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REVIEW ARTICLE

New anticoagulants

J. I. WEITZ*† and S. M. BATES*
*Departments of *Medicine and †Biochemistry, McMaster University, and the Henderson Research Centre, Hamilton, Ontario, Canada*

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Summary. The limitations of heparin and warfarin have prompted the development of new anticoagulant drugs for prevention and treatment of venous and arterial thromboembolism. Novel parenteral agents include synthetic analogs of the pentasaccharide sequence of heparin that mediates its interaction with antithrombin. Fondaparinux, the first synthetic pentasaccharide, is licensed for prevention of venous thromboembolism (VTE) after major orthopedic surgery and for initial treatment of patients with VTE. Idraparinux, a long-acting pentasaccharide that is administered subcutaneously once-weekly, is being compared with warfarin for treatment of VTE and for prevention of cardioembolic events in patients with atrial fibrillation. New oral anticoagulants include direct inhibitors of thrombin, factor Xa and factor IXa. Designed to provide more streamlined anticoagulation than warfarin, these agents can be given without routine coagulation monitoring. Ximelagatran, the first oral direct thrombin inhibitor, is as effective and safe as warfarin for prevention of cardioembolic events in patients with atrial fibrillation. However, ximelagatran produces a three-fold elevation in alanine transaminase levels in 7.9% of patients treated for more than a month, the long-term significance of which is uncertain. Whether other direct thrombin inhibitors or inhibitors of factors Xa or IXa also have this problem is under investigation. After a brief review of coagulation pathways, this paper focuses on new anticoagulants in advanced stages of clinical testing.

Keywords: anticoagulant, antithrombotic, arterial thromboembolism, direct thrombin inhibitor, pentasaccharide, venous thromboembolism.

Introduction

Currently available parenteral anticoagulants include heparin, low-molecular-weight heparin (LMWH) and fondaparinux. LMWH is gradually replacing heparin for treatment of most patients with venous thromboembolism (VTE) and acute coronary syndromes because LMWH has similar efficacy but is more convenient and cost-effective than heparin in these patients [1–5]. Although its niche is more limited than that of LMWH, fondaparinux also is more convenient to administer than heparin and is licensed for VTE prevention in patients undergoing surgery for hip fracture or hip or knee replacement and for initial VTE treatment. Despite advances with LMWH and fondaparinux, however, there remains a need for more potent parenteral anticoagulants. For long-term use, there also is a need for safer oral anticoagulants that do not require routine coagulation monitoring. Coumarin derivatives, the only oral anticoagulants now available, have a narrow therapeutic window because their metabolism is under genetic control and is influenced by dietary factors and concomitant medications [6]. Consequently, time-consuming and expensive monitoring is essential to ensure that a therapeutic anticoagulant effect is achieved.

New anticoagulants target specific steps in coagulation. This paper (a) presents a simplified view of the coagulation system and highlights the targets of new anticoagulants, (b) reviews the pharmacology of the new agents, (c) describes the results of clinical trials with drugs in advanced stages of clinical development, and (d) provides clinical perspective as to the opportunities and challenges for the various new anticoagulants.

Correspondence: Jeffrey I. Weitz, Henderson Research Centre, 711 Concession Street, Hamilton, Ontario L8V 1C3, Canada.
Tel.: +1 905 574 8550; fax: +1 905 575 2646; e-mail: jweitz@thrombosis.hhscr.org

Coagulation system

The coagulation system can conveniently be divided into three stages, initiation, propagation and fibrin formation, each of which will be briefly discussed.

Initiation

The coagulation system is triggered by the tissue factor (TF)/factor VIIa (FVIIa) complex, which forms at sites of vascular injury (Fig. 1). With severe injury, TF-expressing cells in the subendothelium of veins or in the lipid-rich core of atherosclerotic plaques are exposed to the blood when the endothelial lining is disrupted. Exposed TF binds FVIIa, small amounts of which are found in plasma.

Circulating TF also can be targeted to sites of non-denuding endothelial injury (Fig. 1) as TF-expressing monocytes or microparticles become tethered to the endothelium in an interaction mediated by the binding of P-selectin glycoprotein ligand (PSGL-1) on the surface of leukocytes or leukocyte-derived microparticles to P-selectin expressed on the surface of activated endothelial cells [7, 8]. If the endothelial injury is sufficient to induce platelet activation and aggregation,

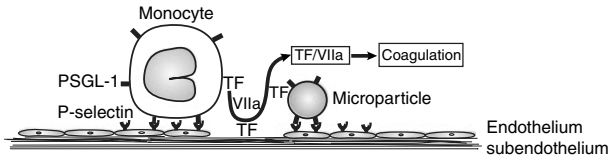

Fig. 1. Initiation of coagulation. Coagulation is initiated by the TF/FVIIa complex that forms at sites of vascular injury. Endothelial denudation exposes TF-expressing cells in the subendothelium. Circulating TF is targeted to sites of non-denuding vascular injury because activated endothelial cells express P-selectin on their surface, which binds PSGL-1 on TF-expressing monocytes or leukocyte-derived microparticles.

additional TF accumulates when TF-expressing microparticles bind to P-selectin on the surface of activated platelets [9]. Regardless of its source, TF binds FVIIa to form extrinsic tenase, which activates FIX and FX, although FX activation is more efficient [10]. FXa then converts small amounts of prothrombin to thrombin. This low concentration of thrombin is sufficient to amplify coagulation by activating factors V and VIII (key cofactors in coagulation), platelets, and platelet-bound factor XI.

Propagation

Coagulation is propagated when FIXa binds to FVIIIa on the surface of activated platelets to form intrinsic tenase, the complex that efficiently activates FX. FXa binds to factor Va on the activated platelet surface to form prothrombinase, the complex that converts prothrombin to thrombin. Activation of platelet-bound FXI by thrombin also promotes FXa generation [10].

Fibrin formation

In the final step of coagulation, thrombin converts fibrinogen to fibrin. Thrombin also activates factor XIII, which cross-links and stabilizes the fibrin network.

New anticoagulants

New anticoagulant drugs target specific steps in coagulation (Fig. 2). In general, anticoagulant strategies that inhibit thrombogenesis focus on blocking initiation of coagulation, preventing thrombin generation by attenuating the propagation of coagulation, or by reducing fibrin formation by inhibiting thrombin. Initiation of coagulation can be inhibited by agents that target the TF/FVIIa complex, whereas thrombin generation can be blocked by drugs that target FIXa or Xa, or by inactivation of FVa or VIIIa. Thrombin inhibitors not only prevent fibrin formation, but also block thrombin-mediated feedback activation of FV, VIII, and XI, and attenuate thrombin-induced platelet aggregation.

Inhibitors of initiation of coagulation

Because the TF/FVIIa complex initiates thrombosis [10], drugs that target this complex are potent inhibitors of coagulation.

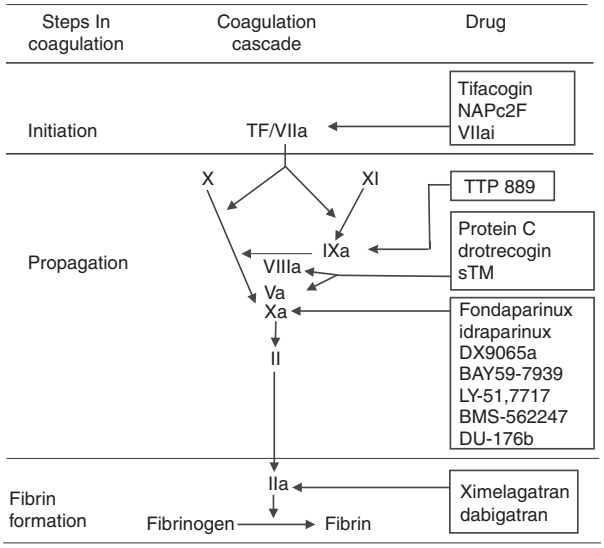

Fig. 2. New anticoagulants and their targets in the coagulation pathway.

Agents in the most advanced stage of development are recombinant tissue factor pathway inhibitor (TFPI), nematode anticoagulant peptide (NAPc2), and active site-blocked FVIIa (FVIIai).

TFPI

Based on studies in animals demonstrating that TFPI attenuates the coagulopathy and improves survival in sepsis models [11–13], a recombinant form of TFPI (tifacogin) has been evaluated for this indication in humans. With promising Phase II data [14], TFPI was compared with placebo in a Phase III clinical trial in 1754 patients with severe sepsis [15]. The primary endpoint, all-cause mortality at 28 days, was similar in both groups (34.2% and 33.9% with tifacogin and placebo, respectively) and the rate of bleeding was significantly higher with tifacogin than with placebo (6.5% and 4.8%, respectively). The utility of tifacogan is currently being evaluated in patients with community-acquired pneumonia.

NAPc2

An 85-amino acid anticoagulant protein isolated from the nematode, *Ancylostoma caninum*, NAPc2 binds to a non-catalytic site on both FX and FXa and inhibits FVIIa within the TF/FVIIa complex [16]. Functionally, therefore, NAPc2 behaves much like TFPI. Because NAPc2 binds to FX, as well as FXa, it has a half-life of almost 50 h after subcutaneous injection. Consequently, NAPc2 can be given on alternate days.

In a phase II study, NAPc2 showed promise in preventing VTE after elective knee replacement surgery [17]. However, prospective randomized trials are needed to compare the efficacy and safety of NAPc2 with those of anticoagulants currently approved for this indication. Currently, a series of phase II studies are underway to evaluate the utility of NAPc2

in patients with unstable angina or non-ST-elevation myocardial infarction (MI) and in those undergoing percutaneous coronary interventions (PCI). In these trials, NAPc2 is added to routine therapy that includes aspirin, clopidogrel, heparin or LMWH and, in some cases, a glycoprotein (GP)IIb/IIIa antagonist. The hemorrhagic consequences of adjunctive NAPc2 in these settings remain to be established and the long half-life of NAPc2 may be problematic if patients require urgent coronary artery bypass surgery.

FVIIai

By competing with FVIIa for TF binding, FVIIai, an inactivated form of FVIIa, serves as a competitive inhibitor of TF-dependent FIX or FX activation. Based on promising preclinical studies in which FVIIai infusion prevented thrombus formation on artificial surfaces or injured vasculature [18–23], FVIIai, with or without adjunctive heparin, was compared with heparin alone in a Phase II study of patients undergoing PCI [24]. There was no significant difference between the two groups in the primary endpoint, a composite of death, MI, need for urgent revascularization, abrupt vessel closure, or bailout use of GPIIb/IIIa antagonists or heparin at day 7 or hospital discharge. Further, rates of major bleeding were similar in patients receiving FVIIai or heparin. Because of these disappointing results, FVIIai has not been developed further for the treatment of arterial thrombosis.

Inhibitors of propagation of coagulation

Drugs that block FIXa or Xa, or their respective cofactors, FVIIIa and FVa, inhibit the propagation of coagulation. By so doing, these agents attenuate thrombin generation.

Factor IXa inhibitors

Factor IXa is essential for amplification of coagulation [25]. Parenteral agents that block FIXa activity include active site-blocked FIXa (FIXai), which competes with FIXa for incorporation into the intrinsic tenase complex that assembles on the surface of activated platelets, and monoclonal antibodies against FIX/IXa. FIXai inhibits clot formation *in vitro* and has been shown to attenuate injury-induced coronary artery thrombosis in a canine model [26]. A chimeric-humanized derivative of an antibody against FIX/IXa that inhibits FXI-mediated activation of FIX and blocks FIXa activity has demonstrated antithrombotic activity in rat arterial thrombosis models [27–29]. TPP-889, an orally active FIXa inhibitor, has completed phase I clinical testing, but neither it nor the parenteral FIXa inhibitors have reached phase II evaluation.

Factor Xa inhibitors

New FXa inhibitors include agents that block FXa indirectly or directly. The former catalyze FXa inhibition by antithrombin. In contrast, direct FXa inhibitors bind directly to the active site of FXa, thereby blocking its interaction with its substrates. Unlike the heparin/antithrombin complex, direct FXa inhibitors not only inhibit free FXa, but also inactivate FXa bound to platelets within the prothrombinase complex [30–32]. This property might provide these agents with an advantage over indirect FXa inhibitors. Synthetic pentasaccharides (fondaparinux and idraparinux), analogs of the pentasaccharide sequence of heparin that mediates its interaction with antithrombin [33,34], are new indirect FXa inhibitors that are administered parentally. A parenteral (DX9065a) and several orally active direct FXa inhibitors (BAY 59-7939, LY-51, 7717, BMS-562247 and DU-176b) are currently undergoing phase II clinical testing. Of these new agents, only fondaparinux is licensed for VTE thromboprophylaxis in high-risk orthopedic surgery and as an alternative to heparin or LMWH for initial treatment of VTE.

Indirect factor Xa inhibitors Fondaparinux and idraparinux have features that distinguish them from LMWH (Table 1). Because they are too short to bridge antithrombin to thrombin, fondaparinux and idraparinux enhance the rate of FXa inactivation by antithrombin, thereby blocking thrombin generation, but have no effect on the rate of thrombin inhibition. Both agents have almost complete bioavailability after subcutaneous injection. Neither fondaparinux nor idraparinux interacts with plasma proteins other than antithrombin. Consequently, these drugs produce a predictable anticoagulant response that precludes the need for routine coagulation monitoring.

Fondaparinux exhibits a dose-independent elimination half-life of approximately 17 h [35] and can be administered subcutaneously once daily. Fondaparinux is not metabolized and its clearance almost exclusively performed by the kidneys [36]. Consequently, dose adjustments are necessary in patients with renal insufficiency and fondaparinux should not be used in patients with renal failure. Although placental transfer of fondaparinux was not observed in a dually perfused human cotyledon model [37], limited clinical experience suggests that fondaparinux passes the placental barrier *in vivo*, resulting in low but measurable anti-FXa activity in umbilical-cord blood [38]. Fondaparinux does not bind to platelets or platelet factor 4 (PF4). Because it does not induce formation of heparin/PF4 complexes that serve as the antigenic target for antibodies that cause heparin-induced thrombocytopenia (HIT), this condition

Table 1 Comparison of the properties of LMWH, fondaparinux and idraparinux

Feature	LMWH	Fondaparinux	Idraparinux
Bioavailability	80–90%	100%	100%
Half-life (hours)	4	17	80
Target	FXa and thrombin	FXa	FXa
Renal clearance	Yes	Yes	Yes
Neutralized by PF4	Little	None	None
Potential for HIT	Low	None	None
Neutralized by protamine sulfate	Partial	No	No

is unlikely to occur with fondaparinux. Small studies have shown no cross-reactivity of fondaparinux with sera from patients with HIT [39–41]. Although the drug has been used successfully to treat small numbers of patients with HIT [42], clinical trials are needed to better establish the role of fondaparinux for this indication.

Idraparinux, a hypermethylated derivative of fondaparinux, binds antithrombin with such high affinity that it assumes a plasma half-life of 80 h [34], similar to that of antithrombin. Consequently, idraparinux can be given subcutaneously, once-weekly. Like fondaparinux, idraparinux is not metabolized and is cleared by the kidneys. Consequently, dose adjustments are needed in patients with renal insufficiency and the drug should not be used in patients with renal failure.

Neither fondaparinux [33] nor idraparinux interacts with protamine sulphate, the antidote for heparin. If uncontrolled bleeding occurs, a procoagulant, such as recombinant FVIIa may be beneficial [43,44]. However, recombinant FVIIa is not available in all hospitals, and the drug is expensive and can induce thrombotic complications. Because of its longer half-life, the absence of an antidote is more of a drawback for idraparinux than for fondaparinux.

Fondaparinux has been evaluated for prevention and treatment of VTE and for treatment of arterial thrombosis. The antithrombotic efficacy of fondaparinux was demonstrated in four Phase III trials comparing this agent with enoxaparin for thromboprophylaxis after surgery for hip fracture or after elective hip or knee arthroplasty [45–48]. In these trials, which involved over 7 300 patients, fondaparinux started 6 h after surgery reduced the risk of VTE by approximately 55% compared with enoxaparin [49]. Although major bleeding occurred more frequently in fondaparinux-treated patients ($P = 0.008$), the incidence of bleeding in a critical organ or bleeding leading to death or reoperation was similar to that in patients receiving enoxaparin [49]. The reduced risk of VTE with fondaparinux may be due to the fact that it was started 6 h after surgery, whereas initiation of enoxaparin was delayed until 12–24 h after surgery. The earlier start with fondaparinux also could explain the increase in major bleeding observed with this agent. In support of this concept, *post hoc* analysis revealed rates of major bleeding similar to those with enoxaparin in patients whose fondaparinux was started 6–8 h after surgery.

Extended prophylaxis with fondaparinux was studied in a phase III trial (PENTHIFRA-Plus) of 656 patients undergoing surgery for hip fracture. Prolonging the duration of prophylaxis with fondaparinux from 1–4 weeks after hip fracture surgery reduced the primary endpoint, a composite of deep vein thrombosis (DVT) detected on routine venography, and symptomatic VTE, from 35% to 1.4% ($P < 0.001$) [50]. More importantly, the rate of symptomatic VTE was reduced from 2.7% to 0.3% with extended fondaparinux prophylaxis ($P = 0.021$).

Fondaparinux has also been evaluated for thromboprophylaxis in general medical and general surgical patients. In a double-blind, randomized study of 849 medical patients 65 years or older, the primary endpoint (a composite of venographically diagnosed and symptomatic DVT, as well as non-fatal and fatal pulmonary embolism by day 15) occurred in 5.6% of those given fondaparinux and 10.5% of those who received placebo ($P = 0.03$). Major bleeding was infrequent [51]. In a double-blind phase III trial in which 2297 patients undergoing abdominal surgery were randomly assigned to receive prophylaxis with fondaparinux or dalteparin, the primary endpoint (a composite of venographically documented DVT, symptomatic DVT and non-fatal and fatal pulmonary embolism by postoperative day 30) occurred in 4.6% and 6.1% of patients, respectively ($P = 0.14$). Major bleeding occurred in a similar proportion of patients in both treatment arms [52].

Fondaparinux also has been investigated for the initial treatment of VTE. The results of the MATISSE DVT trial [53] and the MATISSE PE trial [54] suggest that fondaparinux is as effective and safe as LMWH or unfractionated heparin for initial treatment of patients with DVT and pulmonary embolism, respectively.

In a randomized, open-label, dose-finding trial (PENTALYSE), coadministration of fondaparinux and alteplase in ST-elevation MI produced similar angiographic patency rates at 90 min as did treatment with heparin and alteplase [55]. Bleeding rates also were similar in those receiving fondaparinux and in those randomized to heparin. Fondaparinux also compared favorably with enoxaparin in a large phase II trial of patients with acute coronary syndrome without ST-elevation (PENTUA) [56]; both the primary outcome (a composite of death, MI, or recurrent angina at day 9) and bleeding occurred in similar proportions of patients randomized to fondaparinux or enoxaparin. Phase III trials with fondaparinux in patients with acute coronary syndromes with and without ST-elevation are well underway.

Once-weekly subcutaneous idraparinux was compared with warfarin in a phase II dose-finding trial of 659 patients with proximal DVT. Participants were randomized to warfarin or one of four doses of idraparinux after 5 to 7 days of initial therapy with enoxaparin [57]. The rates of normalization and deterioration of ultrasonography and perfusion lung scanning were similar in all idraparinux dosing groups, and did not differ from that in the warfarin control group. However, there was a clear dose–response with respect to major bleeding in patients given idraparinux, with an unacceptably high frequency of bleeding in those given 10 mg of idraparinux. Two patients, both of whom received 5 mg of idraparinux, suffered a fatal bleed. Patients given the lowest dose of 2.5 mg had less bleeding than those randomized to warfarin ($P = 0.029$). Phase III trials comparing 2.5 mg of idraparinux subcutaneously once-weekly with enoxaparin followed by warfarin for treatment of patients with DVT or pulmonary embolism are ongoing, as is another phase III study comparing once-weekly idraparinux with warfarin for prevention of cardioembolic events in patients with atrial fibrillation.

Direct factor Xa inhibitors DX-9065a [58,59] is a synthetic non-peptidic low-molecular-weight inhibitor that binds reversibly to the active site of FXa. The drug has a half-life

of 45 min after bolus i.v. injection and it is cleared by the kidneys. DX9065a has been shown to be an effective antithrombotic agent in various animal models. Although DX-9065a exhibits oral bioavailability in animals, it must be given in high doses to produce an antithrombotic effect [58]. Consequently, in humans, the drug is administered by i.v. infusion. In a phase I study of patients with stable coronary artery disease, i.v. DX-9065a appeared safe and did not cause excess bleeding [60]. In the XANADU-PCI pilot study [61], 175 patients undergoing PCI were randomly allocated to different doses of DX9065a or to heparin. DX-9065a appeared to be a promising alternative to heparin. This requires confirmation in phase III clinical trials.

An orally active agent razaxaban is an aminobenzisoxazole that binds to the active site of FXa with high affinity and is given twice daily. The antithrombotic potential of this agent was investigated in a phase II trial of thromboprophylaxis in knee arthroplasty patients in which participants were randomized to various doses of razaxaban or to enoxaparin for 10 days after surgery [62]. The primary endpoint, a composite of venographically detected DVT and symptomatic VTE, occurred in 8.6% of patients given the lowest dose of razaxaban and in 15.9% of those treated with enoxaparin. Major bleeding occurred in 0.7% of patients given this dose of razaxaban and in none of those treated with enoxaparin. The three higher doses razaxaban arms of the study were stopped prematurely because of increased rates of major bleeding. Although promising, further development of razaxaban has been halted. Ongoing studies are being conducted with BMS-562247, a variant with superior pharmacological properties.

BAY 59-7939, LY-51, 7717, BMS-562247 and DU-176b are orally active, small molecule, direct FXa inhibitors that are currently undergoing phase II testing for thromboprophylaxis in patients undergoing elective hip or knee arthroplasty and for treatment of DVT.

Modulators of the protein C pathway

Factors VIIIa and Va, key cofactors for intrinsic tenase and prothrombinase, respectively, are critical for propagation of coagulation. Both cofactors are inactivated by activated protein C (along with its cofactor protein S). Strategies aimed at enhancing the protein C anticoagulant pathway include administration of protein C, activated protein C, or soluble thrombomodulin.

Protein C and activated protein C Both plasma-derived and recombinant forms of protein C and activated protein C are available. Although promising results with protein C concentrates have been reported in patients with meningococcemia [63,64], activated protein C may be a better choice in patients with severe sepsis because inflammatory cytokines down-regulate thrombomodulin expression on the endothelial surface. In a Phase III trial in which i.v. recombinant activated protein C, drotrecogin alpha (activated), was compared with placebo in 1690 patients with severe sepsis, activated protein C produced a 19% reduction in 28-day mortality (from 30.8% to 24.7%, $P = 0.005$) [65]. The rate of major bleeding was higher with activated protein C than with placebo (3.5% vs. 2%, respectively; $P = 0.06$). Based on these results and economic analyses [66] supporting the benefits of this agent, drotrecogin alpha (activated) is licensed in North America for adults with severe sepsis. An ongoing study is evaluating the utility of this agent in children with severe sepsis.

Soluble thrombomodulin Soluble thrombomodulin is a recombinant analog of the extracellular domain of thrombomodulin [67]. Like membrane-bound thrombomodulin, soluble thrombomodulin binds thrombin and converts it from a procoagulant enzyme into a potent activator of protein C. Recombinant soluble thrombomodulin has a half-life of 2–3 days after subcutaneous injection. This agent has been shown to have antithrombotic activity in a variety of animal models [68,69]. In an open-label, dose-escalation study, soluble thrombomodulin attenuated coagulation abnormalities in patients with disseminated intravascular coagulation [59]. In a phase II dose-ranging trial examining the utility of soluble thrombomodulin for VTE prophylaxis after elective hip arthroplasty, the primary endpoint (a composite of venographically detected DVT and symptomatic pulmonary embolism) occurred in 4.3% of the 94 patients given the lower dose of soluble thrombomodulin and in none of the 99 patients receiving the higher dose [70]. Major bleeding occurred in 1.6% and 5.7% of patients receiving the low or high dose of soluble thrombomodulin, respectively. Phase III clinical trials are necessary to compare soluble thrombomodulin with other forms of thromboprophylaxis, such as LMWH.

Inhibitors of fibrin formation

Thrombin effects the conversion of fibrinogen to fibrin. The procoagulant effects of thrombin can be blocked either by inactivating the enzyme itself, or by preventing its generation. Indirect thrombin inhibitors, like unfractionated heparin, LMWH, and dermatan sulphate, act by catalyzing the naturally occurring thrombin inhibitors, antithrombin and/or heparin cofactor II [1,71,72]. In contrast, direct thrombin inhibitors bind directly to thrombin and block its interaction with substrates, thus preventing fibrin formation, thrombin-mediated activation of FV, VIII, XI, or XIII, and thrombin-induced platelet aggregation.

As a class, direct thrombin inhibitors have potential biologic and pharmacokinetic advantages over heparin. Unlike unfractionated heparin and LMWH, direct thrombin inhibitors inactivate fibrin-bound thrombin [73–75], in addition to fluid-phase thrombin. Consequently, direct thrombin inhibitors may attenuate thrombus accretion more effectively. In addition, direct thrombin inhibitors produce a more predictable anticoagulant effect than heparin because they do not bind to plasma proteins and are not neutralized by PF4 [76,77]. Three parenteral direct thrombin inhibitors have been licensed in North America for limited indications. Hirudin [78–82] and

argatroban [82,83] are approved for the treatment of HIT, whereas bivalirudin is licensed as an alternative to heparin in patients undergoing PCI [84–90].

Focusing on new agents, ximelagatran, a prodrug of melagatran, is the first orally available direct thrombin inhibitor and has undergone Phase III clinical evaluation for prevention and treatment of VTE and for prevention of cardioembolic events in patients with atrial fibrillation. Oral ximelagatran and subcutaneous melagatran are licensed in Europe for VTE prevention in patients undergoing hip or knee replacement surgery. Ximelagatran has yet to be licensed for any long-term indication. Dabigatran etexilate (BIBR 1048), another oral direct thrombin inhibitor, is in a less advanced state of clinical development.

Ximelagatran

An uncharged lipophilic drug, ximelagatran, has little intrinsic activity against thrombin. This agent is a prodrug of melagatran, an active site-directed thrombin inhibitor. Ximelagatran is well absorbed from the small intestine with a bioavailability of approximately 20% and undergoes rapid biotransformation to melagatran via two intermediate metabolites, H338/57 and H415/04 [91,92]. Melagatran levels peak in the blood within 2 h. Melagatran has a plasma half-life of 3–4 h in healthy volunteers and 4–5 h in patients. Because of its short half-life, ximelagatran is administered twice daily. To date, no foods or drugs have been documented to influence its absorption. Ximelagatran does not inhibit cytochrome P450 enzymes [93] and, therefore, has a low potential for drug–drug interactions. Ximelagatran produces a predictable anticoagulant response after oral administration and no coagulation monitoring appears to be necessary. Because melagatran, the active agent, is eliminated via the kidneys, however, dose adjustments may be needed in patients with severe renal insufficiency, as evidenced by a creatinine clearance < 30 mL min^{-1} [94,95].

Based on its pharmacological profile, ximelagatran has properties that endow it with potential advantages over vitamin K antagonists, such as warfarin (Table 2). However, one of the side effects of ximelagatran is elevation of liver transaminases. Elevations in alanine transaminase of > 3 times the upper limit of normal occur in about 7.9% of patients receiving long-term therapy. Concomitant elevations in serum bilirubin occur in 0.5% of patients. Typically, changes in liver enzymes occur after 6 weeks to 4 months of therapy and are asymptomatic and reversible, even if the medication is continued. Although the increase in transaminases with ximelagatran appears to be benign, the long-term sequelae have yet to be determined. The lack of this information has, at least thus far, prevented licensing of ximelagatran in North America. If ximelagatran is approved for long-term indications, liver function tests will need to be monitored. As with other direct thrombin inhibitors, there is no antidote for ximelagatran. However, this drug's short half-life makes it unlikely that this will be a substantial problem.

Table 2 Potential advantages of ximelagatran over warfarin and their consequences

Advantage	Consequence
Rapid onset of action	Obviates need for a parenteral anticoagulant when initiating therapy in patients with thrombosis or at high-risk of thrombosis
No food or drug interactions	Predictable anticoagulant response
Wide therapeutic window	Can be given in fixed doses without routine coagulation monitoring
Short half-life	Reduces need for an antidote

Ximelagatran has been evaluated for thromboprophylaxis in high-risk orthopedic patients, treatment of VTE, prevention of cardioembolic events in patients with atrial fibrillation and prevention of recurrent ischemia in patients with recent MI. In phase II studies, ximelagatran, in combination with subcutaneous melagatran or as monotherapy, was shown to be safe and to have antithrombotic efficacy when used as prophylaxis against VTE after elective hip or knee arthroplasty [96,97]. Results of phase III studies suggest that the combination of a single subcutaneous injection of 3 mg of melagatran preoperatively followed by oral ximelagatran (24 mg b.i.d.) postoperatively is more effective than enoxaparin for thromboprophylaxis after hip or knee arthroplasty, but may cause more bleeding [98]. While a single injection of subcutaneous melagatran postoperatively followed by ximelagatran [91] or ximelagatran alone at a dosage of 24 mg b.i.d. [99] appears less effective than enoxaparin in patients undergoing joint arthroplasty, postoperative ximelagatran in doses of 36 mg b.i.d. is more effective than warfarin for thromboprophylaxis after knee arthroplasty [100,101].

Based on phase II data suggesting that ximelagatran also is effective for acute treatment of VTE [102], a phase III trial comparing 6 months of ximelagatran monotherapy (36 mg b.i.d.) with LMWH followed by warfarin in 2489 patients with VTE was performed [103]. The results suggest that oral ximelagatran is as effective and safe as conventional anticoagulation. Ximelagatran (at a dose of 24 mg b.i.d.) has been compared with placebo in 1233 patients who had completed a 6-month course of anticoagulant therapy for VTE. Ximelagatran treatment significantly reduced the risk of recurrent thrombosis without increasing the risk of major bleeding [104].

Promising data from phase II studies comparing ximelagatran with warfarin in patients with non-valvular atrial fibrillation [105,106] prompted two phase III trials [107,108]. In a randomized, open-label, parallel-group study of about 3400 patients at high-risk of embolism (SPORTIF III), ximelagatran at a dosage of 36 mg b.i.d. was at least as effective as warfarin targeted to an international normalized ratio (INR) of 2.0–3.0 in preventing stroke and systemic thromboembolism. Although the combined incidence of major and minor bleeding was significantly lower in those receiving ximelagatran than in those receiving warfarin, there was no statistically significant difference between the two groups with respect to major bleeding or intracranial hemorrhage. The results of a double-blinded,

randomized trial comparing ximelagatran with warfarin (SPORTIF V) confirmed that unmonitored fixed-dose ximelagatran is as effective and safe as dose-adjusted warfarin. It is important to note that the SPORTIF trials compare ximelagatran with optimally controlled warfarin; using an expanded INR range of 1.8–3.2, over 80% of INR values were within range in these studies. In contrast, reports suggest that < 50% of INR values are therapeutic when warfarin is managed in the community setting.

In the phase II ESTEEM trial [109], ximelagatran was compared with placebo in 1883 patients with ST-elevation or non-ST-elevation MI within the past 14 days. All patients were given aspirin and optimal medical management that included statins and ACE inhibitors. Compared with placebo, all four ximelagatran doses significantly reduced the frequency of the primary endpoint, a composite of all-cause mortality, recurrent MI and severe recurrent ischemia. Major bleeding occurred in 1% of patients treated with placebo and 2% of those given ximelagatran, a difference that was not statistically significant. Based on these data, a phase III trial is under consideration.

Dabigatran etexilate (BIBR 1048)

Dabigatran etexilate, another oral direct thrombin inhibitor [110], is in a less advanced state of clinical development than ximelagatran. Like ximelagatran, dabigatran etexilate is a prodrug that is converted to its active metabolite, dabigatran (BIBR 953), once it is absorbed from the gastrointestinal tract. The bioavailability of dabigatran is < 5%. Levels of dabigatran peak in the blood about 2 h after dabigatran etexilate administration and dabigatran is eliminated via the kidneys. The half-life of dabigatran is approximately 8 h after single dose administration and up to 17 h with repeated dosing. Consequently, it may be possible to give the drug once daily. Dabigatran and dabigatran etexilate have been shown to be effective in animal models of venous thrombosis [111,112]. While early clinical studies are promising [113–115], further work is needed to establish the safety and efficacy of this agent. Dose finding studies for thromboprophylaxis and for stroke prevention in atrial fibrillation are underway.

Conclusions

Although several promising new anticoagulants have been evaluated, the role of many of these agents remains to be delineated. Even if new anticoagulants prove superior to currently available agents, their advantages have to be substantial to offset additional costs.

Fondaparinux is licensed for thromboprophylaxis in patients undergoing major orthopedic surgery and for the initial treatment of VTE. Ongoing studies will determine the utility of this agent in patients with acute coronary syndromes.

Idraparinux and ximelagatran have the potential to streamline long-term anticoagulant therapy by eliminating the need for routine coagulation monitoring. With once-weekly subcutaneous administration, idraparinux is easy to administer and ongoing studies will determine its efficacy and safety relative to warfarin for treatment of VTE and for prevention of cardioembolic events in patients with atrial fibrillation. The latter is an area where there is considerable room for improved treatment. Although warfarin is more effective than aspirin at reducing the risk of embolization in this setting, the need for frequent monitoring and difficulties in maintaining the INR within the therapeutic range limit its use [116].

The results with ximelagatran validate the choice of thrombin as a target for new anticoagulants. As an orally active agent, ximelagatran shows promise for prevention and treatment of venous thrombosis. Based on the results of the SPORTIF III and V trials, unmonitored ximelagatran appears to be as effective and safe as dose-adjusted warfarin for prevention of cardioembolic events in patients with atrial fibrillation. With no need for coagulation monitoring, ximelagatran is more convenient than warfarin, a feature that may increase anticoagulant use in this setting. Before ximelagatran can be embraced for extended treatment, however, more information about its long-term hepatic effects is needed. Elevation in transaminase levels has yet to be reported in significant numbers of patients receiving dabigatran etexilate suggesting that this phenomenon is not a class effect of direct thrombin inhibitors. With dabigatran etexilate and oral FXa inhibitors under investigation, it is likely that we will soon have alternatives to warfarin, even if ximelagatran fails to be licensed for long-term indications.

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