A New Strategy for Uncontrollable Bleeding After Treatment With Rivaroxaban or Apixaban

Discussants

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Abstract: Anticoagulants are used in several settings to reduce the risk of thromboembolic events, but they can be associated with severe complications, such as potentially fatal bleeding. Two of the most widely used direct oral anticoagulants (DOACs), rivaroxaban and apixaban, are factor Xa inhibitors. If a patient receiving treatment with a factor Xa inhibitor presents with a major bleeding event, the physician must determine whether reversal of anticoagulation is needed. Rivaroxaban and apixaban have relatively short half-lives. In some cases, it may be sufficient to provide supportive care while the agent is metabolized. The administration of a specific agent to reverse factor Xa inhibition may be clinically indicated in certain settings, such as when rivaroxaban and apixaban were given less than 12 hours earlier (assuming normal renal function), when the timing of the previous dose is unknown, or in the event of a catastrophic bleed. The US Food and Drug Administration (FDA) recently granted accelerated approval to andexanet alfa, a recombinant protein analogue of factor Xa, for patients treated with rivaroxaban or apixaban who require reversal of anticoagulation owing to life-threatening or uncontrolled bleeding. Off-label treatments used in this setting include prothrombin complex concentrates.

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Rationale for the Use of Rivaroxaban or Apixaban

Direct oral anticoagulants (DOACs) have been approved by the US Food and Drug Administration (FDA) for the management of a variety of conditions associated with increased risk for thromboembolic events. Five DOACs are commercially available in the United States. Rivaroxaban and apixaban are the most frequently prescribed DOACs in this country. Rivaroxaban has several clinical indications, including to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, to treat and prevent deep vein thrombosis or pulmonary embolism in major surgical scenarios, and (in combination with aspirin) to reduce the risk for major cardiovascular events (eg, cardiovascular death, myocardial infarction, embolic stroke) in patients with chronic coronary artery disease or peripheral artery disease.[1] Apixaban is approved to reduce the risk of embolic stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and to treat and prevent primary or secondary deep vein thrombosis or pulmonary embolism.[2]

Rivaroxaban and apixaban are selective and specific inhibitors of factor Xa. Neither agent requires a cofactor (eg, anti-thrombin III) for activity, and both inhibit free circulating factor Xa, thereby reducing thrombin generation by interfering with prothrombinase activity. These agents also inhibit clot-bound factor Xa. They have no direct effect on platelet aggregation. Instead, they decrease thrombin generation and fibrin formation by inhibiting factor Xa, and thus can inhibit platelet aggregation induced by thrombin and mediated by fibrin.[1,2]

Risk for Developing Uncontrollable Bleeding With Rivaroxaban or Apixaban

The ever-increasing prescription of oral factor Xa inhibitor agents is expected to correlate with an accompanying increase in bleeding complications, particularly with an aging population. For example, estimates for the number of bleeding admissions owing to anticoagulation have increased from 90,000 in 2015 to nearly 170,000 in 2018, suggesting an approximate 20% increase each year.[3,4] In 2018, it was estimated that approximately 408 patients were hospitalized each day owing to a rivaroxaban- or apixaban-related bleeding event.[4] When this analysis is supplemented with data from the ROCKET AF (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation) and ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trials, it is estimated that approximately 70 patients die each day following hospitalization for bleeding related to rivaroxaban or apixaban.[4-6] The rate of 30-day mortality related to intracranial hemorrhage (ICH) was 48% in the ROCKET AF trial and 45% in the ARISTOTLE trial (Figure 1). The times to major bleeding events in these trials are shown in Figures 2 and 3.

An initial assessment of the bleed severity in patients receiving factor Xa inhibitor agents is critical to make appropriate treatment decisions. The initial assessment should include a focused history and physical examination that includes vital signs and laboratory evaluation. The time of onset, location, and severity of bleeding should
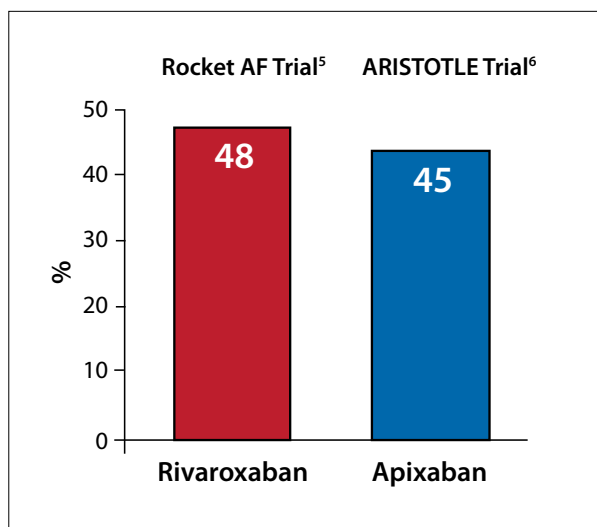
Figure 1. Rates of 30-day mortality related to intracranial hemorrhage in the ROCKET AF and ARISTOTLE trials. ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation. Data from Piccini JP et al. *Eur Heart J.* 2014;35(28):1873-1880[5] and Held C et al. *Eur Heart J.* 2015;36(20):1264-1272.[6]

be determined when possible. Critically, the physician must determine whether bleeding is ongoing. Assessment of hemodynamic instability should occur promptly and repeated frequently.[7]

In 2017, the American College of Cardiology (ACC) Expert Consensus Decision Pathway provided recommendations for the management of bleeding in patients receiving oral anticoagulants.[7] This statement classified a major bleed as those bleeding events that occurred in an anatomically critical site, led to hemodynamic compromise, or were associated with a decrease in hemoglobin levels of at least 2 g/dL (when baseline was known) or requiring transfusion of at least 2 U of packed red blood cells. Critical site bleeds are those that will compromise the function of the affected organ, increasing the risk for severe disability and requiring surgical intervention to achieve hemostasis. The ACC guidelines define several types of critical site bleeds. ICHs include intraparenchymal, subdural, epidural, and subarachnoid hemorrhages. Other critical site bleeds include pericardial tamponade, airway bleeds, extremity bleeds, hemothorax, nongastrointestinal (GI) intra-abdominal bleeding, retroperitoneal hematoma, and hemodynamic instability. Another critical event is a reduction in hemoglobin of 2 g/dL or more or a reduction that requires transfusion of at least 2 U of red blood cells. These bleeding events are associated with

a significantly increased risk for death. This risk is further increased in patients with cardiovascular disease.

Reversal of Anticoagulation

Rivaroxaban and apixaban can both lead to fatal bleeding events in some cases.[1,2] Much effort has focused on the development of agents and strategies to reverse the anticoagulant effect of factor Xa inhibitors, such as rivaroxaban and apixaban. In May 2018, the FDA approved andexanet alfa as the first and only antidote for patients treated with rivaroxaban and apixaban who require reversal of anticoagulation owing to life-threatening or uncontrolled bleeding. Andexanet alfa (also known as coagulation factor Xa [recombinant], inactivated-zhzo) provides specific reversal of factor Xa inhibition by functioning as a decoy factor Xa without procoagulant properties, thus competitively interfering with naturally generated and circulating factor Xa. Approval of andexanet alfa was based on the single-arm phase 3 ANNEXA-4 trial of patients with bleeding (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors).[8] The availability of andexanet alfa will likely increase confidence among physicians who choose to use DOACs such as rivaroxaban and apixaban, by providing a potential specific and rapidly acting antidote in the event of a catastrophic bleed.

Among patients with a critical bleed, physicians must try to determine whether factor Xa inhibition reversal is necessary. Both apixaban and rivaroxaban have short circulating half-lives. In some cases, it may be sufficient to "wait out" the half-life of the drug. Catastrophic bleeds, however, require immediate reversal. Reversal of factor Xa inhibition should also be considered when the anticoagulant effect must be neutralized rapidly so a patient can undergo surgery. Andexanet alfa is a potentially useful drug to meet this unmet need because it can neutralize the anticoagulant effect of apixaban and rivaroxaban within minutes of administration. Once administered, it provides enough time to allow clot formation or surgical intervention to stop the bleed.

In studies of andexanet alfa, the reduction in anticoagulation markers only weakly correlated with improved outcomes.[9] Andexanet alfa has not been evaluated in prospective randomized controlled trials. In addition, the clinical trials showed thrombotic complications with uncertain etiologies; it was not known whether they were caused by the underlying hypercoagulability state, delayed reinitiation of anticoagulation, use of andexanet alfa, or some other factor. A clear finding from ANNEXA-4 is that no thrombotic complications occurred after the DOAC was reinstated, in contrast to low-molecular-weight heparin or unfractionated heparin. Results from ANNEXA-4 may have been biased by enrollment of a population with a better prognosis than would be
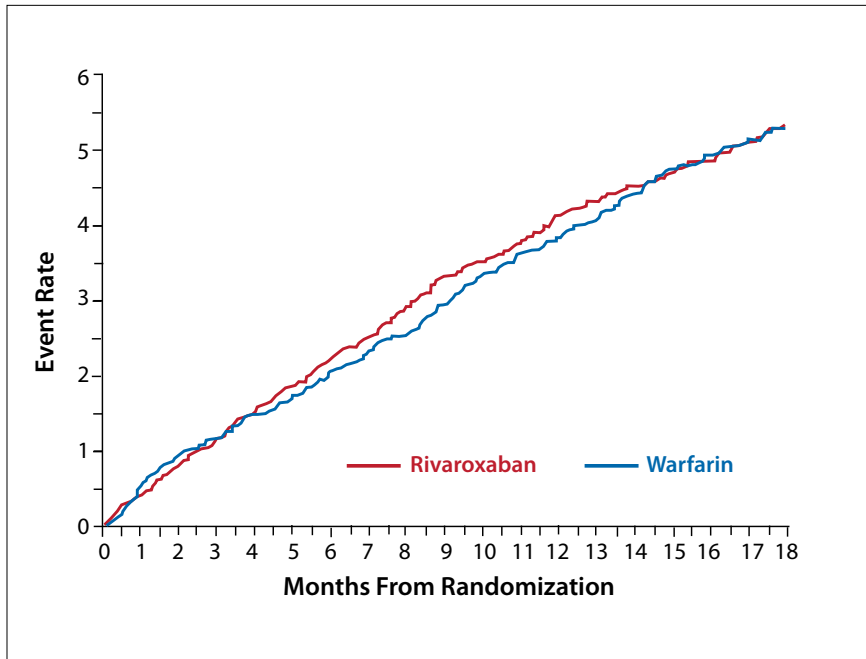
Figure 2. The time to a major bleeding event according to treatment arm in the ROCKET AF trial. ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation. Adapted from Piccini JP et al. *Eur Heart J.* 2014;35(28):1873-1880.[5]
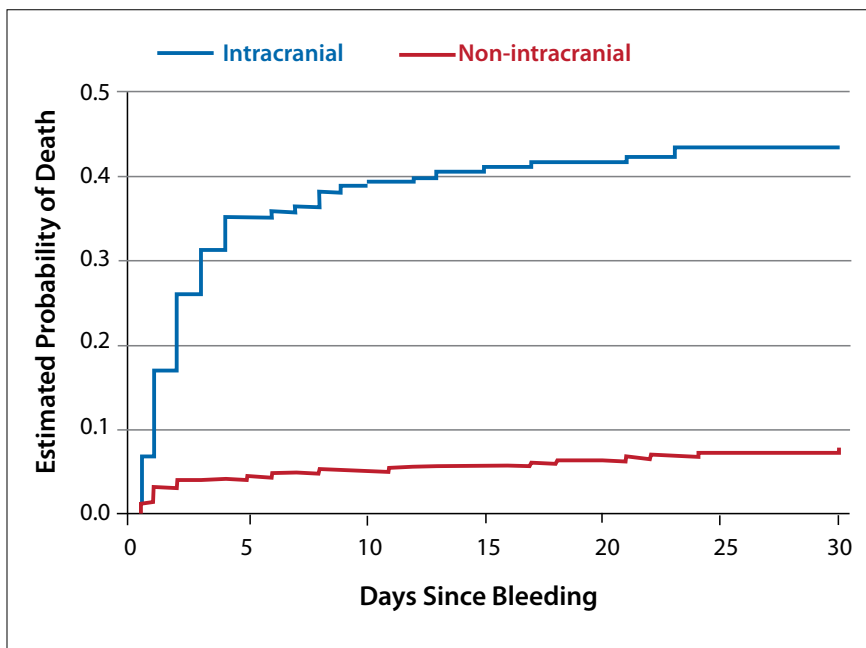
Figure 3. All-cause deaths after major bleeding in the ARISTOTLE trial. ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation. Adapted from Held C et al. *Eur Heart J.* 2015;36(20):1264-1272.[6]

encountered in the real world. There were no anti-drug antibodies noted with andexanet alfa, which is in contrast to idarucizumab. There were several deaths reported in the study. Andexanet alfa is very expensive, so the cost-benefit ratio is important, and the drug is not readily available at many hospitals. Andexanet alfa must be used carefully, and patient selection is critical.

Other treatments, such as prothrombin complex concentrates (PCCs), have been evaluated in this setting, but none have received approval by the FDA for this indication. (The manufacturers have not pursued approval for this indication.) Two clinical trials have shown reasonable efficacy for PCCs to reverse bleeding associated with DOACs, although the data were perhaps inferior to those

reported with andexanet alfa.[10,11] There are no head-to-head studies evaluating DOACs and PCCs. For all of the reversal agents, there is some question as to whether rapid reduction of anticoagulation translates to reduced mortality or improved outcomes.

Disclosure

Dr Kessler is a member of the advisory boards of Portola and Janssen, and he has received honoraria from these companies. He is not a member of any speakers bureaus, he has not received any research grants, and he has no stockholdings to report.

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Andexanet Alfa, an Antidote for Uncontrollable Bleeding After Treatment With Rivaroxaban or Apixaban

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Current Management of Uncontrollable Bleeding After Rivaroxaban or Apixaban

When a patient presents to the emergency department with bleeding while receiving treatment with rivaroxaban or apixaban, a number of factors must be considered. The first consideration is the time at which the last dose was administered, although this information is often unavailable. In an ideal world, there would be a reliable, rapidly available test for anti–factor Xa levels in the patient's blood to guide reversal strategies; however, no such test is currently widely available.

The next consideration is whether the patient can safely wait out the factor Xa inhibition, given the short half-lives of these agents. For example, a patient who presents with GI bleeding but stable vital signs may not be at high risk for hemorrhagic shock. Many of these patients can be appropriately managed with supportive care while their factor Xa inhibitor cycles through its half-life.

In contrast, certain scenarios require consideration of treatment beyond supportive care. An example would be a patient who presents with current or impending hemorrhagic shock. In these situations, the emergency physician must decide if the patient requires reversal or resuscitation. It is important to remember that patients with significant bleeding have lost not only red blood cells, but also their platelets and coagulation factors (beyond just factor Xa), as well as the factor Xa inhibitor that they were taking. For such patients, restoring coagulation requires more than simply reversing whatever factor Xa inhibitor remains, and massive transfusion protocols (including plasma, platelets, and other factors, such as cryoprecipitate) should be considered.

Another category of patients who require treatment beyond supportive care are those with bleeding in critical spaces, such as the brain. In the brain, even a few extra milliliters of blood are catastrophic and can result in significant morbidity or death. For these patients, the primary issue is not blood loss, but rather that blood is filling a critical space and compressing vital structures.

Overview of Andexanet Alfa

Andexanet alfa (also known as coagulation factor Xa [recombinant], inactivated-zhzo) is currently the only therapy approved by the FDA for the reversal of factor Xa inhibition. Initially approved in 2018, andexanet alfa is indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed owing to life-threatening or uncontrolled bleeding.[1] This indication for andexanet alfa was approved under the FDA's Accelerated Approval Program, based on a single-arm clinical trial,[2] and continued approval for this indication may be contingent upon the results of future studies, including an ongoing randomized controlled trial. Andexanet alfa is currently approved only for bleeding related to apixaban or rivaroxaban.[1]

The active ingredient of andexanet alfa is a variant of recombinant human factor Xa.[3] Genetic modification of the protein has resulted in a substitution of the active site serine with the amino acid alanine, rendering the molecule unable to cleave and activate prothrombin. In a further effort to reduce potential anticoagulant effects, the gamma-carboxyglutamic acid (Gla) domain was also removed to eliminate the protein's ability to assemble into the prothrombinase complex. This genetically modified version of recombinant human factor Xa binds and sequesters factor Xa inhibitors, including rivaroxaban and apixaban. In this mechanism, andexanet alfa works as a decoy, competing with endogenous factor Xa to bind to these factor Xa inhibitors. Therefore, andexanet alfa reverses the anticoagulant effects of factor Xa inhibitors, restoring the activity of endogenous factor Xa. Andexanet alfa also binds to and inhibits the activity of the tissue

Table 1. Dosing of Andexanet Alfa[1]

Factor Xa Inhibitor Agent Received	Previous Dose Level of the Factor Xa Inhibitor	Timing of the Previous Dose of the Factor Xa Inhibitor	
		<8 Hours or Unknown	≥8 Hours
Rivaroxaban	≤10 mg	Low dose of andexanet alfa	Low dose of andexanet alfa
	>10 mg or unknown	High dose of andexanet alfa	
Apixaban	≤5 mg	Low dose of andexanet alfa	
	>5 mg or unknown	High dose of andexanet alfa	

factor pathway inhibitor. Inhibition of this activity increases tissue factor–initiated thrombin generation, resulting in a procoagulant effect.[4]

Andexanet alfa is administered as either a low- or high-dose intravenous (IV) bolus followed by an IV infusion.[1] The low dose is an initial IV bolus of 400 mg at a target rate of 30 mg/min, followed by a 4 mg/min infusion for up to 120 minutes (480 mg total). The high dose is an initial IV bolus of 800 mg at a target rate of 30 mg/min, followed by an 8 mg/min infusion for up to 120 minutes (960 mg total).

The dose of andexanet alfa that reverses the effects of rivaroxaban at its highest approved dose exceeds that required to reverse the effects of apixaban at its highest approved dose, owing to both the greater initial maximum plasma concentration of rivaroxaban and its larger volume of distribution.[5] Therefore, the recommended dosing of andexanet alfa is based on the specific factor Xa inhibitor used (rivaroxaban or apixaban), the dose level, and the time since the administration of the previous dose (Table 1).

Clinical Data Supporting the Use of Andexanet Alfa

The efficacy and safety of andexanet alfa were initially evaluated in 2 randomized controlled trials that enrolled healthy volunteers. Patients in the ANNEXA-R trial (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Rivaroxaban) had received rivaroxaban, and those in ANNEXA-A (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Apixaban) had received apixaban.[5] Efficacy and safety were further evaluated in the single-arm phase 3 ANNEXA-4 trial of patients with bleeding (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors).[2]

ANNEXA-R and ANNEXA-A
ANNEXA-R and ANNEXA-A were parallel clinical trials designed to evaluate the efficacy and safety of andexanet alfa for the reversal of anticoagulation with apixaban

or rivaroxaban in older healthy volunteers.[5] Both were randomized, double-blind, placebo-controlled phase 3 studies that evaluated the efficacy of andexanet alfa in reversing anticoagulation caused by apixaban or rivaroxaban. Each study was conducted at a different single clinical site.

The trials randomly assigned healthy volunteers ages 50 to 75 years in either a 2:1 fashion (ANNEXA-R) or a 3:1 fashion (ANNEXA-A) to receive andexanet alfa or matching placebo.[5] Each study consisted of 2 consecutive parts. Part 1 assessed only a bolus administration of andexanet alfa. Part 2 assessed outcomes after administration of both the bolus and follow-up infusion of andexanet alfa. To adequately evaluate these outcomes, the healthy participants were housed at the study site for 8 days. Additional safety follow-up occurred on days 15, 36, and 43 after administration of andexanet alfa.

In the ANNEXA-R study, participants first received rivaroxaban (20 mg orally once daily) for 4 days to achieve steady-state plasma levels at the highest approved dose of rivaroxaban.[5] Four hours after the last dose of rivaroxaban on day 4, patients received an 800-mg IV bolus of andexanet alfa (in part 1) or an 800 mg IV bolus followed by a continuous 8 mg/min infusion for 120 minutes (960 mg in total; in part 2).

In the ANNEXA-A study, participants first received apixaban at 5 mg orally twice daily for 3.5 days to achieve steady-state plasma levels at the highest approved dose.[5] Three hours after the last dose of apixaban on day 4, patients received a 400-mg IV bolus of andexanet alfa (in part 1) or a 400 mg IV bolus followed by a continuous 4 mg/min infusion for 120 minutes (480 mg in total; in part 2).

In both studies, the primary endpoint was the percent change in anti–factor Xa activity from baseline (before administration of either andexanet alfa or placebo) to nadir (after administration of andexanet alfa or placebo).[5] Anti–factor Xa activity was measured using a validated chromogenic enzymatic assay of factor Xa enzymatic activity. Secondary efficacy endpoints included the proportion of participants with a reduction of 80% or higher in anti–factor Xa activity from baseline to nadir, the change

in unbound inhibitor plasma concentration from baseline to nadir, the change in thrombin generation (measured as the change in endogenous thrombin potential), and the occurrence of an endogenous thrombin potential above the lower limit of the normal range derived at baseline. Based on the lack of a clinically validated reference range for endogenous thrombin potential, the normal range was prospectively defined as the mean endogenous thrombin potential at baseline on day 1, plus or minus 1 standard deviation. An additional secondary endpoint limited to part 2 of each study was the percent change in anti–factor Xa activity from baseline to the postbolus nadir. All efficacy endpoints were assessed in the modified intention-to-treat population, which was defined as those participants who underwent randomization, received any amount of andexanet alfa or placebo, and had a baseline measurement of anti–factor Xa activity and at least 1 measurement of anti–factor Xa activity after administration of andexanet alfa or placebo.

A total of 145 healthy volunteers were enrolled in the 2 studies from March 2014 through May 2015.[5] Among the 80 participants enrolled in ANNEXA-R, 53 were randomly assigned to receive andexanet alfa and 27 to placebo. Among the 65 participants enrolled in ANNEXA-A, 48 were randomly assigned to receive andexanet alfa and 17 to placebo. Across both studies, the mean age of the healthy volunteers was 57.9 years, and 39% were female. Baseline characteristics were balanced between the treatment arms.

The primary endpoint, percent change in anti–factor Xa activity from baseline to nadir, showed rapid reductions immediately (within 2 and 5 minutes) following bolus administration of andexanet alfa. Mean reductions of anti–factor Xa activity from baseline to nadir were higher with andexanet alfa compared with placebo in subjects who had received either rivaroxaban (92% vs 18%, respectively; $P<.001$) or apixaban (94% vs 21%, respectively; $P<.001$).

Following bolus administration of andexanet alfa, the reversal of anti–factor Xa activity was maintained for 2 hours, after which anti–factor Xa activity gradually returned to levels similar to those in placebo-treated participants (Figures 4 and 5).[5] When anti–factor Xa activity was assessed after both bolus and follow-up infusion (in part 2), andexanet alfa was associated with a greater reduction in activity as compared with placebo among patients treated with rivaroxaban (97% vs 45%, respectively; $P<.001$) and apixaban (92% vs 33%, respectively; $P<.001$).

Nearly all study subjects who received andexanet alfa experienced an 80% or higher reversal of anti–factor Xa activity.[5] The one exception was a participant in the ANNEXA-R study who did not receive the full planned dose of andexanet alfa. In contrast, none of the placebo-treated participants experienced an 80% or higher reversal ($P<.001$). The study authors noted that among those subjects treated with placebo, anti–factor Xa activity decreased over time at the expected rate, assuming typical clearance of the anticoagulant agent.

Study participants treated with andexanet alfa showed more rapid restoration of thrombin generation compared with those who received placebo.[5] In part 1, the mean change in thrombin generation was significantly greater following andexanet alfa bolus compared with placebo bolus for both rivaroxaban (1314.2 nM/min vs 173.9 nM/min; $P<.001$) and apixaban (1323.2 nM/min vs 88.2 nM/min; $P<.001$). In part 2, the mean change in thrombin generation was also significantly greater with andexanet alfa bolus plus follow-on infusion vs placebo for both rivaroxaban (1510.4 nM/min vs 264.4 nM/min; $P<.001$) and apixaban (1193.1 nM/min vs 189.4 nM/min; $P<.001$).

In part 1 of each study, treatment with andexanet alfa led to rapid generation of thrombin (within 2 to 10 minutes after bolus) to beyond the lower limit of the normal range in 96% of the treatment arm in ANNEXA-R and 100% in ANNEXA-A.[5] In the placebo arms, these rates were 7% and 11%, respectively ($P<.001$ for each comparison). As with the primary endpoint, the only subject who did not achieve this endpoint was the individual who mistakenly did not receive the full planned dose of andexanet alfa. Similarly, in part 2, treatment with andexanet alfa was associated with restored thrombin generation in 100% of all participants in both studies. In comparison, this endpoint was achieved by 0% of the placebo arm in ANNEXA-R and 25% of the placebo arm in ANNEXA-A ($P<.001$ for each comparison).

In part 1, the mean concentration of unbound (active) factor Xa inhibitor in plasma was reduced within 2 to 5 minutes by a significantly greater amount with bolus andexanet alfa vs placebo. These reductions were 23.4 ng/mL vs 4.2 ng/mL ($P<.001$), respectively, for rivaroxaban and 9.3 ng/mL vs 1.9 ng/mL for apixaban ($P<.001$). This reversal was sustained with a bolus plus an infusion of andexanet alfa. In part 2, the reductions in mean plasma concentrations of unbound rivaroxaban were 30.3 ng/mL in the treatment group vs 12.1 ng/mL in the control arm ($P<.001$). The reductions in mean plasma concentrations of unbound apixaban were 6.5 ng/mL vs 3.0 ng/mL, respectively ($P<.001$).

After administration of andexanet alfa, the mean concentration of unbound rivaroxaban was less than 4.0 ng/mL, and the mean concentration of unbound apixaban was less than 3.5 ng/mL. Following completion of the bolus or infusion of andexanet alfa, the concentrations of unbound factor Xa inhibitor returned to placebo levels within 1 to 3 hours.
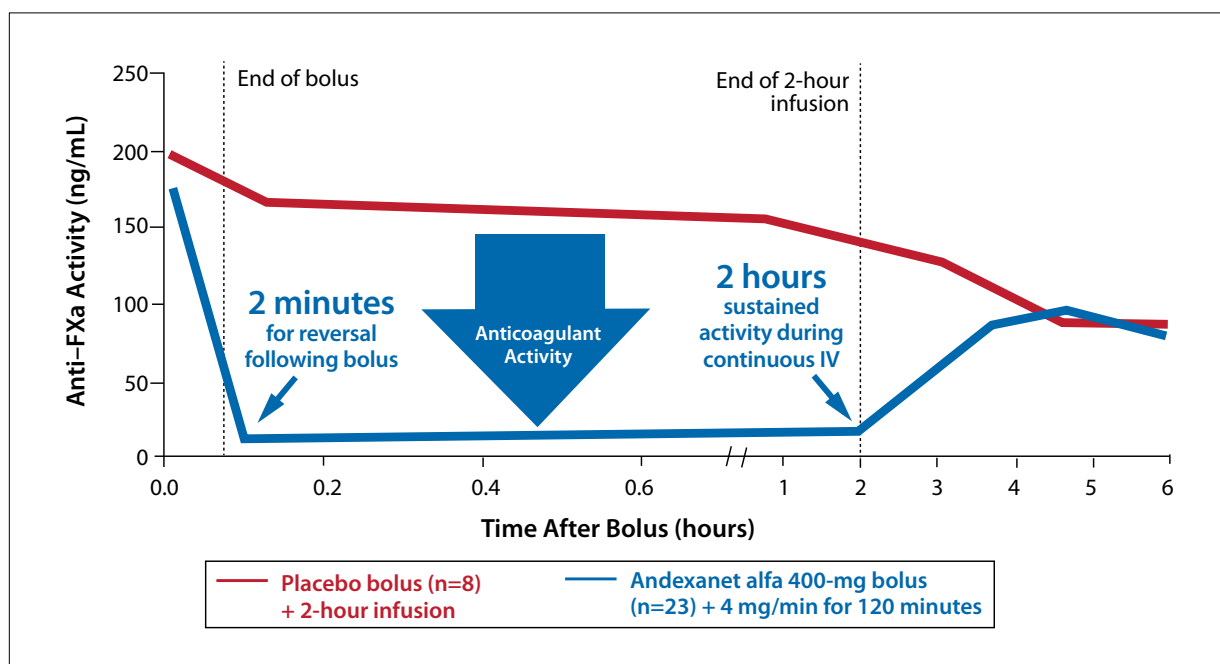
Figure 4. Levels of rivaroxaban among healthy participants treated with andexanet alfa or placebo in the ANNEXA-R trial. ANNEXA-R, Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Rivaroxaban; IV, intravenous. Adapted from Siegal DM et al. *N Engl J Med.* 2015;373(25):2413-2424.[5]
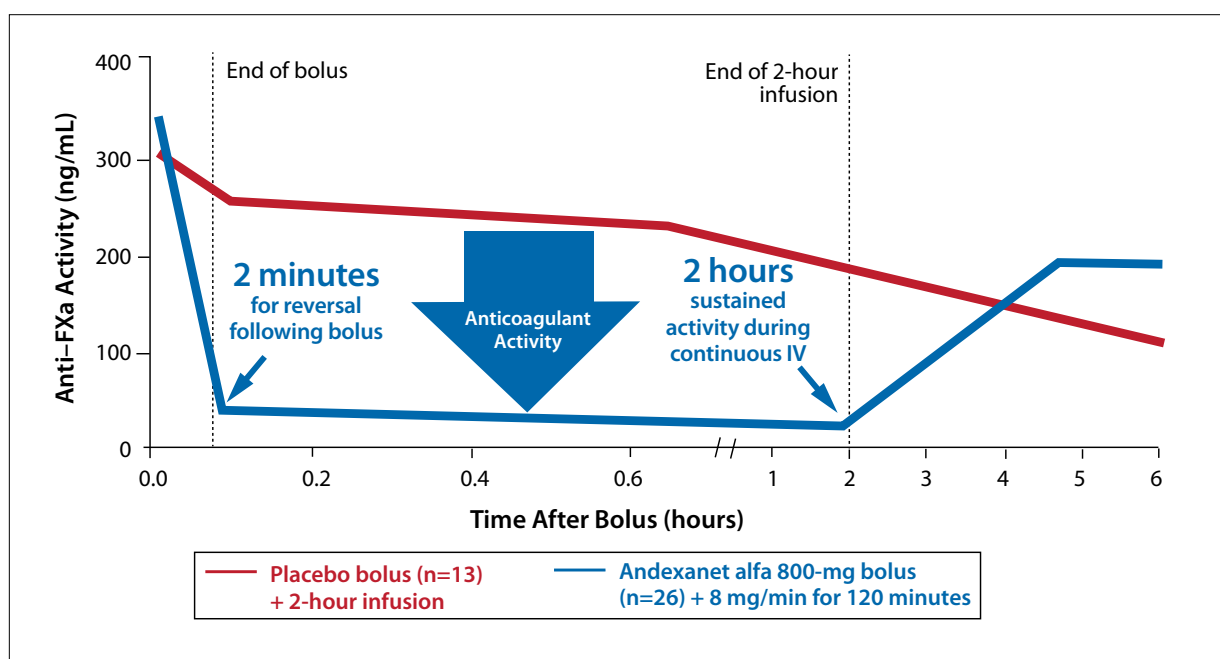
Figure 5. Levels of apixaban among healthy participants treated with andexanet alfa or placebo in the ANNEXA-A trial. ANNEXA-A, Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Apixaban; IV, intravenous. Adapted from Siegal DM et al. *N Engl J Med.* 2015;373(25):2413-2424.[5]

All adverse events associated with andexanet alfa administration were mild. No serious or severe adverse events were reported. Additionally, no thrombotic events were reported. The andexanet alfa infusion led to erythematous hives in 1 study participant, who had a history of hives. The hives were resolved with a single oral dose of diphenhydramine.

Throughout the entire study follow-up period, there

was no detection of antibodies to factor X or factor Xa, or of neutralizing antibodies against andexanet alfa. Non-neutralizing antibodies against andexanet alfa were detected in 1 study participant who received placebo and in 17 of 101 participants (17%) who received andexanet alfa. In general, these non-neutralizing antibodies appeared within 15 to 30 days following treatment with andexanet alfa.

The study investigators concluded that andexanet alfa was associated with rapid reversal of rivaroxaban-induced and apixaban-induced changes in anti–factor Xa activity and thrombin generation, and that these effects were observed in the absence of serious adverse events or clinical thrombosis.[5] The authors noted that these data were consistent with the known mechanism of action of andexanet alfa, whereby high-affinity binding to the factor Xa inhibitor (either rivaroxaban or apixaban) prevented factor Xa inhibition by reducing unbound plasma levels of the anticoagulant. Reversal of the anticoagulant effect occurred rapidly, within 2 to 5 minutes after bolus administration, and was sustained during the continuous infusion. Anticoagulation returned to placebo levels within 1 to 3 hours following andexanet alfa treatment.

ANNEXA-4

The ANNEXA-4 study was conducted to evaluate the efficacy and safety of andexanet alfa in patients experiencing an acute major bleeding event during treatment with a factor Xa inhibitor. Interim results from the ANNEXA-4 study were originally published in 2016, and the final analysis was published in early 2019.[2,6] ANNEXA-4 was a multicenter, prospective, open-label, single-group cohort study that enrolled adult patients from 63 centers throughout North America and Europe from April 2015 through May 2018.[2] The study enrolled patients who had presented with acute major bleeding and had received within the prior 18 hours a dose of a factor Xa inhibitor (either apixaban, rivaroxaban, or edoxaban at any dose, or enoxaparin at a dose of ≥1 mg/kg/day). Acute major bleeding was defined by 1 of the following criteria: potentially life-threatening bleeding with signs or symptoms of hemodynamic compromise (such as severe hypotension, poor skin perfusion, mental confusion, or low cardiac output); bleeding associated with a decrease of 2 g/dL or more in the hemoglobin level; or bleeding in a critical area or organ (for example, retroperitoneal, intra-articular, pericardial, epidural, or intracranial bleeding, or intramuscular bleeding with compartment syndrome). Exclusion factors included surgery planned within 12 hours after andexanet alfa treatment, an expected survival time of less than 1 month, the occurrence of a thrombotic event within 2 weeks prior to enrollment, and receipt of any of the following agents within the 7 days prior to planned administration of andexanet alfa: a vitamin K antagonist, dabigatran, a prothrombin complex concentrate (PCC), recombinant factor VIIa, whole blood, or plasma.

For a portion of the study, enrollment was limited to patients with ICH in order to enrich the study population for this group. Exclusion criteria specific to this group included a Glasgow Coma Scale score of less than 7 and ICH volume exceeding 60 cc.

All patients received andexanet alfa administered first as an initial 15- to 30-minute bolus, followed by a 2-hour infusion. Andexanet alfa was administered as a bolus dose of 400 mg and an infusion dose of 480 mg to all patients who had received apixaban and to patients who had received rivaroxaban more than 7 hours earlier. A bolus dose of 800 mg and an infusion dose of 960 mg were administered to patients who had received enoxaparin, edoxaban, or rivaroxaban 7 hours or less before administration of andexanet alfa.

The ANNEXA-4 study had 2 co–primary efficacy outcomes.[2] The first was the percent change from baseline in anti–factor Xa activity following treatment with andexanet alfa. The second was the percentage of patients with excellent or good hemostatic efficacy 12 hours after the andexanet alfa infusion. Primary safety outcomes included death, thrombotic events, and the development of antibodies (directed to andexanet alfa or to endogenous factor X and factor Xa). All analyses were censored at 30 days.

Two patient populations were analyzed. A safety population (N=352) included all the patients who had received andexanet alfa. An efficacy population (N=254) included only those patients with a baseline anti–factor Xa activity of at least 75 ng/mL (measured at a central core laboratory after enrollment) and confirmed major bleeding at presentation.

In the safety population of the ANNEXA-4 trial, 53% of patients were male, 87% were white, and the mean patient age was 77.4 years.[2] The primary site of bleeding was intracranial in 64% of patients and GI in 26% of patients. Most patients were receiving anticoagulation therapy to treat underlying atrial fibrillation (80%) or venous thromboembolism (17%). The most common factor Xa inhibitor agents were apixaban (55%; median daily dose of 10 mg) and rivaroxaban (36%; median daily dose of 20 mg). The remaining patients had received either enoxaparin (6%) or edoxaban (3%). Patients had significant medical histories, including atrial fibrillation (81%), diabetes mellitus (30%), stroke (20%), heart failure (20%), deep vein thrombosis (19%), myocardial infarction (14%), and pulmonary embolism (12%).

The first co–primary endpoint, percent change from baseline in anti–factor Xa activity following andexanet alfa, was assessed in the efficacy population according to the specific factor Xa inhibitor agent received. Among the
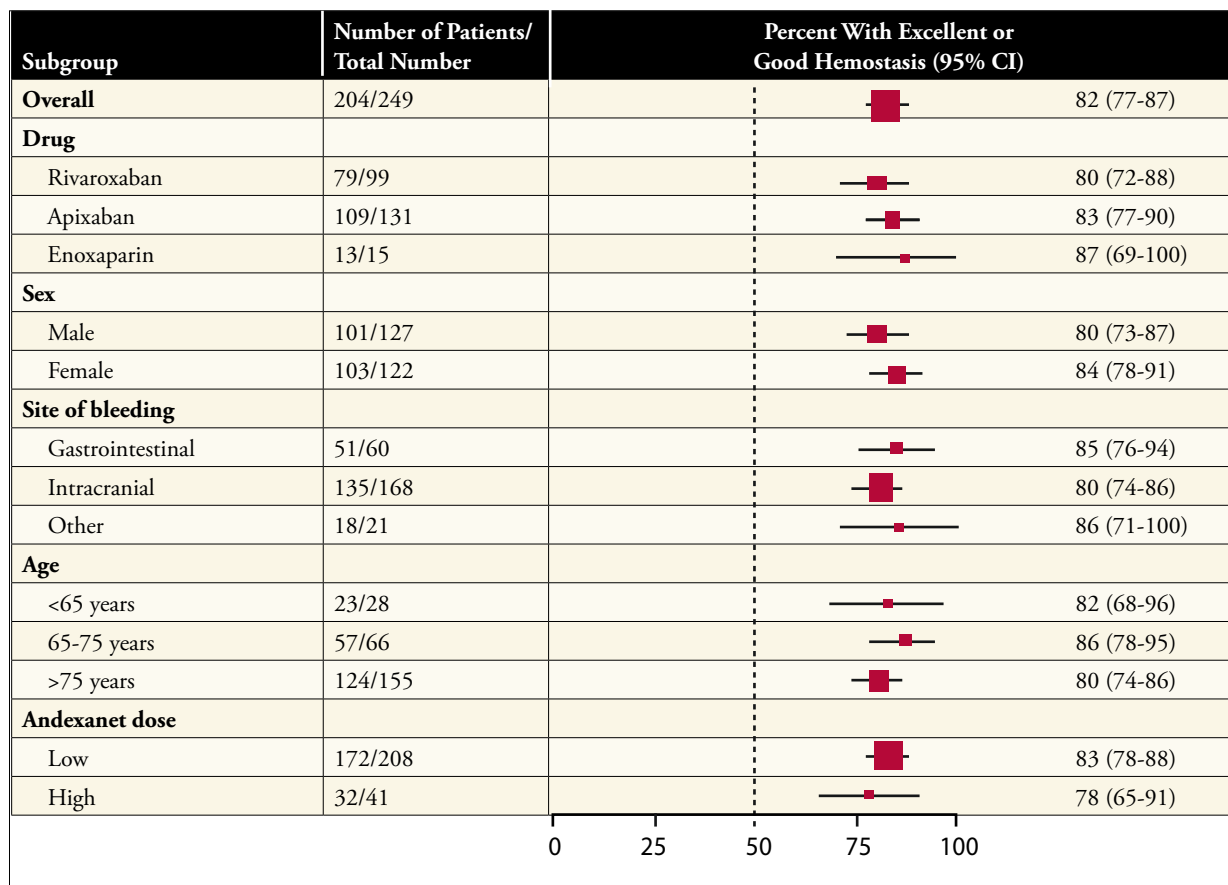
Subgroup	Number of Patients/ Total Number	Percent With Excellent or Good Hemostasis (95% CI)	
Overall	204/249		82 (77-87)
Drug			
Rivaroxaban	79/99		80 (72-88)
Apixaban	109/131		83 (77-90)
Enoxaparin	13/15		87 (69-100)
Sex			
Male	101/127		80 (73-87)
Female	103/122		84 (78-91)
Site of bleeding			
Gastrointestinal	51/60		85 (76-94)
Intracranial	135/168		80 (74-86)
Other	18/21		86 (71-100)
Age			
<65 years	23/28		82 (68-96)
65-75 years	57/66		86 (78-95)
>75 years	124/155		80 (74-86)
Andexanet dose			
Low	172/208		83 (78-88)
High	32/41		78 (65-91)

0   25   50   75   100

Figure 6. Patients with excellent or good hemostasis at 12 hours in the ANNEXA-4 trial. The size of the red squares reflects the number of patients included in each subgroup analysis. Hemostatic efficacy was not adjudicated in 5 patients in the efficacy population. ANNEXA-4, Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors. Adapted from Connolly SJ et al. *N Engl J Med*. 2019;380(14):1326-1335.[2]

patients who had been treated with rivaroxaban, median anti–factor Xa activity decreased from 211.8 ng/mL at baseline to 14.2 ng/mL after the andexanet alfa bolus, for a reduction of 92% (95% CI, 88%-94%). Among the patients who had been treated with apixaban, median anti–factor Xa activity decreased from 149.7 ng/mL at baseline to 11.1 ng/mL after the andexanet bolus, for a reduction of 92% (95% CI, 91%-93%). The reduction in anti–factor Xa activity was rapid for both rivaroxaban (median values reduced by 42%, 48%, and 62% at 4, 8, and 12 hours, respectively) and apixaban (median values reduced by 32%, 34%, and 38% at 4, 8, and 12 hours, respectively).

The second co–primary endpoint, the percentage of patients with excellent or good hemostatic efficacy 12 hours after the andexanet alfa infusion, was assessed in 249 patients from the efficacy population.[2] Among these patients, hemostatic efficacy at 12 hours was good or excellent in 204 overall (82%; 95% CI, 77%-87%), with similar rates of 80% (95% CI, 72%-88%) for the rivaroxaban group and 83% (95% CI, 77%-90%) for the apixaban group (Figure 6). The percentage of patients with excellent or good hemostatic efficacy at 12 hours, adjudicated according to prespecified criteria, was relatively consistent across all patient subgroups. The percentage of patients with excellent or good hemostatic efficacy was 85% (95% CI, 76%-94%) for those with GI bleeding and 80% (95% CI, 74%-86%) for those with intracranial bleeding. Excellent or good hemostatic efficacy was achieved in 83% (95% CI, 78%-88%) of patients treated with a low andexanet alfa dose, and in 78% (95% CI, 65%-91%) of patients treated with a high dose. Similar rates of excellent or good hemostatic efficacy were also observed across age (82% [95% CI, 68%-96%] in patients <65 years, 86% [95% CI, 78%-95%] in patients ages 65-75 years, and 80% [95% CI, 74%-86%] in patients >75 years) and sex (80% [95% CI, 73%-87%] in men and 84% [95% CI, 78%-91%] in women).

The relationship between the 2 co–primary efficacy endpoints was evaluated to determine if a change in

anti–factor Xa activity during treatment with andexanet alfa was predictive of hemostatic efficacy. Overall, receiver operating characteristic (ROC) curves showed there was no significant association between these outcomes in the total study population (area under the ROC curve of 0.53; 95% CI, 0.44-0.62; Figure 7). Among patients with ICH, the magnitude of the reduction in anti–factor Xa activity from baseline to nadir during treatment was predictive of hemostatic efficacy, as demonstrated by an area under the ROC curve of 0.64 (95% CI, 0.53-0.74; Figure 8). However, the study authors noted that this relationship was not strong.

Safety outcomes were assessed throughout the 30-day follow-up period in the safety population.[2] During this time, 34 patients (10%) experienced a thrombotic event. These events occurred within 5 days after receiving andexanet alfa in 11 patients, between 6 and 14 days in 11 patients, and between 15 and 30 days in 12 patients. Thrombotic events included ischemic stroke or stroke of uncertain classification (n=14), deep vein thrombosis (n=13), myocardial infarction (n=7), pulmonary embolism (n=5), and transient ischemic attack (n=1). Infusion reactions were reported in 2 patients; neither event was severe. After treatment, no patients developed antibodies to factor X or Xa or neutralizing anti–andexanet alfa antibodies.

A total of 49 patients (14%) died within 30 days after enrollment. Of these deaths, 8 occurred during the first 5 days following bolus andexanet alfa, 21 occurred 6 to 14 days after bolus, and 20 occurred in the 15 to 30 days following bolus. Most of the deaths were attributed to cardiovascular causes (n=35); the remaining were deemed noncardiovascular (n=12) or unknown (n=2).

Per the ANNEXA-4 study protocol, factor Xa inhibitor therapy was immediately stopped in all patients at the time of enrollment.[2] During the 30 days after bolus andexanet alfa treatment, 220 patients (62%) received at least 1 dose of either parenteral or oral anticoagulant therapy. Anticoagulant therapy was restarted within the first 5 days in 41%. It was restarted on days 6 to 14 in 13% and on days 15 to 30 in 8%. A thrombotic event occurred prior to restart of parenteral or oral anticoagulants in 7% of cases and after restart in 2% of cases. Among the 220 patients, 100 (28%) were restarted on oral anticoagulation therapy during follow-up. Once oral anticoagulation therapy was restarted, no patient experienced a thrombotic event during the 30-day follow-up period.

Ongoing Phase 4 Study

The ANNEXA-4 study investigators noted that the study was limited in that it lacked a control arm.[2] To address this concern, the manufacturer of andexanet alfa is working under the guidance of the FDA to sponsor an open-label, randomized trial in this setting.[7] This phase 4 trial is currently enrolling patients who present with acute ICH within 12 hours of symptom onset and within 15 hours of administration of an oral factor Xa inhibitor (either apixaban, rivaroxaban, or edoxaban). Patients are randomly assigned to the usual standard of care or andexanet alfa. The primary efficacy outcome, the proportion of patients with either good or excellent hemostatic efficacy, will be adjudicated by a blinded Endpoint Adjudication Committee. The change in anti–factor Xa activity from baseline will be the secondary efficacy endpoint. The study investigators aim to enroll 440 patients for analysis, with an estimated primary completion date of March 2023.

Incorporation of Andexanet Alfa Into Clinical Practice

Based on the available data, the right patient to consider for andexanet alfa is likely one who requires reversal of factor Xa inhibition for a sufficient duration, perhaps from 4 to 6 hours, that will allow them to form a clot and stop hemorrhaging. Therefore, appropriate candidates are patients with critical bleeding who are at risk for hemorrhagic shock or patients experiencing a bleed into a critical space.

The andexanet alfa label includes a boxed warning on the risk of arterial and venous thromboembolic events, ischemic events (including myocardial infarction and ischemic stroke), cardiac arrest, and sudden death.[1] In the ANNEXA-4 trial, 10% of patients experienced a thromboembolic event.[2] However, given the single-arm design of the study, it was not clear which, if any, of these events were caused by andexanet alfa or the patient's underlying disease state and hospitalization. Patients treated with factor Xa inhibitors, such as rivaroxaban or apixaban, are receiving that therapy specifically because of their increased risk of thromboembolism. Additionally, hospitalized patients with life-threatening bleeding associated with factor Xa inhibitor therapy are typically very ill and can require extended stays in the intensive care unit, which can also raise the risk for thromboembolism. Reversal of factor Xa inhibitor therapy, whether by andexanet alfa, by any future agent, or even simply by holding anticoagulant therapy, likely exposes patients to the thrombotic risk conferred by their underlying disease. Anticoagulant therapy should be resumed as soon as medically appropriate.[1]

Off-Label Use of Other Agents

Other agents used for reversal of factor Xa inhibitors include PCCs.[8] It has been postulated that administration of sufficient quantities of excess factor X has the potential to overcome factor Xa inhibition. However, this hypothesis has never been tested in a randomized, controlled
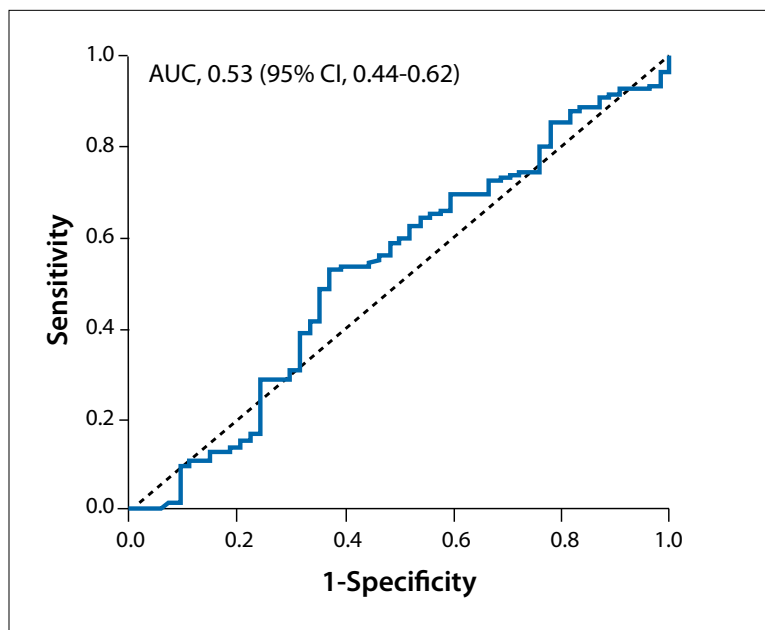
Figure 7. AUC showing the association between anti–factor Xa activity (measured in nanograms per milliliter) and hemostatic efficacy (excellent or good vs poor or none) in all patients who were receiving an oral factor Xa inhibitor in the ANNEXA-4 trial. The dashed line provides a reference indicating the chance prediction. ANNEXA-4, Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors; AUC, area under the receiver operating characteristic curve. Adapted from Connolly SJ et al. *N Engl J Med.* 2019;380(14):1326-1335.[2]
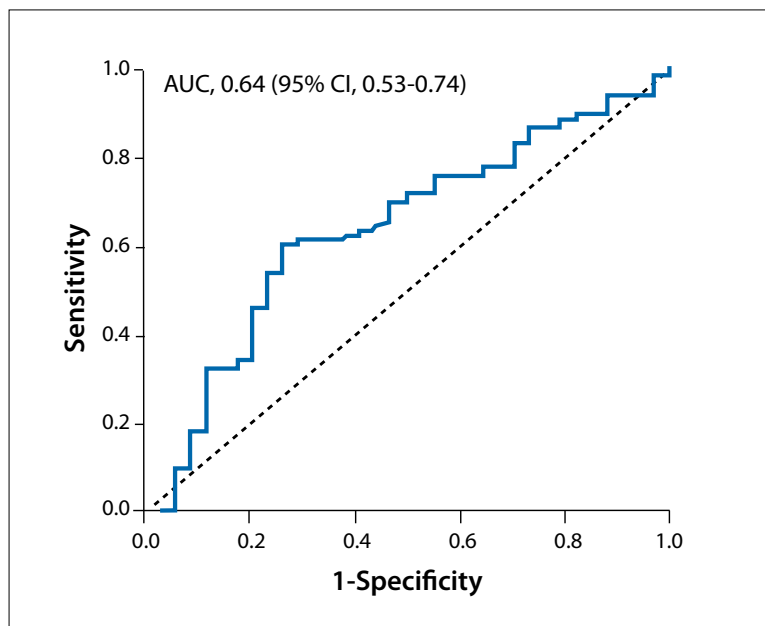

Figure 8. AUC showing the association between anti–factor Xa activity (measured in nanograms per milliliter) and hemostatic efficacy (excellent or good vs poor or none) among patients with an intracranial hemorrhage who were receiving an oral factor Xa inhibitor in the ANNEXA-4 trial. The dashed line provides a reference indicating the chance prediction. ANNEXA-4, Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors; AUC, area under the receiver operating characteristic curve. Adapted from Connolly SJ et al. *N Engl J Med.* 2019;380(14):1326-1335.[2]

trial or a prospective cohort clinical trial. The clinical studies that have assessed these agents in the setting of factor Xa inhibition have been limited to retrospective, observational trials or small human or animal studies.[9] As a result, PCCs are not currently FDA-approved for the reversal of apixaban or rivaroxaban anticoagulation. Some hospitals, however, use them off-label in this setting, and some guidelines (written before the availability of andexanet alfa) have recommended their use.[10]

Guideline Recommendations Regarding Andexanet Alfa

Several guidelines now include treatment recommendations for the use of reversal agents for life-threatening or uncontrolled bleeding related to factor Xa inhibition. The ACC Guidance for Anticoagulation Reversal recommends administration of andexanet alfa as a first-line agent for the reversal of anticoagulation in

patients receiving apixaban or rivaroxaban who develop life-threatening or uncontrolled bleeds.[11] If andexanet alfa is not available, the guidelines instead recommend administration of IV 4-factor PCC (50 U/kg) or IV activated PCC (50 U/kg). The ACC guidelines note that andexanet alfa is not currently approved for reversal of edoxaban, and instead recommend IV 4-factor PCC (50 U/kg) as first-line treatment (or IV activated PCC [50 U/kg] if 4-factor PCC is not available). That noted, based on mechanism of action, andexanet alfa may well have a similar effect on edoxaban as it does on rivaroxaban and apixaban. For all patients, the ACC guidelines state that neither idarucizumab nor plasma is indicated for reversal of factor Xa inhibition. The guidelines further recommend that activated charcoal should be considered in all patients with known recent ingestion of these agents (within 2-4 hours).

The 2019 American Heart Association/ACC Heart Rhythm Society Guideline Update for Management of Patients With Atrial Fibrillation state that andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding.[12] This is the only recommendation regarding reversal of rivaroxaban and apixaban provided in this guideline update.

The 2018 CHEST Guideline and Expert Panel Report states that patients who develop serious bleeding during treatment with a non–vitamin K antagonist oral anticoagulant drug can be treated with a specific reversal agent (where available).[13] The guidelines note that general nonspecific hemostatic agents are less effective for the reversal of anticoagulation abnormalities, have not improved outcomes, and are potentially prothrombotic. These guidelines were published before the FDA approval of andexanet alfa. This agent is described as a specific reversal agent for direct (apixaban, rivaroxaban, and edoxaban) and indirect (low-molecular-weight heparins and fondaparinux) factor Xa inhibitors that act through antithrombin.

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A New Strategy for Uncontrollable Bleeding After Treatment With Rivaroxaban or Apixaban: Q&A

Craig M. Kessler, MD, MACP, and Joshua N. Goldstein, MD, PhD

Craig M. Kessler, MD, MACP What do you think about using coagulation laboratory measures as a tool to indicate whether patients have received an anticoagulant? For example, if a screening activated partial thromboplastin time (PTT) test was normal, but the patient was scheduled to receive a direct oral anticoagulant, would you have confidence to proceed to surgery?

Joshua N. Goldstein, MD, PhD One concern is that different laboratories use different reagents for prothrombin time (PT) and PTT. Therefore, it can be uncertain whether these tests accurately indicate the level of rivaroxaban or apixaban. In my experience, many urgent surgeries can be delayed for enough time to allow the anticoagulant to metabolize further, leaving us less reliant on the PT or PTT. If the times are prolonged, there is certainly reason to be hesitant. But even if the tests have a normal result, there is still reason to wait when clinically feasible.

Craig M. Kessler, MD, MACP I typically rely on these tests as a negative predictor. In a patient with a normal PT or PTT who is receiving apixaban or rivaroxaban, I tend to feel confident that there is not enough anticoagulant activity left to impact the safety of surgery. At my institution, we evaluate anti–factor Xa levels to help measure the drug level. When the PTT and PT tests have normal results, I will then check the level of anti–factor Xa. If the anti–factor Xa level is low (<0.2 U/mL), I usually let the patient proceed to surgery.

Joshua N. Goldstein, MD, PhD I agree that the best practice would be to check the anti–factor Xa level (although this test is not routine at my hospital). The ANNEXA-4 trial highlights the utility of testing this level. In the trial, anti–factor Xa levels were measured centrally, so the local providers did not have ready access to the results. Many of the patients had very low levels of anti–factor Xa activity and were not included in the final efficacy analysis. Therefore, even when a patient presents with a critical bleed and reports that the last dose of rivaroxaban or apixaban was administered within 18 hours, often they will have low levels of anti–factor Xa activity and likely do not require reversal. The level of anti–factor Xa may provide a useful tool to identify which patients with a critical bleed require reversal therapy.

Craig M. Kessler, MD, MACP I agree that, when feasible, it is better to wait several half-lives to perform emergency surgery. The complexities in trying to identify which patients are most likely to benefit from anticoagulation reversal were demonstrated by the difficulty in recruiting patients for the ANNEXA-4 trial. Real-world clinical experience may differ from outcomes in the trial.

Joshua N. Goldstein, MD, PhD I agree. The trial had strict inclusion criteria. In addition, both patients and clinical providers had to be amenable to the use of an investigational treatment rather than the institution's standard of care, which might have been a difficult choice when confronting life-threatening bleeding in an emergency setting.

There are complicated discussions surrounding the cost of andexanet alfa that encompass how it is billed, reimbursement from the Centers for Medicare & Medicaid Services, and the extent of coverage by commercial payers. There is a great deal of variability regarding the use of andexanet alfa among institutions, and many community hospitals transfer these critically ill patients to large academic centers. I would suggest that the simplest solution is for the provider to focus on the biology, and to question whether the patient truly requires an emergency reversal. The discussion of whether this agent should be available for emergency situations should be decided at the hospital level.

Craig M. Kessler, MD, MACP Obviously, we all have to be responsible citizens in the health care market. However, I never like to make clinical decisions based on cost. From your perspective as an emergency physician, is andexanet alfa now the standard of care for reversal of anticoagulation in patients treated with apixaban or rivaroxaban? Or is the standard of care to wait several half-lives before surgery?

Joshua N. Goldstein, MD, PhD It is not the standard of care to administer andexanet alfa in every circumstance; we have a formal guideline in place for providers. The ANNEXA-4 trial clearly showed a biologic effect. Given the single-arm design, however, it is not known whether the outcome is superior among patients who are treated with andexanet alfa vs those who are not.

Clinicians must use their best judgment based on the patient's circumstance. For example, say a patient has an intracerebral hemorrhage with more than 60 cc of blood in the brain. This event can be catastrophic. The patient may have a high risk of ongoing bleeding, leading to an opportunity to try to reverse anticoagulation and stop the bleeding. However, this patient may also have an extremely small chance of meaningful neurologic recovery, and any benefit from reversal may be low if much of the brain damage has already occurred. Conversely, a patient with a very small subdural hemorrhage, who has a headache but is awake and talking, may have a lower risk of expansion, but a large opportunity to benefit. If the hemorrhage does worsen, it becomes a life-changing event resulting in permanent disability. In this second case, the opportunity to benefit from andexanet alfa may be high, even in the setting of a relatively lower risk of hemorrhage expansion. Overall, it can be a tremendously complex decision for the clinical care team to determine whether a patient will benefit.

Craig M. Kessler, MD, MACP The ANNEXA-4 trial was nonrandomized, lacked a control arm, and used a surrogate endpoint (in fact, a laboratory endpoint). I am not ready to assume that reversal of a particular anticoagulation endpoint should establish a new treatment as a standard of care. The results suggest that andexanet alfa is a tool, but its best use will require a clinical thought process on the part of health care providers.

Joshua N. Goldstein, MD, PhD Clinicians know that some patients do well unexpectedly, whereas others do poorly even with the best possible care. It is difficult to look back at a specific patient and know with certainty what changes in treatment would have elicited a different outcome, particularly in the absence of randomized clinical trial data.

Craig M. Kessler, MD, MACP At my institution, a multidisciplinary committee was convened to determine guidelines for the utilization of andexanet alfa. Essentially, the decision to use the first dose of andexanet alfa belongs to the physician who is responsible for the immediate care of the patient. Any subsequent dose or evidence of a continued hemorrhagic complication requires a hematology consult.

Joshua N. Goldstein, MD, PhD At my institution, clinicians can order andexanet alfa in specific circumstances: if there is life-threatening intracranial bleeding or bleeding into a critical space, or if emergency surgery cannot wait. In all other cases, a hematology consultation is required to discuss risks vs benefits. These discussions are intended not to save money, but to best determine who can truly benefit from the use of this agent.

Slide Library

Use of Anticoagulants

- Rivaroxaban and apixaban are among the most frequently used anticoagulants
- Rivaroxaban and apixaban are selective inhibitors of factor Xa. Neither agent requires a cofactor (eg, anti-thrombin III) for activity, and both inhibit free factor Xa, as well as prothrombinase activity
- Apixaban also inhibits clot-bound factor Xa
- Rivaroxaban and apixaban have no direct effect on platelet aggregation. Instead, they decrease thrombin generation by inhibiting factor Xa, and thus can inhibit platelet aggregation induced by thrombin

Risk for Developing Uncontrollable Bleeding With Rivaroxaban or Apixaban

- Estimates for the number of bleeding admissions have increased from 90,000 in 2015 to nearly 170,000 in 2018, suggesting an approximate 20% increase each year[1,2]
- In 2018, it was estimated that approximately 408 patients were hospitalized each day owing to a rivaroxaban- or apixaban-related bleeding event[2]
- It is estimated that approximately 70 patients die each day following hospitalization for bleeding related to rivaroxaban or apixaban[2-4]

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Assessment of the Bleed Severity: ACC Recommendations

- An initial assessment of the bleed severity in patients receiving factor Xa inhibitors is critical to make appropriate treatment decisions
- The initial assessment should include a focused history and physical examination that includes vital signs and laboratory evaluation
- The time of onset, location, and severity of bleeding should be determined when possible
- Critically, the physician must determine whether bleeding is ongoing
- Assessment of hemodynamic instability should occur promptly and repeated frequently

ACC, American College of Cardiology. Data from Tomaselli GF et al. *JACC.* 2017;70(24):1-26.

Reversal of Anticoagulation

- Among patients with a critical bleed, physicians must try to determine whether factor Xa inhibition reversal is necessary. Both apixaban and rivaroxaban have short circulating half-lives. In some cases, it may be sufficient to "wait out" the half-life of the drug
- Catastrophic bleeds require immediate reversal. Reversal of factor Xa inhibition should also be considered when the anticoagulant effect must be neutralized rapidly so a patient can undergo surgery

FDA, US Food and Drug Administration.

Andexanet Alfa

- In May 2018, the FDA approved andexanet alfa as the first and only antidote for patients treated with rivaroxaban and apixaban who require reversal of anticoagulation owing to life-threatening or uncontrolled bleeding. Andexanet alfa (also known as coagulation factor Xa [recombinant], inactivated-zhzo) provides specific reversal of factor Xa inhibition

The ANNEXA-R and ANNEXA-A Trials

- ANNEXA-R and ANNEXA-A were parallel clinical trials designed to evaluate the efficacy and safety of andexanet alfa for the reversal of anticoagulation with apixaban or rivaroxaban in older healthy volunteers
- The trials randomly assigned healthy volunteers ages 50 to 75 years who received rivaroxaban (ANNEXA-R) or apixaban (ANNEXA-A) to treatment with andexanet alfa or matching placebo
- The primary endpoint, percent change in anti–factor Xa activity from baseline to nadir, showed rapid reductions immediately (within 2 and 5 minutes) following bolus administration of andexanet alfa
- Mean reductions of anti–factor Xa activity from baseline to nadir were higher with andexanet alfa compared with placebo

Data from Siegal DM et al. *N Engl J Med.* 2015;373(25):2413-2424.

The ANNEXA-R and ANNEXA-A Trials: Conclusions

- Andexanet alfa was associated with rapid reversal of rivaroxaban-induced and apixaban-induced changes in anti–factor Xa activity and thrombin generation, and these effects were observed in the absence of serious adverse events or clinical thrombosis
- These data were consistent with the known mechanism of action of andexanet alfa, whereby high-affinity binding to the factor Xa inhibitor (either rivaroxaban or apixaban) prevented factor Xa inhibition by reducing unbound plasma levels of the anticoagulant
- Reversal of the anticoagulant effect occurred rapidly, within 2 to 5 minutes after bolus administration, and was sustained during the continuous infusion. Anticoagulation returned to placebo levels within 1 to 3 hours following andexanet alfa treatment

Data from Siegal DM et al. *N Engl J Med.* 2015;373(25):2413-2424.

The ANNEXA-4 Study

- The ANNEXA-4 study was conducted to evaluate the efficacy and safety of andexanet alfa in patients experiencing an acute major bleeding event during treatment with a factor Xa inhibitor
- ANNEXA-4 was a multicenter, prospective, open-label, single-group cohort study that enrolled adult patients from 63 centers
- The study found that treatment with andexanet alfa markedly reduced anti-factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours
- Reduction in anti-factor Xa activity did not predict hemostatic efficacy overall, but was modestly predictive in patients with intracranial hemorrhage

Data from Connolly SJ et al. *N Engl J Med.* 2019;380(14):1326-1335.

The ANNEXA-4 Study: Safety

- Safety outcomes were assessed throughout the 30-day follow-up period in the safety population. A thrombotic event was reported in 34 patients (10%). These events occurred within 5 days after receiving andexanet alfa in 11 patients, between 6 and 14 days in 11 patients, and between 15 and 30 days in 12 patients. Thrombotic events included ischemic stroke or stroke of uncertain classification (n=14) and deep vein thrombosis (n=13)
- A total of 49 patients (14%) died within 30 days after enrollment. Eight deaths occurred during the first 5 days following bolus andexanet alfa, 21 occurred 6 to 14 days after bolus, and 20 occurred in the 15 to 30 days following bolus. Most of the deaths were attributed to cardiovascular causes (n=35)

Data from Connolly SJ et al. *N Engl J Med.* 2019;380(14):1326-1335.

Guideline Recommendations Regarding Andexanet Alfa

- The ACC Guidance for Anticoagulation Reversal recommends administration of andexanet alfa as a first-line agent for the reversal of anticoagulation in patients receiving apixaban or rivaroxaban who develop life-threatening or uncontrolled bleeds[1]

- The 2019 AHA/ACC Heart Rhythm Society Guideline Update for Management of Patients With Atrial Fibrillation state that andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding[2]

1. Guidance for Anticoagulation Reversal. American College of Cardiology website. https://www.acc.org/~/media/Non-Clinical/Images/Tools%20and%20Practice%20Support/Mobile%20Resources/ManageAnticoag/B18120_ManageAntico-ag_App_Fact_Sheet.pdf. Updated July 2018. Accessed January 9, 2019. 2. January CT et al. *J Am Coll Cardiol.* 2019;74(1):104-132.

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