Reversal Agents for Anticoagulants: Focus on Andexanet Alfa

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ABSTRACT

Due to projected increases in the incidence of venous thromboembolism in the United States (based on healthcare claims data), anticoagulation has become an extremely pertinent subject of interest. An anticoagulant’s efficacy must be favored to, or balanced with, its safety profile. In overdose or emergent situations, reversal agents play a crucial role. Examples of anticoagulants that have specific antidotes are warfarin (with vitamin K) and heparin (with protamine). Newer anticoagulants, such as direct thrombin inhibitors or factor Xa inhibitors (direct or indirect), do not have specific reversal agents aside from activated charcoal and blood products. To alleviate bleeding associated with these anticoagulants, providers have utilized prothrombin complex concentrates (activated, three-factor, four-factor), recombinant factor VIIa, and/or fresh frozen plasma. Andexanet alfa is an investigational reversal agent for direct (e.g., apixaban, betrixaban, edoxaban, rivaroxaban) and indirect (e.g., enoxaparin, fondaparinux) factor Xa inhibitors. As there are no specific reversal agents for factor Xa inhibitors yet, this protein potentially addresses an unmet need. Andexanet alfa is a modified factor Xa devoid of procoagulant and anticoagulant properties, which has shown promising results via pre-clinical and clinical studies. More data on its safety and efficacy is expected in the upcoming years.

INTRODUCTION

Virchow’s Triad explains that vascular injury, disruption in blood flow, and an imbalance in hemostasis are interconnected pathological mechanisms leading to thrombus formation.¹ Thrombi may form either in arteries or veins, and thromboembolism occurs when these formed clots dislodge and travel to the distal circulation.¹ ² In the venous circulation, a clot commonly presents as deep vein thrombosis (DVT) and could lead to a pulmonary embolism (PE).² When formed in the arterial circulation, thrombi could ultimately lodge into arteries within organs and cause ischemia, such as a stroke in the brain.²

The exact incidence and prevalence of venous thromboembolism (VTE) in the United States is unknown because of variances in study methodologies (i.e., inclusion and exclusion criteria).³ Based on a retrospective analysis of healthcare claims data, there were 317 cases per 100,000 patients (in 2002) and 422 cases per 100,000 patients (in 2006), representing a 33.1% in-
increase. In addition, about 2.7 million people had atrial fibrillation (AF) in 2010, and this number is expected to increase to 12 million by 2050. AF increases the risk of an ischemic stroke by 5-fold and leads to 15-20% of all ischemic strokes.

Targeting clot formation is a crucial therapeutic objective that has resulted in the development of many anticoagulant medications. However, preventing coagulation may increase bleeding risk, with an average incidence of major bleeding estimated to be around 0.5% per year in studies and up to 3.4% per year based on surveys. In emergency situations, rapid anticoagulation reversal is crucial prior to invasive procedures or for preventing hemorrhagic complications (e.g., intracranial hemorrhage). Anticoagulants also have different therapeutic indices (e.g., drug level, age, renal function) affecting the likelihood of a bleed.

Patients who unfortunately present with bleeding complications may require hemodynamic support (e.g., volume expanders, oxygen, correction of acidosis and hypothermia), reduction of drug exposure (e.g., antiplatelet, anticoagulant), and enhanced hemostasis (e.g., bleeding site compression, topical epinephrine/thrombin/fibrin, desmopressin, correction of hypocalcemia).

Although there are specific reversal agents for certain drugs (e.g., warfarin, heparin), “true” antidotes for direct thrombin inhibitors (DTI) and factor Xa inhibitors (fXa) are not yet available on the market. This is concerning because novel oral anticoagulants have rapidly entered outpatient settings, mostly due to comparative clinical efficacies to warfarin and less routine blood level monitoring.
Recently, a protein called andexanet alfa (PRT064445 or PRT4445®, Portola) has shown efficacy in reversing the anticoagulant effects of fXa. Other potential reversal agents, including an antibody against dabigatran and a “universal” small molecule antidote for DTI and fXa, are also under development.5

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**BRIEF REVIEW OF SELECTED ANTICOAGULANTS**

**Vitamin K Antagonists (VKA)**

Warfarin (Coumadin, Bristol-Myers Squibb) is the most commonly utilized oral anticoagulant in medical practice.11 Post-ribosomal synthesis of vitamin K dependent clotting factors requires an important cofactor: vitamin K.11 By inhibiting the C1 subunit of vitamin K epoxide reductase (VKORC1) and reducing vitamin K1 epoxide regeneration, warfarin interferes with the synthesis of factors II, VII, IX, and X in the coagulation cascade (along with the anticoagulant proteins C and S).12

Warfarin is approved by the United States Food and Drug Administration (FDA) for the prophylaxis and treatment of VTE (DVT and PE) and thromboembolic complications (e.g., stroke) of AF and cardiac valve replacement.12 It is also indicated for reducing the risk of death, recurrent myocardial infarction (MI), and thromboembolic events (e.g., stroke, systemic embolization) after an MI.12

The safety and efficacy of warfarin depends on the international normalized ratio (INR), a calculation based on the prothrombin time (PT) and a measure of the extrinsic pathway in the coagulation cascade.13 For the majority of patients requiring anticoagulation with warfarin, the 2012 CHEST guidelines from the American College of Chest Physicians recommend goal INR levels between 2 and 3 (with an ideal target of 2.5).13,14

The goal INR is generally higher (i.e., 2.5 to 3.5) in patients who have received mechanical valve replacements (e.g., aortic, mitral).13,14 The risk of bleeding increases with higher INR values, and interventions may be required to reverse the anticoagulant’s effects.13

Along with dietary vitamin K intake, there are many factors affecting the INR, leading to either sub- or supra-therapeutic levels.14 While age >70 years, the absence of chronic diseases, and male gender have been found to be independent predictors of stability, some factors associated with unstable INR are congestive heart failure, diabetes, and a target INR ≥3.14 In the inpatient setting, the INR is typically monitored on a daily basis for patients on warfarin, whereas, anecdotally, an outpatient monitoring schedule may initially be weekly, transition to every two weeks, and eventually become monthly for stable patients.14 Outpatient monitoring of warfarin therapy realistically depends on individual institution practices and patients’ respective abilities to arrive to clinics for blood work.14 These and other challenges are perceived as drawbacks, adding to the allure for utilizing new oral anticoagulants that could be administered at fixed doses without much laboratory monitoring.14

Fortunately, there are several reversal strategies for warfarin, based on the INR and need for reversal.13-18 When patients are actively bleeding, first-line recommendations typically include discontinuing warfarin and administering intravenous (IV) phytonadione (vitamin K) with an infusion of prothrombin complex concentrate (PCC).13,17 The combination is used because PCC replaces clotting factors immediately, while vitamin K promotes future production of clotting factors.13,17 Of note, IV vitamin K leads to earlier reversal of warfarin-based anticoagulation compared to oral vitamin K, but both routes of administration seem to have similar clinical outcomes.17,19
A four-factor PCC (PCC4) approach is preferred because it would replace the clotting factors inhibited by warfarin (II, VII, IX, and X). This includes either using a PCC4 product (Kcentra, CSL Behring) or the combination of a three-factor PCC (PCC3) product (Bebulin VH, Baxter; Profilnine SD, Grifols; and many others) with rtVIIa / recombinant coagulation factor VIIa (NovoSeven RT, Novo Nordisk). Activated PCC (aPCC) / factor eight inhibitor bypass activity (FEIBA NF, Baxter) and fresh frozen plasma (FFP) are additional, but less preferable, options based on current evidence and guidelines.

Unfractionated Heparin (UFH) and Low-Molecular-Weight Heparins (LMWH)

By increasing the activity of antithrombin III (ATIII), UFH affects thrombin, plasmin, and factors IX, X, XI, and XII. UFH also prevents the conversion of fibrinogen to fibrin. The drug is used in numerous settings, including acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), the prophylaxis and treatment of VTE (i.e., DVT and PE), and line patency maintenance. In hospitalized patients who become eligible for outpatient treatment, UFH may be bridged with warfarin until the INR is therapeutic (or bridged with other oral anticoaguants based on the respective manufacturers’ recommendations). Of note, bridge therapy (i.e., using UFH simultaneously with warfarin and discontinuing UFH once the INR is therapeutic) is important because the anticoagulant effects of UFH are more immediate, while it may take warfarin several days to decrease the production of new vitamin K-dependent clotting factors. In addition, the inhibition of factors C and S by warfarin establishes an initial procoagulant state and UFH could minimize the risk of clotting in this period. UFH treatment is usually monitored with the activated partial thromboplastin time (aPTT).

Enoxaparin (Lovenox, Sanofi-Aventis) has a higher ratio of factor Xa to IIa (or thrombin) inhibition compared to UFH. It has been used for VTE prophylaxis and treatment, PCI, ST-elevation MI (STEMI), and unstable angina (UA) or non-ST-elevation MI (NSTEMI). Although dalteparin (Fragmin, Eisai) and tinzaparin (Innohep, Celgene) have mechanisms of action similar to enoxaparin, they are prescribed less frequently. Dalteparin is used for the prophylaxis and treatment of VTE and UA or non-Q-wave MI. Tinzaparin is approved for VTE prophylaxis and treatment, as well as anticoagulation in extracorporeal circuit during hemodialysis. Similar to UFH, each LMWH may be used as bridge therapy with oral anticoagulants. LMWH therapy may be monitored with anti-Xa levels in select populations (e.g., dialysis, obese, long-term anticoagulation). Bleeding situations with LMWHs may be more complicated due to their longer half-lives compared to UFH.

Recommendations for reversing UFH or LMWH include discontinuing the respective anticoagulant and administering protamine sulfate. Cationic hydrogenated protamine (pH of 6.8 to 7.1) reacts with anionic UFH (pH of 5 to 7.5) or LMWH (e.g., enoxaparin with a pH of 5.5 to 7.5) to form a stable, inactive salt com
plex.\textsuperscript{25,26,30} Doses of protamine depend on the route of, and time since, the previous administration of UFH or LMWH.\textsuperscript{17,30}

**Direct Thrombin Inhibitors (DTI)**

In the 2012 CHEST guidelines, dabigatran (Pradaxa, Boehringer Ingelheim) is favored over warfarin for the prevention of stroke and systemic embolism in patients with non-valvular AF.\textsuperscript{31,32} First-line recommendations for the emergent reversal of dabigatran include discontinuing the drug, using prolonged dialysis, and administering a PCC.\textsuperscript{17} If dabigatran was recently ingested (within two hours) and the patient does not have a gastrointestinal bleed, activated charcoal should be given.\textsuperscript{18,32} Other options include using a PCC4 product or a PCC3 product with rfVIIa.\textsuperscript{18} Potential antidotes for dabigatran are discussed later in the "Other Upcoming Antidotes" Section.\textsuperscript{5,33}

**Factor Xa Inhibitors (fXa)**

Fondaparinux (Arixtra, GlaxoSmithKline) is a synthetic pentasaccharide that exhibits activity via an ATIII-mediated selective inhibition of factor Xa (\textit{i.e.}, it is an indirect fXa).\textsuperscript{34} While the pentasaccharide structure is similar to the units in UFH, fondaparinux does not have affinity for platelet factor 4 (PF-4) and it is less likely to induce heparin-induced thrombocytopenia (HIT).\textsuperscript{34} Although it is FDA-approved for the VTE prophylaxis and treatment, fondaparinux is usually reserved for patients who are allergic to UFH or LMWH and have normal renal function (\textit{i.e.}, creatinine clearance >50 mL/min).\textsuperscript{17,34,35} Fondaparinux may also be used as bridge therapy with oral anticoagulants.\textsuperscript{15,34} Anti-Xa levels could be monitored if the calibrator drug is fondaparinux; otherwise, results will be inaccurate.\textsuperscript{34} If patients require fondaparinux reversal, the drug should be discontinued and aPCC or rfVIIa could be administered.\textsuperscript{17}

As of March 2014, apixaban (Eliquis, Bristol-Myers Squibb) and rivaroxaban (Xarelto, Janssen) are the only FDA-approved oral, direct fXa.\textsuperscript{36,37} Similar to dabigatran, apixaban is labeled for reducing the risk of stroke and systemic embolism in patients with non-valvular AF.\textsuperscript{36} Apixaban has been used off-label for VTE prophylaxis postoperatively (knee or hip replacement surgery) and VTE treatment.\textsuperscript{38,39} Rivaroxaban (Xarelto, Janssen) has the broadest FDA-approved indications for an oral fXa, as it is labeled for reducing the risk of stroke and systemic embolism in non-valvular AF patients, the prophylaxis and treatment of VTE, and postoperative (knee or hip replacement surgery) VTE prophylaxis.\textsuperscript{37} Betrixaban (PRT054021, Portola) is a fXa currently in phase 3 trials; it has a long half-life, minimal hepatic metabolism, and minimal renal clearance.\textsuperscript{40}

Current recommendations for the emergent reversal of apixaban or rivaroxaban are discontinuing the respective fXa and administering activated charcoal if the last dose of the fXa was taken with the past two hours.\textsuperscript{18,36,37} Activated charcoal should be given again six hours after its first administration.\textsuperscript{18,36,37} Preferred clotting factor supplements in this setting include PCC4, aPCC, PCC3 with rfVIIa, and/or PCC3.\textsuperscript{17,18}

**ARTICLE FOCUS: ANDEXANET ALFA**

**History**

Andexanet alfa is currently being studied for the reversal of anticoagulation due to direct (\textit{e.g.}, apixaban, rivaroxaban, betrixaban) and indirect (\textit{e.g.}, enoxaparin, fondaparinux) fXa.\textsuperscript{5,9,41-47} Since there are no specific reversal agents for fXa yet, this protein potentially addresses an
unmet need. The FDA designatedandexanet alfa as a breakthrough therapy in late 2013. As of March 2014, there are ongoing phase 3 trials and manufacturers of apixaban, edoxaban, and rivaroxaban have entered clinical collaborations to study the promising antidote.

**Biochemical Composition**

Andexanet alfa is a modified recombinant protein derived from human coagulation factor X, with an approximate molecular weight of 39 kDa (i.e., ~11 kDa light chain and ~28 kDa heavy chain). The protein lacks a membrane-binding γ-carboxyglutamic acid (GLA) domain and it is not catalytically active due to a serine → alanine residue mutation (S419A) in the protease catalytic triad (which is typically composed of histidine, aspartic acid, and serine). Andexanet alfa was expressed in its functional (or activated) form in mammalian cell (Chinese Hamster Ovary [CHO]) culture. Unlike the coagulation cascade with factor X (to obtain factor Xa), andexanet alfa did not require any activation steps by factors VIIa (from the extrinsic pathway) or IXa (from the intrinsic pathway).

**Clinical Pharmacology**

In contrast to human coagulation factor Xa, andexanet alfa is unable to assemble into a prothrombinase complex to cleave prothrombin (factor II) to thrombin (factor IIa) and prothrombin fragments F1 and F2. The investigational antidote does not exhibit detectable procoagulant or anticoagulant activity, as found in a clotting assay examining the effects of rivaroxaban (1 micromole) and andexanet alfa (up to 1.9 micromoles) on human plasma PT prolongation.
As a result of aforementioned modifications, andexanet alfa has high affinity for direct fXa (e.g., apixaban, betrixaban, rivaroxaban). The protein acts as a decoy for direct fXa, binding to these drugs in dose-dependent manner and preventing the antidote-direct-fXa complex from acting on the coagulation cascade. As depicted in Fig. 2, andexanet alfa could also bind to, and modulate the activity of, the complex formed by ATIII and indirect fXa (e.g., LMWH, fondaparinux).

### Pre-Clinical Studies

A study of rivaroxaban 0.23 micromoles in human and rat plasma found that at least 0.5 micromoles of andexanet alfa reversed most of the anticoagulant’s anti-Xa activity. Studies in rats infused with fXaI and andexanet alfa are described in Table 2. In general, while the plasma concentrations (Cp) of the fXaI increased after bolus and infusion administrations of andexanet alfa (secondary to redistribution from extravascular compartments), the overall percentage of unbound or free drug dramatically decreased within 90 minutes. These decreases in the plasma free fractions (Fp) of fXaI correlated with respective INR normalizations.

To confirm if the normalization of aforementioned surrogate markers (e.g., anti-Xa, PT/INR, aPTT) correlated with the cessation of clinical bleeding, investigators utilized a rabbit model of liver laceration. Anesthetized rabbits were injected with a bolus of rivaroxaban 1 mg/kg, and after 30 minutes, the rabbits either received a bolus of the vehicle or andexanet alfa 75 mg. The experiment found that andexanet alfa reduced blood loss by more 85%, as well as decreased peak anti-Xa activity by 98%, PT by 74%, aPTT by 66%, and the Fp of rivaroxaban from 26% +/− 0.9% to 0.5% +/− 0.3% (i.e., a 98% reduction).

In addition to direct fXaI, researchers also tested the effects of andexanet alfa on LMWH (e.g., enoxaparin) and pentasaccharide (e.g., fondaparinux) anticoagulants, both of which increase the activity of ATIII. Results from a rat tail resection model of blood loss with bolus doses of enoxaparin and andexanet alfa are summa-

<table>
<thead>
<tr>
<th></th>
<th>Post-fXaI</th>
<th>Post-fXaI + Andexanet Alfa</th>
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<tbody>
<tr>
<td></td>
<td>Drug Cp µM</td>
<td>Drug Fp %</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.4 +/− 0.3</td>
<td>1.5 +/− 0.3</td>
</tr>
<tr>
<td>0.5 mg/kg/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betrixaban</td>
<td>0.2 +/− 0.01</td>
<td>40 +/− 7.2</td>
</tr>
<tr>
<td>1 mg/kg/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.4 +/− 0.4</td>
<td>2.2 +/− 0.8</td>
</tr>
<tr>
<td>0.25 mg/kg/hr</td>
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</table>

Table 2. Studies in rats infused with direct factor Xa inhibitors and andexanet alfa. Direct fXa were infused for 30 minutes, followed by andexanet alfa bolus over 5 minutes and infusion for 90 minutes. Measured in micromoles, with the mean +/− standard deviation.

fXa: factor Xa inhibitors; Cp: plasma concentration; Fp: plasma free fraction; hr: hour.
### Table 3. Study of rats infused with boluses of enoxaparin and andexanet alfa.

<table>
<thead>
<tr>
<th>Andexanet Alfa</th>
<th>Reduction in Anti-Xa Activity</th>
<th>Reduction in Blood Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg</td>
<td>13%</td>
<td>N/A</td>
</tr>
<tr>
<td>1 mg</td>
<td>35%</td>
<td>60%</td>
</tr>
<tr>
<td>2 mg</td>
<td>52%</td>
<td>56%</td>
</tr>
<tr>
<td>4 mg</td>
<td>81%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Indirect fXa (i.e., enoxaparin 4.5 mg/kg) were given as an intravenous bolus over 5 minutes; the rat’s tail was then resected; 10 minutes after the injury, andexanet alfa was given as a bolus over 5 minutes. Blood loss was measured for an additional 45 minutes after andexanet alfa was administered.

Overall, an IV bolus of andexanet alfa immediately decreased the C<sub>9</sub> of apixaban and rivaroxaban compared to placebo. 46,47 Similar to what was observed in pre-clinical studies, there were also initially significant, dose-dependent decreases in anti-Xa activity, but anti-Xa activity slowly increased to high levels again within 2 hours. 9,46,47 This phenomenon will most likely be alleviated in future studies with an IV bolus plus extended-infusion regimen of andexanet alfa (as performed in a pre-clinical experiment). 9,60

### Adverse Drug Reactions

Researchers have presented some data, but the true incidence and complete description of adverse reactions from andexanet alfa will require larger study populations. 46,47

In a phase 2 cohort of patients who received apixaban and andexanet alfa, there were transient reductions in tissue factor pathway inhibitor (TFPI) activity. 46 Of note, TFPI is an endogenous, reversible fXa. 61 There were increases in prothrombin fragments F1 and F2, but no changes in D-dimer. 46 Andexanet alfa was well-tolerated; no thrombotic, allergic-type, or serious adverse events were observed, and there were no deaths. 46 Although 5 of 9 (56%) of pa
tients experienced some type of adverse event, Crowther M, et al. described all of the reactions as mild in nature. 

Patients who received rivaroxaban andandexanet alfa in a phase 2 cohort had no increases in prothrombin fragments F1 and F2, thrombin-antithrombin, or D-dimer (highlighting the inability of andandexanet alfa to form a prothrombinase complex with factor Va or exhibit other prothrombotic properties). As observed previously, TFPI activity expectedly decreased due to binding with andandexanet alfa. The investigational antidote was well tolerated; no thrombotic, serious, or severe adverse events were observed. Reported adverse events in the nine-patient cohort included mild infusion-related reactions (n=3; 33%), post-procedural hematoma (n=2; 22%), headache (n=2; 22%), postural dizziness (n=2; 22%).

### OTHER UPCOMING ANTIDOTES

**Idarucizumab**

Idarucizumab (aDabi-Fab / BI 655075, Boehringer Ingelheim) is a fully humanized antibody fragment (Fab) against dabigatran. Based on X-ray crystallization techniques, there are many structural similarities between the dabigatran-thrombin and dabigatran-idarucizumab complexes; in the latter complex, there

<table>
<thead>
<tr>
<th>FXaI (days 1 to 6)</th>
<th>Andexanet alfa dose (IV bolus)</th>
<th>Total Subjects</th>
<th>Andexanet alfa to FXaI Cₚ molar ratio</th>
<th>Anti-Xa activity after andandexanet alfa</th>
<th>Anti-Xa activity after placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5 mg BID (11 doses)</td>
<td>90 mg</td>
<td>9</td>
<td>0.66 (474:314)</td>
<td>2 min: -65%</td>
<td>2 min: +6%</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg QD (6 doses)</td>
<td>210 mg</td>
<td>9</td>
<td>0.8 (1.2:1.6)</td>
<td>2 min: -20%</td>
<td>2 min: +0%</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg QD (6 doses)</td>
<td>420 mg</td>
<td>9</td>
<td>1.2 (2.6/2.1)</td>
<td>2 min: -53%</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

Table 4. Preliminary results from ongoing phase 2 trials of andandexanet alfa and factor Xa inhibitors. FXaI: factor Xa inhibitors; Cₚ: plasma concentration; BID: twice daily; IV: intravenous
is a 350-fold stronger affinity for the oral DTI.\textsuperscript{33} Idarucizumab does not seem to bind known thrombin substrates nor does it demonstrate prothrombotic properties.\textsuperscript{33}

Promising results from pre-clinical (rat and pig models) and phase 1 trials have been presented, and more data is expected as the potential antidote enters larger studies.\textsuperscript{62-74}

**Aripazine**

Aripazine (PER977, Perosphere) is a rationally-designed, synthetic, small molecule with broad reversal activity.\textsuperscript{75-79} Based on dynamic light scattering (DLS) techniques, it is a potential antidote for oral (e.g., direct fXaI [apixaban, edoxaban, rivaroxaban], DTI [dabigatran]) and parenteral (e.g., UFH, LMWH, fondaparinux) anticoagulants.\textsuperscript{75-79} As with andexanet alfa and idarucizumab, the agent is devoid of procoagulant properties.\textsuperscript{75-79}

Pre-clinical (rat and dog models) data is promising, but more studies need to be conducted to elucidate its safety and efficacy.\textsuperscript{75-79}

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**CONCLUSION**

In addition to vitamin K and protamine, andexanet alfa has the potential to become an approved, specific antidote for currently irreversible and increasingly prescribed anticoagulants \textit{(i.e.,} direct and indirect fXaI\textit{)}. Pre-clinical and clinical studies have only provided glimpses of the novel protein’s pharmacokinetics and pharmacodynamics. Andexanet alfa is expected to benefit both patients and providers, as it successfully reversed the anticoagulant effects of rivaroxaban and apixaban without establishing a pro-coagulant state in pre-clinical and initial human trials. As the protein enters larger-scale trials to reverse anticoagulation, more data will be published related to its safety and efficacy. Additional antidotes for fXaI and DTI are also under investigation, and their respective clinical outcomes data is highly anticipated.

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55. Morita T, Jackson CM. Preparation and properties of derivatives of bovine factor X and factor Xa from which the gamma-carboxyglutamic acid containing domain has been removed. J Biol Chem. 1986 Mar 25;261(9):4015-23.


