagulants can lead to microvascular thrombosis and subsequent organ dysfunction.

Anticoagulants are used to prevent or treat thrombosis. The present cornerstones of anticoagulant therapy are heparin, low molecular weight heparin (LMWH) and warfarin. Although effective, all of these agents have limitations.

3. Limitations of conventional anticoagulants

The first parenteral anticoagulant was heparin. The pharmacokinetic limitations of heparin include poor bioavailability following subcutaneous injection, a short half-life and an unpredictable anticoagulant response [13]. These properties reflect the propensity of heparin to bind to endothelial cells and to plasma proteins other than antithrombin. Binding to endothelial cells explains the dose-dependent clearance of intravenous heparin. At low doses, the half-life is short because heparin rapidly binds to endothelial cells. With higher doses, the half-life is longer because endothelial cell-binding sites are saturated and heparin can now enter the circulation. Once in the circulation, heparin produces an unpredictable anticoagulant response because it binds to a variety of plasma proteins, the levels of which vary between patients. One of these heparin-binding proteins is platelet factor 4 (PF4). The heparin–PF4 complex is also the antigenic target against which the antibodies that cause heparin-induced thrombocytopenia (HIT) are directed. Finally, binding of heparin to osteoblasts and subsequent alteration in the dynamic balance between osteoblastic and osteoclastic activity is likely to explain the osteoporosis that can complicate long-term heparin treatment.

Because of its pharmacokinetic limitations, heparin is usually administered by continuous intravenous infusion when used for the treatment of thrombosis and frequent monitoring is required to ensure that a therapeutic level of anticoagulation has been achieved. These features render heparin inconvenient and costly to administer.

The biophysical limitations of heparin include a reduced capacity to inhibit Factor Xa incorporated into the prothrombinase complex [14] and thrombin bound to fibrin [15]. The reduced capacity of the heparin–antithrombin complex to inhibit clotting factors sequestered within thrombi and neutralization of heparin by PF4 released from platelets may limit heparin's capability to attenuate thrombus expansion. These limitations have prompted the development of new anticoagulants.

LMWH overcomes the pharmacokinetic limitations of heparin [13]. Shorter heparin chains exhibit less binding to proteins and cells than longer chains. Consequently, LMWH has better bioavailability after subcutaneous injection, a longer plasma half-life and produces a more predictable

anticoagulant response compared with heparin. Therefore, LMWH can be administered subcutaneously on a once- or twice-daily basis and rarely requires coagulation monitoring. This renders LMWH more convenient to administer than heparin. LMWH is also safer than heparin because, with less binding to PF4 and osteoblasts, the risks of HIT and osteoporosis are lower.

When long-term anticoagulation is required, oral anticoagulants are preferred over parenteral agents. For > 60 years, the only orally available anticoagulants have been the vitamin K antagonists, such as warfarin. Although warfarin is effective, it has a slow onset of action and its activity is influenced by diet, a wide variety of drugs and common genetic polymorphisms that are involved in its metabolism [16]. Consequently, warfarin dose requirements are variable and its anticoagulant effects are unpredictable. Therefore, routine coagulation monitoring is essential to ensure that a therapeutic level of anticoagulation is maintained. Such monitoring is inconvenient for patients and physicians and is costly for the healthcare system. These limitations are highlighted by the observation that many atrial fibrillation patients who are candidates for anticoagulant therapy for stroke prevention do not receive this treatment. This unmet need has prompted the development of new oral anticoagulants that are easier to administer than warfarin. Ideally, such agents should have a rapid onset of action to obviate the need for overlap with a parenteral anticoagulant when initiating therapy, should exhibit no food or drug interactions and should possess predictable pharmacokinetics so as to permit fixed dosing without the need for monitoring. The availability of a parenteral formulation for patients who are unable to take oral medications would be helpful, as would a safe and effective antidote.

Many new anticoagulants have been developed. Evaluation of these novel agents often follows conventional pathways starting with small proof-of-concept studies followed by large clinical trials to compare the new agents with existing anticoagulants.

4. Clinical evaluation of new anticoagulants

Evaluation of new anticoagulants often starts in patients who are undergoing major orthopedic surgery because breakthrough thrombosis, which can be objectively detected by venography, is not uncommon, despite prophylaxis with available anticoagulants. Therefore, evidence of efficacy can be obtained in relatively small numbers of patients. In addition to identifying effective doses, orthopedic surgery also allows assessment of safety because excessive anticoagulation after surgery is associated with increased bleeding. Once potentially effective and safe doses of the new anticoagulant have been identified in Phase II studies, confirmatory Phase III trials can be conducted in the orthopedic setting. However, because orthopedic surgery represents a limited market for new anticoagulants, the focus of development often then shifts to

the treatment of venous and/or arterial thrombosis: indications that require much larger clinical trials.

Analogs of natural anticoagulants may follow a different development pathway. These drugs are often evaluated in patients with severe sepsis based on the notion that the consumption of natural anticoagulants is a major cause of organ dysfunction in this setting. This hypothesis can be tested by examining the effect of these agents on mortality in sepsis patients.

Focussing primarily on new anticoagulants that have at least completed one Phase II trial, the authors have listed new agents according to the step in coagulation that they inhibit (Figure 1).

5. New anticoagulants

5.1 Inhibitors of initiation of coagulation

Drugs that target the TF–FVIIa complex include parenteral agents, such as tifacogin, nematode anti-coagulant peptide (NAPc2) and active site-blocked FVIIa (FVIIai). Orally active FVIIa inhibitors have yet to reach Phase II clinical testing.

5.1.1 Tifacogin

Expressed in *Saccharomyces cerevisiae*, recombinant TFPI inhibits TF-bound FVIIa in a FXa-dependent fashion. Tifacogin has a half-life of minutes, which necessitates intravenous infusion, and is cleared by the liver. Despite promising Phase II data [17], a Phase III trial comparing tifacogin with placebo in patients with severe sepsis failed to demonstrate a significant reduction in all-cause mortality at 28 days [18]. An ongoing Phase III trial is comparing two different doses of tifacogin with placebo in patients with severe community-acquired pneumonia.

5.1.2 NAPc2

Originally isolated from the nematode hookworm *Ancylostoma caninum*, and now available in a recombinant format, NAPc2 binds to a noncatalytic site on FX or FXa and the FXa–NAPc2 complex then inhibits TF-bound Factor VIIa [19]. Because, unlike tifacogin, NAPc2 binds to FX as well as FXa, NAPc2 has a longer half-life. With a lower molecular weight than tifacogin, NAPc2 can be administered by subcutaneous injection and, with its half-life of 50 h, can be given on alternate days.

NAPc2 was evaluated in a Phase II dose-finding study for the prevention of VTE in patients undergoing elective knee replacement [20]. Although the results were promising, further development of NAPc2 has focussed on acute coronary syndromes (ACS). In a Phase II trial, addition of NAPc2 to the usual antithrombotic therapy in 203 patients with ACS resulted in dose-related inhibition of thrombin without an increase in clinically significant bleeding [21]. In another Phase II trial, NAPc2 3.5–10 µg/kg body weight given prior to elective coronary angioplasty seemed to suppress systemic

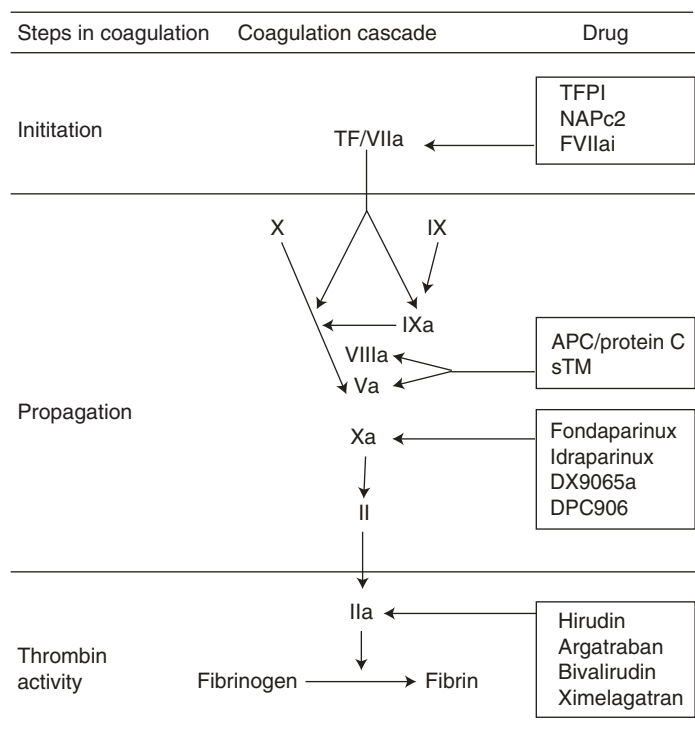


Figure 1. New anticoagulants and their targets in the coagulation pathway.

Figure modified from LINKINS L, WEITZ JI: New anticoagulants. *Semin. Thromb. Hemost.* (2003) **29**:619-631. APC: Activated protein C; sTM: Soluble thrombomodulin; TF: Tissue factor; TFPI: TF pathway inhibitor.

thrombin generation as measured by the level of prothrombin fragment 1+2 [22]. Ongoing studies are evaluating NAPc2 as a substitute for heparin in patients undergoing percutaneous coronary interventions (PCIs).

5.1.3 FVIIai

Active site-blocked FVIIa inhibits coagulation by competing with FVIIa for TF binding. As with FVIIa, FVIIai has a short half-life and is administered by intravenous infusion. FVIIai was evaluated in patients undergoing elective PCI in one small Phase II trial [23]. Compared with heparin alone, FVIIai with or without adjunctive heparin had no significant effect on the primary end point; a composite of death, myocardial infarction (MI), need for urgent revascularization, abrupt vessel closure or bailout use of glycoprotein IIb/IIIa antagonists or heparin at day 7 or at hospital discharge. Based on these results, further development of FVIIai was halted.

5.2 Inhibitors of propagation of coagulation

Propagation of coagulation is inhibited by drugs that target FIXa or FXa, or by agents that inactivate their respective cofactors, FVIIIa and FVa. The efficacy of FIXa inhibitors has yet to be proven. Agents that are under investigation include

TTP-889 (an oral direct FIXa inhibitor) and RB-006 (a Factor IXa-binding RNA aptamer whose inhibitory activity can be rapidly reversed with a complementary aptamer). TTP-889 has completed initial Phase II evaluation but the results are not yet available. RB-006, which is a parenteral agent, is undergoing Phase I evaluation at present.

A plethora of FXa inhibitors are under investigation. These agents are further subcategorized as indirect or direct inhibitors. Indirect FXa inhibitors, which act by catalyzing anti-thrombin, include fondaparinux, idraparinux and SSR-126517E. Direct FXa inhibitors, which target the active site of FXa, include parenteral inhibitors, such as DX-9065a and otamixaban, and numerous oral FXa inhibitors, including rivaroxaban, razaxaban, apixaban, LY-517717, YM-150 and DU-176b. FVIIIa and FVa can be inhibited directly by administering recombinant activated protein C (drotrecogin alfa [activated]) or by enhancing the activation of endogenous activated protein C with protein C concentrates or recombinant soluble thrombomodulin.

5.2.1 Fondaparinux

As a synthetic analog of the antithrombin-binding pentasaccharide sequence that mediates the anticoagulant activity of heparin and LMWH, fondaparinux catalyzes FXa inhibition

by antithrombin. Fondaparinux exhibits complete bio-availability following subcutaneous injection and has a half-life of 17 h. Consequently, it is administered once daily [24]. Because fondaparinux is cleared via the kidneys [25], dose reductions are necessary in patients with renal insufficiency and the drug is contraindicated in patients with renal failure. Although placental transfer of fondaparinux was not observed in a dually perfused human cotyledon model [26], limited clinical experience suggests that fondaparinux may pass the placental barrier *in vivo*, resulting in low, but measurable, anti-Xa activity in umbilical cord blood [27].

As with heparin and LMWH, fondaparinux seems to induce the formation of anti-PF4/heparin antibodies. However, with fondaparinux, these antibodies do not seem to cause HIT [28]. Thus small studies have shown no cross-reactivity of fondaparinux with sera from patients with HIT [29-32] and, based on the results of two small case series, fondaparinux may be a useful anticoagulant for HIT patients [33,34]. However, more data are needed before fondaparinux can be recommended in this setting [35].

There is no specific antidote for fondaparinux. Unlike heparin, fondaparinux is not neutralized by protamine sulfate [36]. Although recombinant FVIIa may be useful if there is uncontrolled bleeding, FVIIa is expensive, not always available and may cause thrombotic complications [37,38].

Fondaparinux is licensed for the prevention and initial treatment of VTE. In general medical patients, fondaparinux was superior to placebo for the prevention of VTE [39], whereas fondaparinux was equivalent to dalteparin in general surgery patients [40]. Recently, fondaparinux was evaluated in patients with ACS. OASIS (Organization to Assess Strategies for Ischemic Syndromes)-5, a non-inferiority double-blind trial, randomized 20,078 patients with non-ST segment elevation ACS to either fondaparinux (2.5 mg/day s.c.) or enoxaparin (1 mg/kg b.i.d. s.c.) for 2 – 8 days [41]. The primary efficacy end point, a composite of death, MI or refractory ischemia at 9 days, was similar in patients who were administered fondaparinux or enoxaparin (5.7 and 5.8%, respectively). However, the rate of major bleeding was 47% lower with fondaparinux than with enoxaparin (2.2 and 4.1%, respectively; $p < 0.001$). At 30 days, mortality was significantly lower with fondaparinux than with enoxaparin (2.9 and 3.5%, respectively; $p = 0.02$). Most of the excess deaths in the enoxaparin-treated patients occurred in those who bled, raising the possibility that bleeding or its treatment increases the risk of recurrent ischemic events.

OASIS-6, a double-blind, controlled trial, randomized 12,092 patients with ST elevation MI to fondaparinux or to usual care within 12 h of onset of symptoms [42]. Patients without an indication for heparin (such as those administered streptokinase) received fondaparinux or placebo for 8 days or until hospital discharge. Patients with an indication for heparin (i.e., those treated with tissue plasminogen activator or undergoing primary PCI) were randomized to heparin for 24 – 48 h or to fondaparinux for 8 days. Overall, the primary

end point, a composite of death or recurrent MI at 30 days, occurred in 9.7% of patients given fondaparinux and in 11.2% of those in the control groups ($p = 0.008$). The rate of major bleeding was similar in the 2 groups (1.8 and 2.1%, respectively; $p = 0.14$). Fondaparinux did not reduce death or recurrent MI in the subgroup of patients who underwent primary PCI. Based on the results of the OASIS-5 and OASIS-6 trials, fondaparinux has value in patients with ACS. However, there is a risk of catheter-associated thrombosis with fondaparinux unless adjunctive heparin is given. Therefore, fondaparinux may have limited use in ACS patients who require urgent or semi-urgent PCI.

5.2.2 Idraparinux

As a hypermethylated derivative of fondaparinux, idraparinux binds antithrombin with such high affinity that its plasma half-life is 80 h, which is similar to that of antithrombin [43]. Consequently, idraparinux is given subcutaneously on a once-weekly basis. Because of its long half-life, the lack of an antidote is of greater concern for idraparinux than it is for fondaparinux. As with fondaparinux, idraparinux is cleared by the kidneys and is contraindicated in patients with renal insufficiency.

Idraparinux has been evaluated as an alternative to warfarin for the treatment of VTE and for stroke prevention in atrial fibrillation. In a Phase II trial, 659 patients with proximal deep-vein thrombosis (DVT) were treated with LMWH for 5 – 7 days and subsequently randomized to warfarin or to 1 of 4 different doses of idraparinux for 12 weeks [44]. The primary end point, change in thrombus burden (as determined by repeated compression ultrasound and perfusion lung scanning), was similar in all of the idraparinux groups and did not differ from that in the warfarin group. However, there was a clear dose-response with respect to major bleeding in patients administered idraparinux, with an unacceptably high frequency of bleeding in those administered idraparinux 10 mg. There were 2 patients, both of whom received idraparinux 5 mg, who suffered a fatal bleed. Patients given the lowest dose of idraparinux 2.5 mg had less bleeding than those randomized to warfarin ($p = 0.029$); consequently, this dose was selected for further evaluation. Phase III trials comparing idraparinux 2.5 mg s.c. once weekly with enoxaparin or heparin followed by warfarin for the treatment of patients with DVT or pulmonary embolism (PE), respectively, have been completed, but the results have yet to be reported.

A Phase III trial comparing once-weekly subcutaneous idraparinux with warfarin for the prevention of stroke in patients with atrial fibrillation was stopped prematurely because of excess bleeding in patients randomized to idraparinux. The results of this trial have yet to be published.

5.2.3 SSR-126517E

This third-generation synthetic pentasaccharide is a biotinylated version of idraparinux. Sharing all of the

properties of idraparinux, SSR-126517E differs only in that its anticoagulant effects can be neutralized by administering recombinant avidin. Avidin, which binds biotin with high affinity, forms a 1:1 complex with SSR-126517E. These complexes are then cleared. Phase II/III trials evaluating SSR-126517E are presently underway.

5.2.4 DX-9065a

A synthetic nonpeptidic direct FXa inhibitor [45-47], DX-9065a is administered parentally, has a dose-dependent half-life that ranges from 40 min to 5 h and is cleared by the kidneys. DX-9065a was evaluated in patients with non-ST elevation ACS and in patients undergoing PCI [48,49]. In the ACS trial, 402 patients were randomized to weight-adjusted heparin, low-dose DX-9065a or high-dose DX-9065a [48]. The primary efficacy end point, a composite of death, MI, urgent revascularization or ischemia, occurred in 33.6, 34.3 and 31.3% of the patients, respectively. Major bleeding occurred in 3.3% of those randomized to heparin and in < 1% of those who received DX-9065a. In the PCI trial, 175 patients were randomized to open-label DX-9065a or heparin in 1 of 4 sequential phases [49]. Although thrombotic events were rare in all phases of the study, enrolment in the phase evaluating the lowest dose of DX-9065 was stopped after the occurrence of one thrombotic event. Major bleeding events were uncommon and there was no apparent dose-response. Although promising, DX-9065a has not undergone further clinical evaluation underscoring the current focus on orally active anticoagulants.

5.2.5 Otamixaban

A noncompetitive inhibitor of FXa, this agent is administered by subcutaneous injection and has a half-life of 2 – 3 h [50]. It is excreted unchanged in the urine, whereas metabolites appear in the feces. A Phase II study comparing otamixaban with heparin in patients undergoing PCI has been completed, but the results have not been published. Similar to DX-9065a, there seems to be little interest in continued development of this parenteral FXa inhibitor.

5.2.6 Razaxaban

Razaxaban, a nonpeptidic oral FXa inhibitor, underwent Phase II evaluation for thromboprophylaxis following knee arthroplasty [51]. The primary end point, a composite of venographically detected DVT and symptomatic VTE, occurred in 8.6% of the patients who were randomized to the lowest dose of razaxaban and in 15.9% of those who were administered enoxaparin. Major bleeding occurred in 0.7% of patients given the lowest dose of razaxaban and in none of those treated with enoxaparin. The three higher dose razaxaban arms were stopped prematurely because of increased rates of major bleeding. Because of the apparently narrow therapeutic index and some pharmacokinetic limitations, further development of razaxaban has been halted.

5.2.7 Apixaban

This agent is a variant of razaxaban that is reported to have superior pharmacologic properties. Apixaban has excellent oral bioavailability and exhibits a dual pathway of excretion that is only partly renal. Apixaban has completed Phase II testing for thromboprophylaxis in patients undergoing knee replacement surgery and is undergoing Phase II testing for the treatment of DVT.

5.2.8 Rivaroxaban

This oral FXa inhibitor is an oxazolidone derivative with a bioavailability of 60% [52]. It has a half-life of 5 – 9 h and is cleared both by the kidneys and the gut. Rivaroxaban has been evaluated for thromboprophylaxis in patients undergoing knee or hip arthroplasty in a series of Phase II trials. A pooled analysis of results from two of these studies failed to demonstrate a statistically significant dose-response for efficacy with rivaroxaban, although the point estimates for both the primary efficacy outcome (DVT, PE and all-cause mortality) and secondary efficacy outcome (proximal DVT, PE and VTE-related death) in all of the rivaroxaban dosing arms were lower than those in enoxaparin-treated controls [53]. There was a significant dose-response for major bleeding with rivaroxaban 10, 20 and 30 mg b.i.d., producing more bleeding than enoxaparin.

A follow-up, double-blind, randomized, dose-finding study in patients undergoing hip arthroplasty compared once-daily rivaroxaban (in 5 doses ranging from 5 to 40 mg started 6 – 8 h postoperatively) with enoxaparin 40 mg/day, started the evening before surgery and given postoperatively ($\geq 6 - 8$ h after skin closure) [54]. The frequencies of both the primary efficacy outcome (a composite of venographically detected DVT, symptomatic VTE and all-cause mortality) and the secondary efficacy outcome (proximal DVT, PE and VTE-related death) were lower with all but the daily dose of rivaroxaban 5 mg than with enoxaparin. Once again, there was no clear dose-response relationship for efficacy. Compared with enoxaparin, the point estimates for major bleeding were higher with rivaroxaban than with enoxaparin with all doses except 10 mg. On the basis of these results, future studies in major orthopedic surgery will use rivaroxaban 10 mg q.d. Phase III studies evaluating rivaroxaban for the prevention and treatment of VTE and for stroke prevention in atrial fibrillation are underway.

5.2.9 LY-517717

An oral FXa inhibitor that is given once-daily, LY-517717 was evaluated in a Phase II non-inferiority study that randomized 511 patients undergoing total hip or total knee replacement to 1 of 6 doses of LY-517717 (started 6 – 8 h after wound closure) or once-daily enoxaparin (started the evening before surgery) [55]. Both treatments were administered for a total of 6 – 10 doses. Randomization to the three lower doses of LY-517717 was stopped early due to a lack of efficacy. Adjudicated major bleeding events were uncommon in all of

the study arms. Additional studies are needed to determine the efficacy and safety of this agent.

5.2.10 YM-150

An oral FXa inhibitor that is given once daily, YM-150 was evaluated in 174 patients undergoing elective hip arthroplasty [56]. YM-150 produced a statistically significant dose–response for efficacy. No major bleeds were reported and there was no dose–response trend for clinically relevant non-major bleeding. Although the point estimates for VTE incidence seemed to favor the two highest doses of YM-150 over enoxaparin, the small study sample size precludes any firm conclusions. A further Phase II trial in patients undergoing elective hip arthroplasty is ongoing.

5.2.11 DU-176b

An oral FXa inhibitor, DU-176b is undergoing Phase II evaluation in hip arthroplasty patients.

5.2.12 Protein C and activated protein C

Both plasma-derived and recombinant forms of protein C are available. Present indications for the use of protein C concentrates include treatment of severe congenital protein C deficiency and sepsis. Drotrecogin alfa (activated), a parental form of recombinant activated protein C, is approved for the treatment of severe sepsis in adults with a high risk of death [57]. However, two further trials, one in adults with sepsis and a low risk of death [58] and the other in children with sepsis, were stopped prematurely due to a lack of efficacy and the potential to cause harm due to bleeding.

5.2.13 ART-123

A recombinant analog of the extracellular domain of thrombomodulin [59], ART-123 binds thrombin and converts it from a procoagulant enzyme into a potent activator of protein C. ART-123 has ~ 100% bioavailability following subcutaneous administration and a half-life of 2 – 3 days. In a Phase IIa dose-ranging study in patients undergoing elective hip arthroplasty, the primary end point (a composite of venographically detected DVT and symptomatic PE) occurred in 4.3% of the 94 patients given lower-dose ART-123 and in none of the 99 patients receiving the higher dose [60]. Major bleeding occurred in 1.6 and 5.7% of patients receiving low or high dose ART-123, respectively. As a parenteral anticoagulant, it is uncertain whether this agent will undergo further evaluation.

5.3 Thrombin inhibitors

The three new thrombin inhibitors include ximelagatran and dabigatran etexilate, which are direct thrombin inhibitors, and odiparil, which is an indirect thrombin inhibitor. Also in this category is SR-123781, a synthetic heparin mimetic. This indirect inhibitor consists of 16 saccharide units that include a synthetic pentasaccharide plus 11 additional

saccharide units. As with heparin, SR-123781 is long enough to bridge antithrombin to thrombin. Therefore, SR-123781 catalyzes the inhibition of both FXa and thrombin by antithrombin. This agent is undergoing Phase II evaluation in orthopedic patients.

5.3.1 Ximelagatran

A prodrug of melagatran, ximelagatran, is absorbed from the gastrointestinal tract with a bioavailability of 20%. Once absorbed, ximelagatran undergoes rapid biotransformation to melagatran via two intermediate metabolites, H338/57 and H415/04 [61]. Melagatran has a half-life of 4 – 5 h and is administered twice daily.

Ximelagatran has many of the properties of an ideal oral anticoagulant because it does not interact with food, has a low potential for drug interactions and produces such a predictable anticoagulant response that it does not require coagulation monitoring. Ximelagatran underwent extensive evaluation for the prevention and treatment of VTE, prevention of cardioembolic events in patients with nonvalvular atrial fibrillation and prevention of recurrent ischemia in patients with recent MI. Initial studies led to its temporary approval in Europe for thromboprophylaxis in patients undergoing major orthopedic surgery. However, the drug was not approved in North America and was eventually withdrawn from the world market because of potential hepatic toxicity. There was one death from hepatorenal failure and two other deaths from hepatic failure. Added to this was a patient who developed severe hepatic injury several weeks after receiving a 4-week course of ximelagatran for thromboprophylaxis after orthopedic surgery. AZD-0837, a follow-up compound to ximelagatran that seems to have a lower risk of hepatic toxicity, is presently undergoing Phase II evaluation.

5.3.2 Dabigatran etexilate

A double prodrug, dabigatran etexilate, is absorbed from the gastrointestinal tract with a bioavailability of 4% [62]. Absorption requires an acid microenvironment and is reduced by acid suppression therapy. Once absorbed, dabigatran etexilate is converted by esterases into its active metabolite, dabigatran (BIBR-953). Levels of dabigatran peak in 2 h and dabigatran has a half-life of 8 h after single-dose administration and ≤ 17 h after multiple doses. Consequently, it may be possible to administer dabigatran etexilate once daily for some indications. Dabigatran is excreted unchanged via the kidneys; therefore, the drug is contraindicated in patients with renal failure.

Dabigatran etexilate has been evaluated for thromboprophylaxis in patients undergoing hip or knee arthroplasty and for the prevention of stroke in patients with atrial fibrillation in Phase II trials. In the arthroplasty trial, 1973 patients were randomized to receive 1 of 4 doses of dabigatran etexilate for 6 – 10 days after surgery (with the first dose administered 1 – 4 h postoperatively) or enoxaparin 40 mg/day started 12 h prior to surgery [63]. The primary efficacy outcome was a

composite of venographically detected DVT or symptomatic VTE. The three highest dabigatran etexilate dose regimens produced a statistically significant reduction in the incidence of VTE compared with enoxaparin. However, this was balanced by a trend for more major bleeding with higher dabigatran doses than with enoxaparin.

A Phase II trial in 502 patients with atrial fibrillation compared a 3-month course of treatment with 3 different doses of dabigatran etexilate (50, 150 or 300 mg b.i.d.) or with warfarin (target international normalized ratio of 2 – 3) [64]. In a factorial fashion, patients were also randomized to aspirin (81 or 325 mg/day) or to placebo. Recruitment into the high-dose dabigatran etexilate plus aspirin arm was stopped early because of 4 gastrointestinal bleeds in 63 patients. Addition of aspirin in the other groups did not seem to increase the risk of bleeding. In the low-dose dabigatran etexilate arm, 2 of 105 patients suffered a thromboembolic event. Building on these data, 361 of the 432 patients randomized to dabigatran etexilate continued open-label treatment at doses of 50, 100 or 300 mg b.i.d. or 150 or 300 mg/day for ≥ 16 months. The 2 lowest doses of dabigatran etexilate (50 mg b.i.d. or 150 mg/day) were discontinued early because of annual stroke rates of 8.4 and 8.1%, respectively. The annual stroke rate with dabigatran etexilate 300 mg/day was 9.5%, whereas rates were lower with the other doses. Based on these data, the ongoing Phase III trial is comparing dabigatran etexilate 110 or 150 mg b.i.d. with warfarin. The cumulative frequency of elevations in alanine aminotransferase of > 3 times the upper limit of normal was 2% in patients receiving dabigatran etexilate for ≥ 12 months compared with 1% in those administered warfarin.

In addition to the study in atrial fibrillation, dabigatran etexilate is also undergoing Phase III evaluation for thromboprophylaxis after major orthopedic surgery and for the treatment of VTE.

5.3.3 Odiparcil

An oral β -D-xyloside, odiparcil primes the synthesis of circulating dermatan sulfate-like glycosaminoglycans [65]. These glycosaminoglycans indirectly inhibit thrombin by catalyzing heparin cofactor II. Steady-state levels of glycosaminoglycans are achieved after 2 – 3 days of odiparcil administration. Therefore, as with warfarin, odiparcil has a delayed onset of action. In contrast to warfarin, the anticoagulant activity of odiparcil is partially reversed with protamine sulfate. Odiparcil has been compared with warfarin for thromboprophylaxis in patients undergoing knee arthroplasty but the results of this Phase II trial have not been reported.

6. Expert opinion

The greatest unmet need in anticoagulation therapy is the replacement of warfarin with an orally active agent that can be given in fixed doses without routine coagulation monitoring. Consequently, most of the present attention has focussed on

new oral anticoagulants (Table 1). Those in the most advanced stages of development are the oral direct thrombin or Factor Xa inhibitors.

Which is the best target for new oral anticoagulants? By blocking thrombin activity, thrombin inhibitors attenuate fibrin formation and thrombin-mediated platelet activation. However, Factor Xa inhibitors also affect these processes by impairing thrombin generation. Therefore, the net effect of blockade at the level of Factor Xa or thrombin is reduced fibrin formation.

We do not yet know whether upstream inhibition is any safer than downstream blockade at the level of thrombin. Studies with ximelagatran validate thrombin as a target for new anticoagulants. In addition, these trials demonstrate that fixed dosing and no coagulation monitoring are achievable properties for new oral agents. The unexpected hepatic toxicity was the downfall for ximelagatran. At present, it is unclear whether the hepatic liability is unique to ximelagatran or whether it represents a class effect. Ongoing studies with dabigatran etexilate and the oral Factor Xa inhibitors will clarify this issue.

Emerging results from clinical trials with fondaparinux confirm the concept that Factor Xa is also a good target for new anticoagulants. Although the use of Factor Xa inhibitors for thromboprophylaxis was expected, the clinical trial data with fondaparinux indicate that Factor Xa inhibitors are also effective for the treatment of established thrombosis. Therefore, thrombin inhibition is not essential when treating thrombosis, provided that ongoing thrombin generation is interrupted.

A large number of oral Factor Xa inhibitors are now in Phase II trials and several have moved on to Phase III. Dose-finding studies in orthopedic patients suggest that these agents are effective. However, as with oral thrombin inhibitors, the Factor Xa inhibitors also produce a dose-dependent increase in bleeding. Therefore, there is no evidence that Factor Xa inhibitors cause less bleeding than thrombin inhibitors as yet. Direct head-to-head comparisons will be needed to evaluate the relative benefit:risk ratios of the two classes of agents. Such studies are unlikely to be conducted for many years. In the interim, parallel clinical trial programs will assess the use of oral direct thrombin or Factor Xa inhibitors for the prevention and treatment of VTE and arterial thromboembolism.

The lack of specific antidotes remains a challenge for the new anticoagulants. This is particularly problematic for drugs with a long half-life, such as idraparinix. Development of a biotinylated version of idraparinix may overcome this limitation provided that avidin, the antidote, is readily available.

With the plethora of new anticoagulants under development, we are at the beginning of a new era in anticoagulation therapy. In addition to assessing antithrombotic efficacy and hemorrhagic potential, the experience with ximelagatran mandates careful attention to off-target side effects, particularly hepatic toxicity. Although the increased

Table 1. The new generation of oral anticoagulants.

Drug	Type of inhibitor	Target	Indication	Status
TTP-889	Direct	FIXa	Thromboprophylaxis post-hip fracture surgery	Phase II
Razaxaban	Direct	FXa	Thromboprophylaxis post-knee arthroplasty	Halted after Phase II
Apixaban	Direct	FXa	Thromboprophylaxis post-knee arthroplasty Treatment of VTE	Phase II Phase II
Rivaroxaban	Direct	FXa	Thromboprophylaxis post-knee or -hip arthroplasty Treatment of VTE Atrial fibrillation	Phase III Phase III Phase III
LY-517717	Direct	FXa	Thromboprophylaxis post-knee or -hip arthroplasty	Phase II
YM-150	Direct	FXa	Thromboprophylaxis post-hip arthroplasty	Phase II
DU-176b	Direct	FXa	Thromboprophylaxis post-hip arthroplasty	Phase II
Ximelagatran	Direct	Thrombin	Thromboprophylaxis post-knee or -hip arthroplasty Treatment of VTE Atrial fibrillation	Halted after Phase III
Dabigatran etexilate	Direct	Thrombin	Thromboprophylaxis post-knee or -hip arthroplasty Treatment of VTE Atrial fibrillation	Phase III Phase III Phase III
Odiparcil	Indirect	Thrombin	Thromboprophylaxis post-knee arthroplasty	Phase II

F: Factor; VTE: Venous thromboembolism.

scrutiny required by regulatory agencies complicates ongoing drug development, it will help to ensure safety. The next few years will determine which class of new anticoagulant is the first to market.

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Disclosure

J Weitz is a consultant for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, The Medicines Company, Bayer, Schering-Plough and Merck.

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