Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

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BACKGROUND
Bleeding is a complication of treatment with factor Xa inhibitors, but there are no specific agents for the reversal of the effects of these drugs. Andexanet is designed to reverse the anticoagulant effects of factor Xa inhibitors.

METHODS
Healthy older volunteers were given 5 mg of apixaban twice daily or 20 mg of rivaroxaban daily. For each factor Xa inhibitor, a two-part randomized placebo-controlled study was conducted to evaluate andexanet administered as a bolus or as a bolus plus a 2-hour infusion. The primary outcome was the mean percent change in anti–factor Xa activity, which is a measure of factor Xa inhibition by the anticoagulant.

RESULTS
Among the apixaban-treated participants, anti–factor Xa activity was reduced by 94% among those who received an andexanet bolus (24 participants), as compared with 21% among those who received placebo (9 participants) (P<0.001), and unbound apixaban concentration was reduced by 9.3 ng per milliliter versus 1.9 ng per milliliter (P<0.001); thrombin generation was fully restored in 100% versus 11% of the participants (P<0.001) within 2 to 5 minutes. Among the rivaroxaban-treated participants, anti–factor Xa activity was reduced by 92% among those who received an andexanet bolus (27 participants), as compared with 18% among those who received placebo (14 participants) (P<0.001), and unbound rivaroxaban concentration was reduced by 23.4 ng per milliliter versus 4.2 ng per milliliter (P<0.001); thrombin generation was fully restored in 96% versus 7% of the participants (P<0.001). These effects were sustained when andexanet was administered as a bolus plus an infusion. In a subgroup of participants, transient increases in levels of d-dimer and prothrombin fragments 1 and 2 were observed, which resolved within 24 to 72 hours. No serious adverse or thrombotic events were reported.

CONCLUSIONS
Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects. (Funded by Portola Pharmaceuticals and others; ANNEXA-A and ANNEXA-R ClinicalTrials.gov numbers, NCT02207725 and NCT02220725.)
The direct factor Xa inhibitors apixaban, rivaroxaban, and edoxaban are used in the prevention and treatment of thromboembolism. Indications for the use of these agents include the prevention of stroke in patients with nonvalvular atrial fibrillation, the treatment and secondary prevention of deep-vein thrombosis and pulmonary embolism, and the prevention of venous thrombosis after orthopedic surgery. In spite of the demonstrated safety and efficacy of factor Xa inhibitors, as well as their practical advantages over vitamin K antagonists such as warfarin, the lack of a specific antidote to reverse their anticoagulant effects is an important limitation. In clinical trials involving patients with atrial fibrillation who were receiving factor Xa inhibitors, major bleeding was found to occur at an annualized rate of 2.1 to 3.5%, and clinical experience has been consistent with these results.4,5 Anticoagulation-related major bleeding is associated with an increased risk of death and thrombotic events, independent of the class of anticoagulant used.4,6 Patients who receive factor Xa inhibitors may also be at increased risk for bleeding if emergency surgery is required. With the increasing use of factor Xa inhibitors, the number of patients who require reversal of the anticoagulant effects is anticipated to rise. Therefore, a specific antidote that can rapidly reverse the anticoagulant effects of factor Xa inhibitors in patients who are bleeding or who require emergency surgery is needed.

Andexanet alfa (andexanet) is a specific reversal agent that is designed to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors. Andexanet is a recombinant modified human factor Xa decoy protein that is catalytically inactive but that retains the ability to bind factor Xa inhibitors in the active site with high affinity and a 1:1 stoichiometric ratio. Andexanet binds and sequesters factor Xa inhibitors within the vascular space, thereby restoring the activity of endogenous factor Xa and reducing levels of anticoagulant activity, as assessed by measurement of thrombin generation and anti–factor Xa activity, the latter of which is a direct measure of the anticoagulant activity.7

In phase 2 proof-of-concept and dose-ranging studies, intravenous administration of andexanet resulted in dose-dependent rapid and reproducible reversal of anticoagulant effects in multiple small cohorts of healthy volunteers who were receiving one of four factor Xa inhibitors (apixaban, rivaroxaban, edoxaban, or enoxaparin) that were administered to steady state. Reversal was assessed as the reduction in anti–factor Xa activity and unbound factor Xa inhibitor concentrations, as well as the restoration of thrombin generation.8-11 Because the pharmacodynamic half-life of andexanet is approximately 1 hour, this agent was also administered as a bolus plus a 1-to-2-hour infusion, which extended the action of the drug throughout the duration of the infusion.8-11 No serious adverse reactions were reported, and no antibodies against factor Xa or factor X were detected.8-11 Given these findings, two parallel trials — Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Apixaban (ANNEXA-A) and Rivaroxaban (ANNEXA-R) — were designed to establish the efficacy and safety of andexanet for the reversal of anticoagulation with apixaban or rivaroxaban in older healthy volunteers.

STUDY DESIGN AND OVERSIGHT

The ANNEXA-A and ANNEXA-R trials were randomized, double-blind, placebo-controlled studies that were designed to evaluate the ability of andexanet to reverse anticoagulation with apixaban (Eliquis; Pfizer and Bristol-Myers Squibb) or rivaroxaban (Xarelto; Bayer and Johnson & Johnson) and to evaluate the safety of andexanet in healthy older volunteers. The study was conducted at two clinical sites (Celerion in Tempe, Arizona [ANNEXA-A], and West Coast Clinical Trials in Cypress, California [ANNEXA-R]). The study protocols were approved by the institutional review board at each study site, and all participants provided written informed consent before enrollment. Healthy volunteers 50 to 75 years of age were randomly assigned, with the use of an interactive Web-response system, in a 3:1 ratio (ANNEXA-A) or a 2:1 ratio (ANNEXA-R), to receive andexanet or matching placebo. Each study was performed in two consecutive parts: in part 1, we examined the intravenous andexanet bolus alone, and in part 2 we studied an intravenous bolus followed by a continuous 120-minute infusion. Study participants were housed at the study site for 8 days, and safety outcomes were assessed on days 15, 36, and 43 after administration of the study drug. An independent safety committee whose members were aware of the study-group assignments reviewed safety data on an ongoing basis.
The studies were conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. They were designed by the academic investigators in collaboration with Portola Pharmaceuticals. All the authors contributed to the writing of the manuscript, made the decision to submit the manuscript for publication, and vouch for the completeness of the data and the accuracy of the results and for the fidelity of this report to the study protocol, which is available with the full text of this article at NEJM.org. Nondisclosure agreements were in place between the sponsor and the academic authors, but the authors had unrestricted access to the data. The study was conducted under the sponsorship of Portola Pharmaceuticals, with additional financial and scientific support from Bayer, Bristol-Myers Squibb, Johnson & Johnson, and Pfizer.

**STUDY TREATMENT**

In the ANNEXA-A study, participants received 5 mg of apixaban orally twice daily for 3.5 days to achieve steady-state plasma levels at the highest approved dose. Three hours after the last dose of apixaban on day 4 (at or near the time of the highest plasma concentration), andexanet was administered as a 400-mg intravenous bolus (30 mg per minute) (part 1) or as a 400-mg intravenous bolus followed by a continuous infusion of 4 mg per minute for 120 minutes (480 mg in total) (part 2). In the ANNEXA-R study, participants received 20 mg of rivaroxaban orally once daily (the highest approved dose) for 4 days. On day 4, at 4 hours after the last dose of rivaroxaban (at or near the maximum plasma concentration), andexanet was administered as an 800-mg intravenous bolus (30 mg per minute) (part 1) or as an 800-mg intravenous bolus followed by a continuous infusion of 8 mg per minute for 120 minutes (960 mg in total) (part 2). The doses were selected on the basis of the phase 2 development program that established the stoichiometric ratio needed for reversal of the effects of each anticoagulant with the use of andexanet. The dose of andexanet required to reverse the effects of 20 mg of rivaroxaban once daily is higher than that required to reverse the effects of 5 mg of apixaban twice daily because of both the higher initial maximum plasma concentration of rivaroxaban and the larger volume of distribution of rivaroxaban.

**STUDY END POINTS**

The primary end point for both studies was the percent change in anti–factor Xa activity, measured with the use of a validated chromogenic assay of factor Xa enzymatic activity, from baseline (before administration of andexanet or placebo) to nadir (after administration of andexanet or placebo). For part 1, the nadir was defined as the value of anti–factor Xa activity at 2 minutes or 5 minutes (whichever value was smaller) after the end of the bolus; for part 2, it was defined as the smallest value between 10 minutes before and 5 minutes after the end of the continuous infusion (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

The secondary efficacy end points were the proportion of participants with an 80% or greater reduction in anti–factor Xa activity from baseline to the nadir after administration of andexanet or placebo; the change in unbound inhibitor plasma concentration from baseline to the nadir after administration of andexanet or placebo; the change in thrombin generation, measured as the change in endogenous thrombin potential, from baseline to peak after administration of andexanet or placebo; the change in thrombin potential above the lower limit of the baseline-derived range at its peak after administration of andexanet or placebo (between 2 and 10 minutes after the end of the bolus) or after the infusion. Because of the absence of a clinically validated reference range for endogenous thrombin potential, the baseline-derived range (hereafter referred to as the normal range) was prospectively defined as the mean endogenous thrombin potential at baseline on day 1 (before anticoagulant administration) plus or minus 1 standard deviation. For part 2, an additional secondary end point was the percent change in anti–factor Xa activity from baseline to the post-bolus nadir. Patients were followed for evaluation of clinical outcomes, including symptomatic thrombosis and bleeding. Details regarding the methods for measurement of the end points are provided in the Supplementary Appendix.

**STATISTICAL ANALYSIS**

The primary efficacy analysis was performed with the modified intention-to-treat population, which included all participants who underwent randomization, who received any amount of andexanet or placebo, and for whom a baseline measurement of anti–factor Xa activity (before admin-
istration of andexanet or placebo) and at least one measurement of anti–factor Xa activity after administration of andexanet or placebo were available for analysis. All efficacy analyses were performed on data from the modified intention-to-treat population, and end points were compared with the use of an exact Wilcoxon rank-sum test. A total of 145 participants treated with apixaban or rivaroxaban were randomly assigned to andexanet or placebo in a 3:1 ratio (ANNEXA-A) or a 2:1 ratio (ANNEXA-R). The samples were sufficient to provide greater than 99% power to detect a difference between andexanet and placebo in the percent change in anti–factor Xa activity from baseline to the primary time point (nadir), at a two-sided alpha level of 5%, within each part of each study. The study was powered under the assumption that the differences relative to placebo that were observed in the previous studies of andexanet represent the true differences (additional information on power calculations are provided in the protocol and statistical analysis plan). The sample size of 145 participants was sufficient to provide safety data on at least 100 participants treated with andexanet and to retain power if the observed difference in previous studies overestimated the true difference. To control the type I error rate, the primary end point was tested first within each part of each study. For the primary end point of each part of each study, a two-sided P value of less than or equal to 0.05 for the percentage change in anti–factor Xa activity was considered to indicate statistical significance. The secondary end points were evaluated in sequence, and a difference between andexanet and placebo was considered to be significant if the two-sided P value was less than or equal to 0.05 and the differences with regard to all previous end points in the sequence were also significant.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

From March 2014 through May 2015, a total of 101 participants (48 in the apixaban study and 53 in the rivaroxaban study) were randomly assigned to receive andexanet, and 44 participants (17 in the apixaban study and 27 in the rivaroxaban study) were randomly assigned to receive placebo. The mean age of the participants was 57.9 years, and 39% were women. The treatment groups were balanced with respect to baseline characteristics (Table S1 in the Supplementary Appendix).

EFFECT OF ANDEXANET ON REVERSAL OF ANTICOAGULATION

Anti–factor Xa activity was rapidly reduced (within 2 to 5 minutes) to a greater extent after administration of a bolus of andexanet than after administration of placebo, both in the apixaban study (mean [±SD] reduction, 94±2% vs. 21±9%; P<0.001) and in the rivaroxaban study (92±11% vs. 18±15%, P<0.001) (Fig. 1A and 1B, and Table S2 in the Supplementary Appendix). After administration of the andexanet bolus was completed, the reversal of anti–factor Xa activity persisted for 2 hours, a finding consistent with the pharmacodynamic half-life of the drug (approximately 1 hour). Anti–factor Xa activity returned gradually to levels seen in participants receiving placebo. When andexanet was administered as a bolus plus a 2-hour infusion, it also reduced anti–factor Xa activity to a greater extent than did placebo, both in the apixaban study (92±3% vs. 33±6%, P<0.001) and in the rivaroxaban study (97±2% vs. 45±12%, P<0.001) (Fig. 1C and 1D). Among participants who received placebo, anti–factor Xa activity decreased over time at the expected rate for clearance of the anticoagulant. The reversal of anti–factor Xa activity with andexanet persisted for 1 to 2 hours after completion of the infusion, depending on the anticoagulant received, followed by a return to placebo levels. All the participants who were treated with andexanet had at least 80% reversal of anti–factor Xa activity with andexanet because of a malfunction with the intravenous administration; none of participants who received placebo had an 80% or greater reversal of anti–factor Xa activity (P<0.001).

Within 2 to 5 minutes after administration, treatment with andexanet also rapidly restored the thrombin generation that had been inhibited by treatment with apixaban or rivaroxaban (Fig. 2, and Table S2 in the Supplementary Appendix). After the bolus alone, the mean change in thrombin generation was significantly greater among participants who received andexanet than among those who received placebo, both in the apixaban study (1323.2±335.4 nM·min vs. 88.2±125.8 nM·min, P<0.001) and in the rivar-
oxaban study (1314.2±331.2 nM·min vs. 173.9±104.2 nM·min, P<0.001) (Fig. 2A and 2B). Thrombin generation increased to above the lower limit of the normal range within 2 to 10 minutes after bolus administration in 100% of participants in the apixaban study who received andexanet and in 96% (26 of 27) of participants in the rivaroxaban study who received andexanet, as compared with 11% (1 of 9) of participants in the apixaban study who received placebo and 7%
The new england journal of medicine (1 of 14) of participants in the rivaroxaban study who received placebo (P<0.001 vs. placebo for each comparison) (Fig. 2A and 2B). The single andexanet-treated participant in the rivaroxaban study who did not meet this end point did not receive the full dose of andexanet because of a malfunction with the intravenous administration.

After administration of bolus plus infusion, the mean change in thrombin generation was significantly greater among participants who received andexanet than among those who received placebo, both in the apixaban study (1193.1±263.3 nM·min vs. 189.4±184.8 nM·min, P<0.001) and in the rivaroxaban study (1510.4±344.8 nM·min vs. 264.4±140.7 nM·min, P<0.001). Among these
participants, andexanet restored thrombin generation (to above the lower limit of the normal range) in all the participants in the apixaban study and in the rivaroxaban study; among participants who received placebo, thrombin generation was restored in 25% of participants in the apixaban study and in no participants in the rivaroxaban study \((P<0.001\) vs. placebo for each comparison) (Fig. 2C and 2D, and Table S2 in the Supplementary Appendix).

The mean thrombin generation at the peak after andexanet administration increased to above the baseline mean in each andexanet-treated group. The mean thrombin generation in the andexanet-treated groups was approximately 22% above the value that represented 1 standard deviation more than the mean and 7% above the value that represented 2 standard deviations more than the mean. Thrombin generation returned to within 2 standard deviations of the mean within 30 minutes after andexanet administration (Fig. 2). Similar results were observed with respect to the reversal of the prolongation of activated clotting time (Fig. S2 in the Supplementary Appendix).

**UNBOUND CONCENTRATIONS OF APIXABAN AND RIVAROXABAN AFTER ANDEXANET ADMINISTRATION**

Only unbound apixaban and rivaroxaban in plasma are pharmacologically active. The mean concentration of unbound apixaban in plasma was reduced within 2 to 5 minutes by a significantly greater amount after administration of a bolus of andexanet than after administration of placebo (by 9.3 ng per milliliter vs. 1.9 ng per milliliter, \(P<0.001\)); similar results were observed with respect to the mean concentrations of unbound rivaroxaban (reduction by 23.4 ng per milliliter vs. 4.2 ng per milliliter within 2 to 5 minutes after administration, \(P<0.001\)) (Fig. 3A and 3B, and Table S2 in the Supplementary Appendix).

These findings are consistent with the mechanism of action of andexanet. This reversal was sustained with a bolus plus an infusion of andexanet; the mean plasma concentrations of unbound apixaban and rivaroxaban were reduced by a significantly greater amount with andexanet than with placebo (apixaban reduction, 6.5 ng per milliliter vs. 3.0 ng per milliliter, \(P<0.001\); rivaroxaban reduction, 30.3 ng per milliliter vs. 12.1 ng per milliliter, \(P<0.001\)) (Fig. 3C and 3D, and Table S2 in the Supplementary Appendix).

The mean concentration of unbound apixaban after andexanet administration was below 3.5 ng per milliliter, and that of unbound rivaroxaban was below 4.0 ng per milliliter — calculated levels at which there is little or no anticoagulant effect (see the Methods section in the Supplementary Appendix).\(^\text{15}\) After the end of the bolus or the infusion of andexanet, the concentrations of unbound factor Xa inhibitor returned to placebo levels within 1 to 3 hours, depending on the anticoagulant (Fig. 3).

**SAFETY OUTCOMES**

There were no serious or severe adverse events, and no thrombotic events were reported. All adverse events related to andexanet administration were nonserious and mild (Table 1). One participant with a history of hives had the andexanet infusion discontinued after 35 minutes, after erythematous hives developed; the hives resolved after treatment with a single oral dose of diphenhydramine (Fig. S3 in the Supplementary Appendix).

Antibodies to factor X or factor Xa (measured through day 43) did not develop in any participants. Neutralizing antibodies against andexanet were not detected. Nonneutralizing antibodies against andexanet were detected in 1 of 44 participants (2%) who received placebo and in 17 of 101 participants (17%) who received andexanet (2 of these participants had nonneutralizing antibodies before andexanet administration). Antibodies tended to appear within 15 to 30 days after andexanet administration, and the titers were generally low (at or below 1:640) among the 18 positive participants, except in 1 participant (who had a titer of 1:2560). These results indicate that andexanet has little immunogenicity after a single intravenous exposure. \(\Delta\)-Dimer and prothrombin fragments 1 and 2 were measured in all participants, and transient elevations were noted that generally returned to the normal range within 24 to 72 hours (Fig. 4).

**DISCUSSION**

The ANNEXA-A and ANNEXA-R studies evaluated the ability of andexanet to safely reverse the anticoagulation effects of apixaban or rivaroxaban in older healthy participants. Andexanet rapidly reversed apixaban-induced and rivaroxaban-induced changes in anti–factor Xa activity and thrombin generation without serious adverse
events or clinical thrombosis. These findings are consistent with the mechanism of action of andexanet, which involves high-affinity binding to the factor Xa inhibitor within the vasculature, thus preventing factor Xa inhibition by reducing unbound plasma levels of the anticoagulant. Reversal of the anticoagulant effect was reproducible, with a maximal effect within 2 to 5 minutes after administration of the bolus, and was sustained during the continuous infusion. The
biomarkers of anticoagulation returned to placebo levels 1 to 3 hours after cessation of andexanet administration. The duration of reversal after cessation of andexanet administration is consistent with the half-life of andexanet. This observation is relevant for situations in which re-anticoagulation is considered. These results are similar to those from previous studies involving younger volunteers.

The strengths of the ANNEXA studies include their randomized, double-blind, placebo-controlled design and the inclusion of older participants, who are more similar than younger persons to those who receive factor Xa inhibitors in the community. The use of a dosing regimen of the factor Xa inhibitors that would achieve steady-state levels in plasma (leading to equilibrium with the extravascular space) and the use of widely accepted biomarkers of coagulation (anti–factor Xa activity, free anticoagulant concentrations, and thrombin generation) are additional strengths.

The correction of anti–factor Xa activity is particularly relevant, given that it is a direct measure of the enzymatic activity of factor Xa, the target of apixaban and rivaroxaban. Furthermore, studies leading to the licensure of these products have shown a relationship between anti–factor Xa activity and bleeding complications, and experience in the treatment of patients with a single-coagulation-factor deficiency, such as hemophilia, has shown that reconstitution of the activity of coagulation factors promptly corrects coagulopathy.

In this report, we do not present data on the efficacy and safety of andexanet in patients who require urgent reversal of factor Xa inhibitor activity because of bleeding or for emergency surgery. Although data on such patients are desirable, the studies required to obtain such data are technically challenging and are less likely to produce detailed pharmacokinetic and pharmacodynamic data in a well-controlled setting than are studies such as the ones reported here. Furthermore, the high frequency of coexisting conditions among patients with acute bleeding makes it challenging to determine whether possible complications, such as thrombosis or death, are related to the reversal treatment or the underlying medical illness. Although the extent and duration of factor Xa inhibitor reversal that is required to achieve hemostasis in patients is unknown, studies in animals of the use of andexanet to control bleeding have shown that a reduction in anticoagulation markers, including anti–factor Xa activity and unbound inhibitor plasma concentration, was associated with a significant reduction in blood loss, which was evident within 10 to 15 minutes after administration of the study drug in these models.

In our studies, we observed transient increas-

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**Table 1. Drug-Related Adverse Events.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
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<tr>
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<td>Bolus + Infusion (N = 24)</td>
<td>Bolus (N = 27)</td>
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<td>Constipation</td>
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<td>Dysgeusia</td>
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<td>0</td>
</tr>
<tr>
<td>General disorders and administration-site conditions</td>
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<td>4</td>
<td>2</td>
</tr>
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<tr>
<td>Urticaria</td>
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<td>1</td>
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</tbody>
</table>
| *Data are shown for all adverse events that occurred more frequently with andexanet than with placebo and that occurred two or more times. All these adverse events were nonserious and mild.

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es in \( \text{d-dimer} \) and prothrombin fragments 1 and 2, with no clinical thrombotic events. Overall, participants with elevations in prothrombin fragments 1 and 2 also had \( \text{d-dimer} \) levels above the normal range, but these elevations were not associated with high levels of thrombin generation. Both prothrombin fragments 1 and 2 and \( \text{d-dimer} \) are highly sensitive and variable markers, the levels of which can rise rapidly without necessarily correlating with a prothrombotic state.\(^{23-25}\) The mechanism for these elevations may be related to the binding of andexanet to tissue factor pathway inhibitor (an endogenous inhibitor of factor Xa) in a manner analogous to its binding to factor Xa. In support of this hypothesis, clinical trials involving humans, in which a tissue factor pathway inhibitor–binding antibody, concizumab, was evaluated, also showed elevations in prothrombin fragments 1 and 2 and \( \text{d-dimer} \) without evidence of thrombotic events, which offers further support that the elevations in these markers are not necessarily associated with the development of thrombotic events.\(^{26}\) The binding of andexanet to tissue factor pathway inhibitor does not appear to play a major role in controlling hemostasis, as evidenced by studies of animal bleeding models. In these studies, andexanet did not decrease bleeding in animals.
that did not receive an anticoagulant and in animals that received a direct thrombin inhibitor (against which andexanet has no reversal activity) as an anticoagulant (Portola Pharmaceuticals: unpublished data).

In conclusion, andexanet is a specific, rapidly acting antidote that is being developed for urgent reversal of factor Xa inhibitor anticoagulant activity. In our studies, andexanet rapidly restored factor Xa activity and thrombin generation and reduced unbound factor Xa inhibitor concentrations in apixaban-treated and rivaroxaban-treated older participants. The reversal of anticoagulation with andexanet was not associated with safety concerns or thrombotic events. The ability of andexanet to reverse anticoagulation markers in participants undergoing anticoagulation with apixaban, rivaroxaban, edoxaban, or enoxaparin makes it a potential universal antidote for both direct and indirect factor Xa inhibitors.\(^\text{8-11}\) The rapid onset and offset of action of andexanet and the ability to administer it as a bolus or as a bolus plus an infusion may provide flexibility with regard to the restoration of hemostasis when urgent factor Xa inhibitor reversal is required. The ongoing ANNEXA-4 phase 3b–4 study (ClinicalTrials.gov number, NCT02329327) is evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor–associated acute major bleeding.

Supported by Portola Pharmaceuticals, Bayer, Bristol-Myers Squibb, Johnson & Johnson, and Pfizer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

### References


