
Current and Future Challenges of Antithrombotic Agents and Anticoagulants: Strategies for Reversal of Hemorrhagic Complications

Craig M. Kessler

Recent years have seen the introduction of a number of new anticoagulant agents, each offering a unique profile of benefits and potential drawbacks. Anticoagulants are now available or in development that target platelet recruitment, aggregation, and adhesion, in addition to a growing number of direct or indirect thrombin inhibitors. However, the potential for anticoagulant-induced hemorrhage and the need for effective antidotes that can reverse this adverse effect remain major considerations when prescribing any anticoagulant therapy. The expanding range of anticoagulants brings with it a renewed challenge of identifying suitable treatments to reverse anticoagulant-induced hemorrhage. This paper reviews different mechanisms of anticoagulant action and the theoretical role of recombinant factor VIIa (rFVIIa) and other agents currently in development to reverse bleeding complications associated with both traditional and novel anticoagulant therapies.

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THERAPEUTIC OPTIONS for anticoagulation have been limited until recently. In 1937, unfractionated heparin (UFH) was extracted from the lungs and gut of cattle and swine, and was subsequently used in humans for the treatment of symptomatic clots. Today, there is an expanding range of anticoagulant therapies, based on an improved understanding of the mechanisms involved in coagulation. However, these agents will be associated with the risk of anticoagulant-induced bleeding, and many of these anticoagulants lack a specific antidote to reverse this adverse effect.

Recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) is a synthetic clotting factor that reduces bleeding at the injury site by interacting with tissue factor (TF) to stimulate thrombin generation and the formation of a stable fibrin clot. rFVIIa is indicated for the treatment or prevention of spontaneous or surgical bleeding in individuals with hemophilia A or B complicated by neutralizing alloantibodies, but recent data on its mechanism of action suggest that rFVIIa may prove useful in reversing anticoagulant-induced bleeding. This paper reviews some of the anticoagulant agents that are currently in use or in development, and the potential role of rFVIIa as an antidote to reverse

untoward bleeding induced by specific anticoagulant agents.

Thrombin Inhibition

Thrombin was the first target for anticoagulant agents, and thrombin inhibition remains a cornerstone of anticoagulant therapy. The main mechanisms of thrombin inhibition are either indirect by enhancing antithrombin III or factor Xa (FXa) activity, or via direct thrombin inhibition. Mechanisms of thrombin inhibition are illustrated in Fig 1.

Indirect Thrombin Inhibitors

Traditional anticoagulants that inhibit thrombin indirectly via antithrombin III binding include UFH, low-molecular-weight heparins (LMWH) and heparinoids. In addition, the synthetic pentasaccharide fondaparinux also exerts its effect on FXa via antithrombin III complex formations, and the oral vitamin K antagonists, such as warfarin, interfere with the post-ribosomal modification of the vitamin K-dependent coagulation factors II, VII, IX, and X. These anticoagulants are summarized in Table 1.

Unfractionated heparin. UFH is a mixture of sulphated glycosamine moieties and remains the most widely used parenteral anticoagulant today, mainly for the acute treatment and prophylaxis of venous and arterial thromboembolism. UFH enhances antithrombin III activity 1,000-fold, resulting in physiologically important and rapid inactivation of thrombin and FXa. UFH is inexpensive and fast-acting (peak plasma levels are achieved 30 to 60 minutes after subcutaneous injection), but has less than 50% bioavailability and carries a risk of adverse events,

From the Departments of Medicine and Pathology, Georgetown University of Medicine, Washington, DC.

Address correspondence to Craig M Kessler, MD, Professor of Medicine and Pathology, Georgetown University of Medicine, 3800 Reservoir Rd, NW, Washington, DC 20007.

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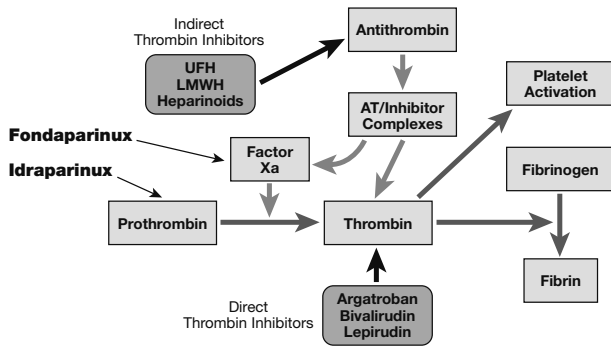


Figure 1. Mechanisms of thrombin inhibition.

including heparin-induced thrombocytopenia (HIT), aldosterone inhibition (hyperkalemia), and osteopenia, with long-term use (about 15% in pregnant women) leading to a 1 in 50 risk of vertebral fracture among treated patients.

Bleeding is the most common complication with UFH and major bleeding events occur in about 2% to 3% of patients receiving therapeutic doses for acute treatment of acute thrombotic conditions, although prophylactic doses rarely cause bleeding. UFH can also lead to thrombocytopenia (defined as 50% fall

from baseline platelet count) due to the formation of heparin-dependent immunoglobulin G (IgG) antibodies directed against multimolecular complexes of platelet factor 4 and heparin. This thrombocytopenia is linked with a paradoxical increase in arterial and/or venous thrombosis, which can lead to catastrophic complications, such as gangrene (and hence limb amputations), strokes, myocardial infarction, etc. The reported incidence of HIT following treatment with porcine-derived UFH is between 1% and 5% in different patient populations.³³ Patients receiving UFH require routine monitoring of activated partial thromboplastin time (aPPT) to assure both safety and efficacy. UFH reaches peak plasma levels in about 30 to 60 minutes, and has a circulating half-life of 1 to 2 hours.

UFH is the only indirect thrombin inhibitor that has a specific antidote to reverse anticoagulant-induced bleeding. This antidote is protamine sulfate, a highly cationic polypeptide that is extracted from salmon sperm. Protamine sulfate is effective immediately, but after 2 hours, rebound UFH activity may be observed. Dosing requires care because excess protamine sulfate can itself cause anticoagulation by inhibiting thrombin-induced cleavage of fibrinogen. The recommended dose is 1 mg protamine sulfate admin-

Table 1. Direct and Indirect Thrombin Inhibitors

	UFH	LMWH	Danaparoid	Fondaparinux	Lepirudin	Bivalirudin	Argatroban	Ximelagatran
Administration	IV	SC	SC	SC	IV	IV/SC	IV	Oral
Main indication	DVT & pulmonary embolism treatment and prevention (with surgery)	DVT prevention and treatment	DVT prevention with surgery and HIT	VTE prevention with orthopedic limb surgery	Anticoagulation in patients with Type II HIT	Anticoagulation during PCI; prevent DVT in orthopedic surgery	Anticoagulation in patients with HIT	VTE treatment
Mode of action	Inhibits thrombin action via complexes with antithrombin III	Inhibits IIa and Xa by binding to and increasing activity of antithrombin III	Inhibits Xa (& IIa)	Binds to antithrombin & potentiates factor Xa neutralisation	Binds directly to thrombin (almost irreversible)	Binds directly to thrombin (transient)	Binds directly to thrombin active site	Binds directly to thrombin
Time to peak plasma levels	30-60 min	4-6 h	4-5 h	2 h	Immediate	IV: 2 min; SC: 2 h	1-4 h	2 h
Circulating half-life	1-2 h	3-5 h	18-28 h	13.3 ± 3.3 h	1-3 hours	25-45 min	39-59 min	3.5 h
Incidence of major bleeds	3%	1.5-3%	~2.5%	2-3%	17%*	0.7%	0.8-1.7%†	~2%‡
HIT incidence	3% (1-5%)	Much less than 1%	Much less than 1%	None	None	None	None	None
Current intervention for bleeding	Protamine sulfate	No specific antidote (protamine sulfate has limited effect)	No specific antidote	No specific antidote	No specific antidote	No specific antidote	No specific antidote	No specific antidote

Abbreviations: UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; IV, intravenous; SC, subcutaneous; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; VTE, venous thromboembolism; PCI, percutaneous coronary intervention.

* Greinacher et al, 1999.²⁰

† Colwell et al, 2003⁹; Francis et al, 2002¹⁸

‡ Matthai, 1999.²⁶

istered intravenously per 100 U residual UFH, but this dose should be maintained below 100 mg over 2 hours. Most clinicians will administer 50% of the calculated dose initially and titrate subsequent doses according to bleeding response. Fresh-frozen plasma (FFP) may be given as an adjunctive therapy. Protamine sulfate also carries a 1 in 10 (10.7%) incidence of severe allergic reactions, including anaphylaxis, and a 1.6% incidence of life-threatening hypotension.³⁶

Low-molecular-weight heparins. A range of parenteral anticoagulants has been developed through the proteolysis and fractionation of UFH into 4,000- to 6,000-dalton polysaccharide fragments, typically consisting of less than 18 polysaccharide units. These therapies include dalteparin, enoxaparin, nadroparin, ardeparin, and tinzaparin. The LMWHs have improved bioavailability (>90%) and a more predictable anticoagulant effect than UFH due to reduced plasma protein/endothelial cell surface binding. Their reduced chain length also results in more specific LMWHs that interact more readily with FXa than with FIIa. The clinical significance of this is unclear, although the theoretical advantage is a reduction in bleeding complications and incidence of HIT when compared with treatment with UFH, by eliminating the higher molecular weight moieties that are responsible for platelet effects.

In fact, LMWHs do appear to offer a reduced risk of HIT compared with UFH, but they may be associated with an increased risk of bleeding.^{1,33,35} Evidence suggests that minor bleeding is more than twice as common with LMWH than UFH (10% v 4.3%), and long-term LMWH use has been linked with an increased risk of major bleeds (odds ratio, 2.26; equivalent to 12 major bleeds per 1,000 patients receiving LMWH).^{1,16} Some LMWH-treated patients require periodic monitoring of anti-FXa activity, including those who are pregnant, obese, or have renal failure (creatinine clearance is < 30 mL/min). LMWHs typically reach maximal plasma concentrations in 4 to 6 hours, and have a circulating half-life of 3 to 5 hours. Protamine sulfate can reverse about 60% of the anti-FXa activity of LMWH.³⁴ However, this degree of reversal may not terminate bleeding and varies between different LMWH preparations, possibly due to variations in their sulfate charge,¹¹ and the success of reversal is rather unpredictable. FFP can also be administered adjunctively.

Variations on the traditional LMWHs. New anticoagulant preparations have been developed, based on UFH and LMWH. Danaparoid is a mixture of 84% heparin sulfate, 12% dermatan sulfate, and 4% chondroitin sulfate, and has a more than 22-fold higher effect on FXa than FIIa. Major bleeding occurs in 2.5% of danaparoid-treated patients, and this preparation has a long half-life of approximately 25

hours.¹⁷ There is a lack of evidence that serious nonsurgical bleeding associated with danaparoid can be consistently reversed. Protamine sulfate can partially reverse danaparoid's anti-FIIa effect, but no agent is available to reverse the anti-FXa effect that accounts for most of danaparoid's activity. Danaparoid is no longer available commercially in the United States, but remains available for the treatment of HIT in Canada and elsewhere.

Fondaparinux is a synthetic, 1,728-dalton pentasaccharide that selectively binds to antithrombin III and potentiates its inactivation of factor Xa 300-fold. Fondaparinux has no effect on FIIa, platelets, fibrinolysis or bleeding time. Bioavailability is 100% following subcutaneous injection, peak plasma levels occur after about 3 hours. Fondaparinux also has an extremely prolonged long half-life of 17 to 21 hours. This agent appears more effective than enoxaparin in preventing venous thromboembolism in the orthopedic surgery setting, but perhaps at the cost of a 10-fold increase in major bleeds. About one in 50 patients (2.1%) receiving fondaparinux for the prevention of venous thromboembolism following total hip replacement (THR) experienced a major bleed, compared with 0.2% on enoxaparin.²

No specific antidote is available for either danaparoid or fondaparinux, and protamine sulfate has unreliable and unpredictable effects on bleeding caused by these agents.

Direct Thrombin Inhibitors

A major disadvantage of indirect thrombin inhibitors is their inability to affect clot-bound thrombin, which promotes further thrombus growth. In addition, UFH has unpredictable effects and is neutralized by platelet factor 4.³⁵ These limitations have prompted the development of direct thrombin inhibitors, which offer predictable anticoagulation that is resistant to platelet factor 4, and are able to inhibit clot-bound thrombin. The direct thrombin inhibitors include recombinant hirudin and synthetic agents such as bivalirudin and argatroban (Table 1). Evidence suggests that these agents offer improved survival and a reduced incidence of myocardial infarction following angioplasty, when compared with UFH.¹⁵

Hirudin occurs naturally in the saliva of the medicinal leech, and binds specifically, and almost irreversibly, to the catalytic site of thrombin. An almost identical recombinant form (lepirudin) is indicated for use in patients who have developed Type II HIT due to heparin (UFH or LMWH) therapy. Lepirudin allows platelet counts to return to normal in patients with HIT, but investigators recommend care in monitoring activated partial thromboplastin time (aPPT), thrombin times, or ecarin venom-based clotting times, and in avoiding trauma during lepirudin therapy for these patients.²⁹ In addition, lepirudin has

been linked with a significant increase in the incidence of bleeding compared with historical controls (44.6% v 27.2%, $P = .0001$).²⁰ Lepirudin has no specific antidote. The circulating half-life of lepirudin is 1 to 3 hours in patients with normal renal function, but is prolonged by either antibody formation—which is very common—or renal failure. Lepirudin is excreted renally, so patients with renal failure require careful monitoring.

Bivalirudin is a semisynthetic derivative of hirudin, comprising an active site-directed peptide linked to an analogue of the carboxy-terminal of hirudin. This compound was developed in response to the relatively high incidence of bleeding observed using hirudin. Bivalirudin exhibits transient binding to thrombin, and has a half-life of 25 to 40 minutes. There is a slight increase in mild or moderate bleeds compared with UFH, but the risk of major bleeding may be reduced.¹⁵ In addition, bivalirudin is non-antigenic and excretion is mainly hepatic, so it is suitable for patients with renal failure. However, there is no specific antidote for bivalirudin-induced bleeding.

Another specific thrombin inhibitor, argatroban, is a synthetic arginine derivative that binds directly to the catalytic site on thrombin. Like bivalirudin, argatroban has a short half-life (40 to 50 minutes), is non-antigenic, and is excreted mainly by the liver. The incidence of anticoagulant-induced bleeding with argatroban is comparable to UFH at 3%, but again, no specific antidote is available.

A number of potential anticoagulants that target thrombin generation are currently under investigation. These agents include inhibitors of the FIX active site, or of FXa (eg, tick peptides, leech peptides, and synthetic pentasaccharides). An inhibitor of the FVIIa/TF complex (recombinant nematode anticoagulant protein c2) has shown promising activity in percutaneous coronary intervention and deep vein thrombosis following total knee replacement in phase II trials.^{25,28} These experimental treatments may also require antidotes for bleeding reversal if they are adopted for clinical use in the future.

Potential Strategies for Reversal of Thrombin Inhibitor-Induced Bleeding

The lack of specific antidotes for recently developed thrombin inhibitors could prove problematic in the clinic, and although several approaches have been tried, data are limited because life-threatening bleeds are rare.³⁴ Low-molecular-weight derivatives of protamine sulfate are in development with the goal of reducing the associated risk of allergic reactions and hypotension, and there are preliminary reports that these agents may also be effective as antidotes to LMWH.⁶ Heparinase is also under investigation as an

antidote to heparin-induced bleeding, although it is unclear whether this approach will be effective as an antidote for LMWH or other indirect thrombin inhibitors. Recombinant platelet factor 4 has been proposed as a potential heparin antidote. However, the use of this agent could theoretically enhance the risk of HIT if the number of platelet factor 4 complexes increases.

In the absence of effective antidotes, hemodialysis has been proposed for the removal of indirect thrombin inhibitors but would be less efficient for UFH, which is not cleared renally. Both activated prothrombin complex concentrates (aPCCs) and rFVIIa have been used as procoagulant agents in patients with hemophilia A and B and alloantibodies, and have been administered empirically for the treatment of bleeding associated with therapeutic anticoagulation. rFVIIa has demonstrated efficacy in reversing clinical bleeding due to fondaparinux, which other-

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Figure 2. Effect of fondaparinux and/or rFVIIa administration pm activated partial thromboplastin time (aPTT) and PT. Subcutaneous administration of fondaparinux or placebo at $t = 0$. After 2 hours, rFVIIa or placebo was injected intravenously. * $P < .05$ (post-hoc Scheffé test) per time point, fondaparinux + rFVIIa v fondaparinux alone; # $P < .05$, fondaparinux + rFVIIa v rFVIIa alone. Reprinted with permission from Bijsterveld et al: Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 106:2550-2554, 2002.

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Figure 3. The international normalized ratios (INRs) of 13 patients relative to treatment with rFVIIa. The 0 on the X-axis represents the time at which rFVIIa was administered. Each line represents a patient with his or her INR. The trends in INR and prothrombin time were identical for all patients. Reprinted with permission from Deveras RA, Kessler CM: Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med* 137:884-888, 2002.

wise currently lacks a specific antidote.⁵ Phase III trial data have shown that rFVIIa can improve coagulation times and thrombin generation within approximately 1.5 hours, and that the effect is sustained for up to 6 hours (Fig 2).⁵ Activated PCCs and rFVIIa have also demonstrated efficacy in reversing bleeding due to high doses of the direct thrombin inhibitor melagatran. However, there is a risk of thrombogenicity and occasionally myocardial infarction when using prothrombin complex concentrates (PCCs) or aPCCs, which may be due to the presence of activated FVII.^{30,31} In addition, both PCCs/aPCCs and FFP (another alternative intervention for severe bleeding) are derived from pooled or recovered plasma, and hence may carry a risk of transmitting blood-borne pathogens.

Vitamin K Antagonists: Warfarin

Oral vitamin K antagonists, such as warfarin, are widely used to reduce the risk of thromboemboli in patients with cardiovascular disease or hypercoagulable disorders. Warfarin has proven more effective than aspirin in the prevention of fatal or nonfatal reinfarction and thromboembolic stroke following myocardial infarction, but it is linked with an increased risk of anticoagulant-induced bleeding.²² The mode of action of warfarin, which interferes with the post-ribosomal modification of vitamin K-dependent clotting factors by the liver, results in pharmacokinetic and anticoagulant effects that are frequently influenced by nutritional issues, drug-drug interactions, gastrointestinal absorption, and hepatic function. Published bleeding rates vary between 0 and 50%,³ and this may reflect variability in hepatic metabolism and cytochrome P450 polymorphisms, and variations in dosing, clinical scenarios,

hepatic function, and patient age. Recently, two large-scale studies have reported bleeding in (1) 15% of patients during the first year of warfarin therapy, including 3.5% for whom bleeding led to death or hospitalization; and (2) approximately 3.5% per year in total.^{21,22} The risk of bleeding rises with increasing age; patients aged ≥ 65 years are at significantly higher risk of major bleeding when receiving warfarin therapy than those aged below 65 years.⁴

Reversing Warfarin-Induced Bleeding

The traditional antidote to warfarin-induced bleeding is vitamin K, but this is unsuitable for acute reversal of serious bleeding incidents because there is a 4- to 6-hour delay in effect.³⁴ Current strategies for acute bleeding include stopping warfarin therapy and administering FFP or PCCs/aPCCs. However, FFP also has a delayed effect and can increase blood volume, while PCC carries a risk of thrombogenicity. Hence, interest has been focused on the potential use of rFVIIa for the acute treatment of warfarin-induced bleeding. Both animal models and clinical studies have generated promising results using rFVIIa.^{13,14} Figure 3 shows the impact of rFVIIa infusion on prolonged international normalized ratio (INR) times due to warfarin overanticoagulation. Randomized, prospective, controlled clinical trials are critical to establish the cost-benefit and risk-benefit profiles of such an approach. To date, no such data exist.

Platelet-Directed Antithrombotic Agents

A range of agents are available or in development that exert their antithrombotic effect by inhibiting platelet recruitment or aggregation/adhesion. The main sites of activity for these agents are summarized in Fig 4.

Adenine Diphosphate Receptor Antagonists: Thienopyridines

The thienopyridines ticlopidine and clopidogrel inhibit platelet function by irreversibly blocking the

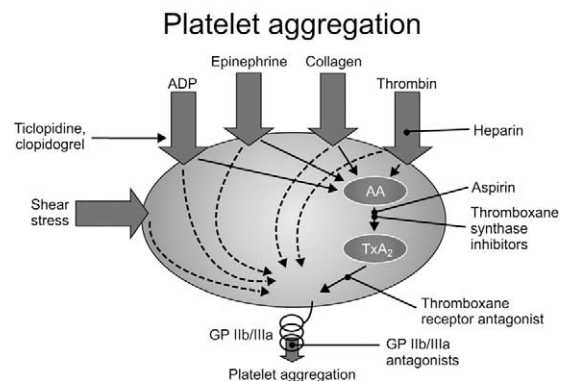


Figure 4. Platelet aggregation and sites of inhibition by anticoagulant agents. ADP, adenine diphosphate; GP, glycoprotein.

platelet adenosine diphosphate (ADP) receptor. They are more effective than aspirin in the prevention of myocardial infarction, transient ischemic attacks, and cerebrovascular accidents. In addition, ticlopidine has proved more effective than aspirin alone or aspirin plus warfarin in maintaining coronary stent patency. However, both thienopyridines are linked with an increased risk of thrombotic thrombocytopenic purpura. Ticlopidine⁸ and clopidogrel¹⁰ are metabolized in the liver.

Glycoprotein IIb/IIIa Receptor Inhibitors

Another recently developed class of antithrombotic agents, the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor inhibitors, targets the final common pathway of platelet interactions and aggregation in response to numerous agonists. The chimeric monoclonal antibody abciximab is the most extensively studied agent in this class. Abciximab blocks platelet aggregation by binding to at least 80% of GPIIb/IIIa platelet-binding sites, and has a circulating half-life of 30 minutes. Many clinicians now regard GPIIb/IIIa receptor inhibitors as the standard of care in percutaneous coronary intervention, and their use may continue to increase.⁷ However, abciximab also binds to vitronectin receptors on platelets and endothelial cells, and possibly also to the intercellular adhesion molecule-1 (ICAM-1) on monocytes. This additional activity may have clinical implications due to possible effects on vessel injury, tumor metastases, atherogenesis, and fibrinolysis.

The synthetic GPIIb/IIIa inhibitors eptifibatid and tirofiban are both available for use in patients who have undergone angioplasty or other percutaneous coronary intervention, and for those who have unstable angina, or myocardial infarction without ST-segment elevation. Oral agents such as xemilofiban and orbofiban may be more effective than aspirin, but are associated with increased bleeding complications. A range of peptides derived from snake venom, described as “disintegrins,” also target the platelet GPIIb/IIIa receptor. However, the therapeutic utility of these agents (trigramin, bitistatin, echistatin, applaggin, and barbourin) is limited because they are antigenic, and have been linked with thrombocytopenia. There is evidence that thrombocytopenia may be a GPIIb/IIIa receptor inhibitor class effect, as it has also been reported with abciximab and eptifibatid.²³ This most certainly increases their hemorrhagic potential.

Experimental Antiplatelet Agents

A variety of agents are in development that exploit different targets on the platelet surface. These include antibodies against the unique transmembrane thrombin receptor, which have shown efficacy in inhibiting

arterial thrombosis in monkeys.¹² Similar peptides may eventually reach the clinic as oral anticoagulants. Other agents that affect the GPIB/IX receptor are also under investigation.

Reversing Bleeding Secondary to Platelet Inhibitors

The traditional agents employed to reverse the acute bleeding associated with excessive anticoagulation act by enhancing humoral coagulation, but have limited direct effects on platelet aggregation at sites of vessel injury. Both rFVIIa and PCCs may offer theoretical advantages in that they indirectly enhance humoral coagulation and platelet activation. More clinical experience and properly defined clinical trials are required to confirm their potential value in this indication.

There is anecdotal evidence that rFVIIa may be effective in reversing bleeding due to thrombocytopenia induced pharmacologically or associated with autoimmune dysfunction. In vitro studies suggest that these benefits are mediated by direct platelet activation with generation of thrombin levels that are adequate to promote normal hemostasis, even in the presence of reduced platelet numbers.^{24,27} Small studies and anecdotal case reports suggest that this may also apply in vivo, although rFVIIa-mediated platelet activation is proportional to available platelet counts.^{19,32} Additional activities are necessary to establish rFVIIa utility for treating hemorrhagic complications due to quantitative and qualitative platelet dysfunction.

Conclusions

- Naturally occurring FVIIa interacting with TF has a central role in humoral coagulation; rFVIIa has also proved to be an effective agent for reducing bleeding in hemophilia A and B complicated by inhibitors.
- Recombinant FVIIa has theoretical advantages over traditional interventions for the reversal of anticoagulant- and antithrombotic-induced bleeding caused by a range of traditional, novel and experimental agents, including bleeding due to anticoagulant-induced thrombocytopenia.
- Anecdotal and in vitro data of rFVIIa support efforts to perform properly defined clinical trials intended to generate confirmatory evidence for the potential benefits of rFVIIa as a therapeutic agent to reverse bleeding complications associated with anticoagulants, antithrombotic medications, and qualitative and quantitative platelet abnormalities.

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