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Management of Life-Threatening Bleeding in the Anticoagulated Patient in the Emergency Setting and the Impact of ANNEXA-4 on the Treatment of Patients Taking Factor Xa Inhibitors

Gregory J. Fermann, MD
Professor and Executive Vice Chairman
Department of Emergency Medicine
University of Cincinnati College of Medicine
University of Cincinnati, Cincinnati, Ohio

Brian C. Hiestand, MD, MPH
Professor and Vice Chair
Department of Emergency Medicine
Wake Forest Baptist Medical Center
Winston-Salem, NC

Charles V. Pollack, Jr., MA, MD
Professor, Department of Emergency Medicine
Associate Provost for Innovation in Education
Thomas Jefferson University
Philadelphia, PA

Objectives

1. Discuss the types of oral anticoagulant agents available for preventing and treating thromboembolic disease and summarize the results of recent trials comparing oral anticoagulants for some of the major indications.
2. Describe the difference between repletion of factors for warfarin-related bleeding and reversal of anticoagulant effect for direct oral anticoagulant-related bleeding.
3. Describe the mechanism of action of the anticoagulant reversal agents, idarucizumab and andexanet alfa.
4. Summarize the latest clinical trial data (ANNEXA-4) regarding the use of andexanet alfa for the reversal of Factor Xa inhibition and discuss its role in management decisions for patients with severe Factor Xa inhibitor-related bleeding.

Introduction: There are multiple indications for chronic use of oral anticoagulants in contemporary medical practice, including treatment and prevention of venous thromboembolic disease (VTE, inclusive of deep vein thrombosis and pulmonary embolism), primary and secondary prevention of stroke and systemic embolism in atrial fibrillation (AF), protection against thromboembolic events in patients with mechanical heart valves, and secondary prevention of major cardiac events in patients with coronary artery disease or peripheral artery disease. As clear as these indications are from an efficacy perspective, it is impossible to provide anticoagulation to a patient without raising that patient's risk of pathologic bleeding. Even properly prescribed, well-controlled anticoagulation results in a non-physiologic state in which spontaneous bleeding is more likely, and in which the briskness of blood loss from vessel injury is accelerated.

Management of severe bleeding in patients taking oral anticoagulants is complicated. Acute care physicians must be knowledgeable about the individual oral anticoagulant agents, the general management of anticoagulant-associated bleeding, and the strategies for effective use of factor repletion and specific reversal agents. With any oral anticoagulant, minor or "nuisance" bleeding is most common and can be managed without repletion or reversal. For major oral anticoagulant-associated bleeding, class-specific approaches should be used and the necessary treatment agents made readily available in the Emergency Department (ED), the Intensive Care Unit (ICU), and the surgical suite. Because the reversal agents for warfarin, the thrombin inhibitor dabigatran and the Factor Xa inhibitors apixaban and rivaroxaban are expensive and, like all therapies, have the potential for causing their own adverse events, acute care physicians must be sufficiently informed as to the risks and benefits before using these important new therapies.

In this newsletter, approved anticoagulant therapies, including warfarin, Factor IIa inhibitors, and Factor Xa inhibitors, will be reviewed. Second, the disease indications for anticoagulation, particularly VTE and AF, will be discussed. Third, the available repletion and reversal agents, including fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), andexanet alfa for the Factor Xa inhibitors rivaroxaban and apixaban, and idarucizumab for the Factor IIa inhibitor dabigatran, will be described. And finally, the ANNEXA-4 Final Study results, published in February 2019 in the New England Journal of Medicine, will be reviewed.

ORAL ANTICOAGULANTS

Vitamin K Antagonists

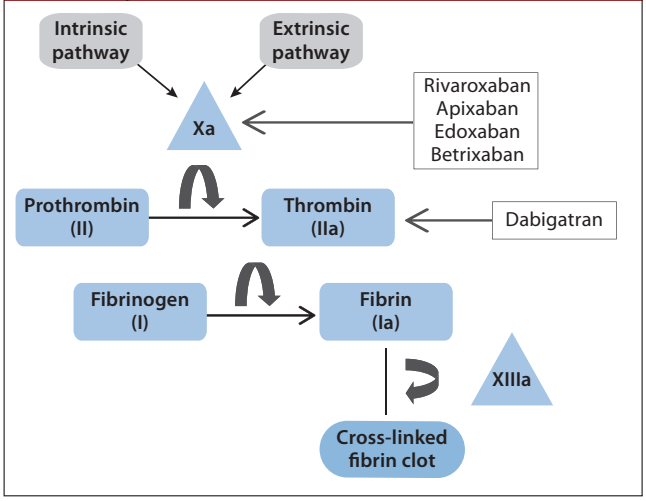
Factor Xa enzymatically converts prothrombin (Factor II) into thrombin, which serves both to activate platelets and to convert fibrinogen into fibrin. Vitamin K metabolism is essential to the hepatic synthesis of coagulation Factors II, VII, IX, and X. The vitamin K antagonists (VKAs) impair vitamin K metabolism in the liver, resulting in greatly diminished reserves of these crucial enzymes and subsequent decreased ability to form thrombus. Of note, however, vitamin K is also required to synthesize protein C and protein S, which serve crucial roles in counterbalancing the coagulation cascade by regulating the conversion of prothrombin into thrombin. Protein C and S levels are also greatly diminished with the use of VKAs, leading to a potentially pro-thrombotic state if a VKA were to be initiated as monotherapy. As a result, bridging therapy with a parenteral anticoagulant, usually low molecular weight heparin (LMWH) or unfractionated heparin (UFH), is advised when starting a VKA until therapeutic levels of anticoagulation are achieved. For most conditions, this is represented by an International Normalized Ratio (INR) between 2 and 3. Warfarin, the most common VKA in use in the U.S., has a direct half-life of 36 to 42 hours. The effective half-life approaches 96 hours, and is dependent on the liver's ability to recover synthetic function and produce prothrombin (Factor II).[1] The VKAs have a vast number of drug interactions with prescription medications, over the counter treatments, nutritional supplements, dietary intake, and alternative/herbal therapies.[2] The efficacy of anticoagulation may either be potentiated or impaired, depending on the interaction in question. In addition, patients with chronic liver disease, end stage renal disease, and advanced age are more sensitive to VKAs. The variability in treatment effect with VKAs is well documented, with studies demonstrating an average time in the therapeutic range on the order of 55-66%.[3] The need for frequent monitoring and dose adjustment, especially in the period of VKA initiation, contributes substantially to health care costs and societal burden, including time off from work and travel to monitoring tests.[4]

Direct Oral Anticoagulants

Factor Xa Inhibitors

This class of medications, currently consisting of apixaban, betrixaban, edoxaban, and rivaroxaban, directly inhibit Factor Xa, which results in decreased conversion of prothrombin to thrombin (Figure 1). Dosing regimens vary by indication. These drugs are contraindicated in the setting of severe hepatic disease, and caution and dosing adjustments may be advised in patients with renal dysfunction or increased bleeding risk. Table 1 lists times to peak effect as well as effective half-lives of the medications. The Factor Xa inhibitors are metabolized by both the P-glycoprotein (P-gp) and the CYP3A4 systems. Strong inhibitors of both systems, such as ketoconazole, itraconazole, ritonavir, and clarithromycin will potentiate their effects, while inducers of CYP3A4 and P-gp such as rifampin, phenytoin, and carbamazepine will inhibit their anticoagulant efficacy. Each direct oral anticoagulant (DOAC) produces variable effects on the coagulation assays commonly available in the clinical setting.[5] None have a direct linear relationship with any of the coagulation assays; at best, an abnormal test may be considered relatively specific for the ongoing presence of the anticoagulant, but the absence of abnormality is not sensitive for the absence of anticoagulant effect.[6] In other words, one cannot rely on normal coagulation assays to exclude clinically relevant anticoagulation effects.

FIGURE 01 Abbreviated Coagulation Cascade: Whereas Warfarin Blocks Synthesis of Factors I, I, VII, IX, and X, DOACs Show Targeted Activity



Adapted with permission from Pollack CV and the Hospital Quality Foundation.

TABLE 01 Overview of Oral Anticoagulants

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Lab monitoring	INR	–	–	–	–	–
Half-life[33]	40 h	12-17 h	5-9 h (young) 11-13 h (elderly)	9-14 h	10-14 h	19-37 h
Renal elimination	None	80%	33%	25%	35-50%	5-7%
Dosing[7, 34-37]	QD	BID	QD, with food	BID	QD	QD
Interactions[33]	Many	P-gp	CYP 3A4, P-gp	CYP 3A4, P-gp	CYP 3A4, P-gp	None reported
Reversal agent	Vitamin K	Idarucizumab[38]	Andexanet alfa[24]	Andexanet alfa	Pending	Pending
If life-threatening bleeding	4-factor PCC	Idarucizumab	Andexanet alfa	Andexanet alfa	4-factor PCC	4-factor PCC

Adapted with permission from Pollack CV and the Hospital Quality Foundation.

Direct Thrombin Inhibitors

Dabigatran is unique in the category of DOACs in that it is a direct thrombin inhibitor, binding to the active site of thrombin (Factor IIa) and preventing downstream thrombin-mediated platelet activation and fibrinogen conversion (Figure 1). Peak effect occurs within three hours of an oral dose and the effective half-life after steady state ranges from 12-17 hours. The drug is renally cleared, resulting in increased anticoagulation as renal function decreases. Dabigatran's anticoagulant effect is potentiated by drugs that inhibit P-gp metabolism, such as amiodarone, ketoconazole, clarithromycin, ticagrelor, and verapamil, and is inhibited by rifampin and other P-gp inducers. Drug dosing varies with renal function. The diluted thrombin time (dTT) and ecarin clotting time (ECT) offer quantitative assessment of dabigatran's activity but are not usually available on a "stat" basis.[4]

DISEASE INDICATIONS FOR ANTICOAGULATION

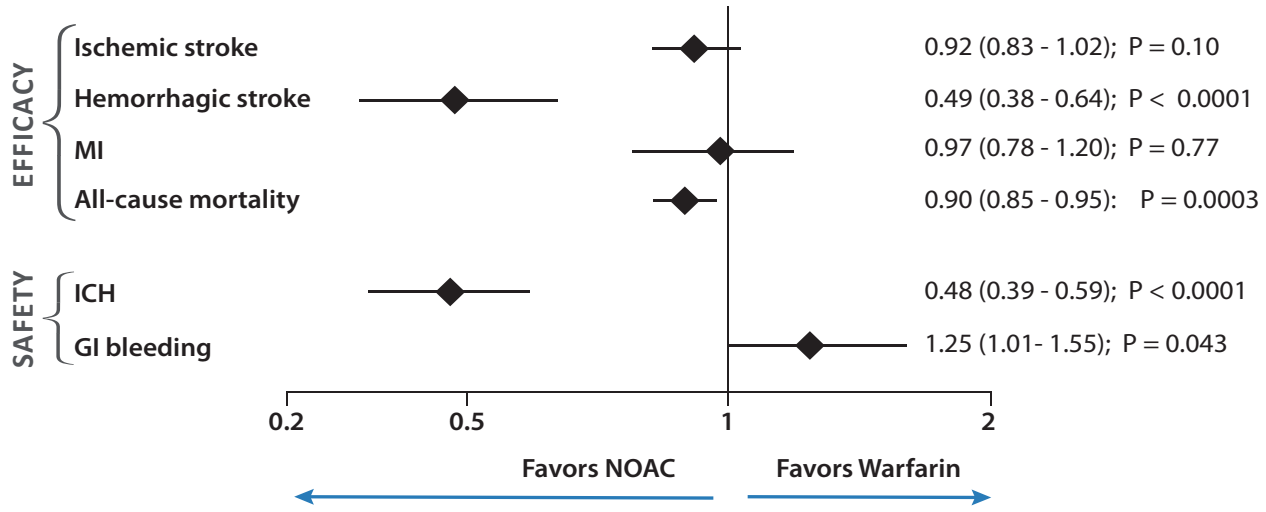
Venous Thromboembolism Prophylaxis in the Medically Ill

Betrixaban is currently the only oral anticoagulant that is indicated for the prevention of VTE in medically ill hospitalized patients during and after the hospital stay.[7] In the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) study, betrixaban was compared to enoxaparin (in hospital, then against placebo for extended thromboprophylaxis) in patients hospitalized for a variety of medical indications, with expected hospitalization of at least three days and immobilization (i.e., bed rest) for at least 24 hours.[8] Patients had to be at least 40 years of age and at risk for VTE as a complication: age > 75 years, age > 60 years with a d-dimer twice the upper limit of normal, or age > 40 and elevated d-dimer with a history of either cancer or prior VTE. Patients were randomized to fixed dose enoxaparin during the hospitalization or betrixaban during hospitalization and after discharge for a total treatment course of 35 to 42 days. There were several hierarchical and pre-specified subgroup analyses; however, the primary outcome of silent or symptomatic VTE occurred in 7% of the overall enoxaparin/placebo cohort versus 5.3% of the betrixaban cohort (relative risk, 0.76; 95% confidence interval [CI], 0.63 – 0.92). This absolute risk reduction resulted in a number needed to treat of 59 patients being treated with betrixaban instead of enoxaparin to prevent one primary outcome. The incidences of major and fatal bleeding were equivalent between groups, although the rate of major or clinically significant non-major bleeding was higher in the betrixaban cohort (3.1% versus 1.6%; relative risk, 1.97; 95% CI, 1.44-2.68).

Stroke Prophylaxis in Atrial Fibrillation

The incidence and prevalence of AF, which greatly increases the risk of thromboembolic stroke, increases with age. Anticoagulation decreases the annual risk of stroke by an average of 66% in comparison to no oral anticoagulant therapy, and is recommended for patients with atrial fibrillation and risk factors for stroke. The American Heart Association/American College of Cardiology guidelines for atrial fibrillation management recommend risk stratification with the validated CHA_2DS_2VASc tool and anticoagulation for those patients found to be at risk.[9] In a recent large meta-analysis (94,656 patients), the composite results of the DOACs versus VKAs for AF prophylaxis were examined and the authors concluded that the balance of the evidence for both safety and efficacy favored DOACs over VKAs, although comparisons could not be directly drawn between individual DOACs (Figure 2).[10] It is clear that there is an opportunity for acute care physicians to initiate anticoagulation in patients presenting with AF and an increased risk profile, although this opportunity is frequently missed.[11]

FIGURE 02 DOAC Efficacy and Safety in Atrial Fibrillation

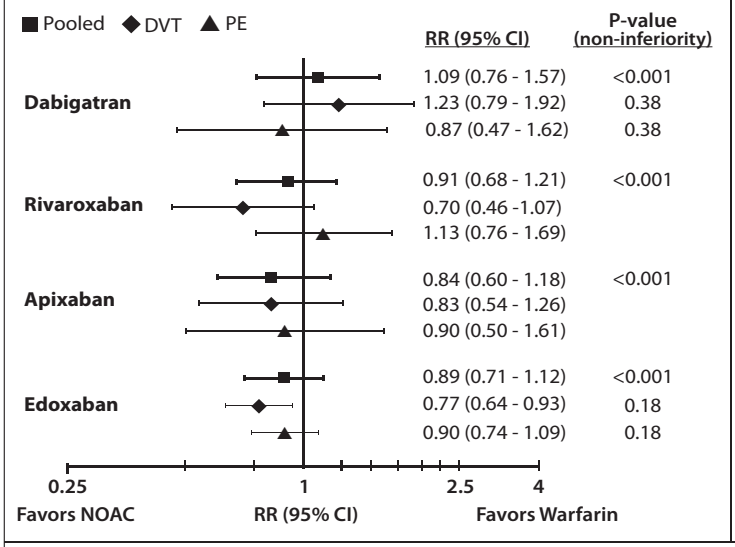


Adapted with permission from Ruff CT et al. Lancet. 2014; 383 (9921): 955-962

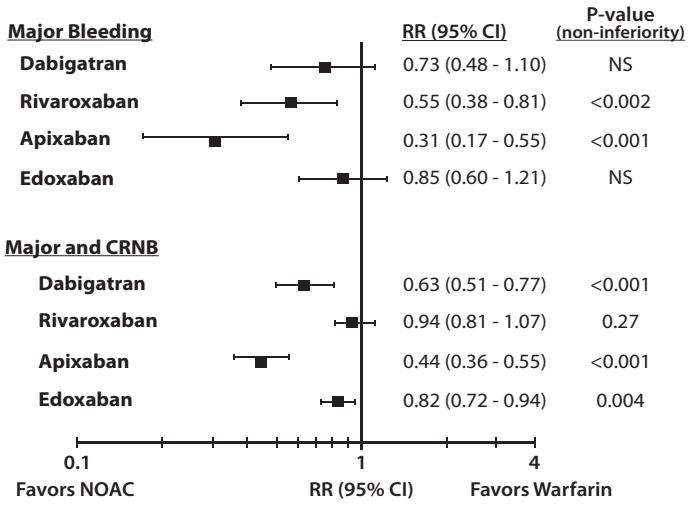
Acute Treatment of Venous Thromboembolism

Apixaban, dabigatran, edoxaban, and rivaroxaban have all been studied against VKAs for the treatment of acute deep venous thrombosis (DVT) or pulmonary embolism (PE) in a number of trials.[12-15] The collective experience with these agents is that the DOACs are consistently superior, or at least non-inferior, to VKAs for both efficacy and safety outcomes in the setting of VTE (Figure 3). As a result, the American College of Chest Physicians recommends the use of DOACs over VKAs in the treatment of non-cancer associated VTE.[16] In the U.S., the preferred agent for an individual patient may depend on which drug is preferentially covered by the patient insurance (if any). However, one key aspect of drug selection is that apixaban and rivaroxaban were both studied, and therefore approved, without lead-in anticoagulation. Both edoxaban and dabigatran were studied with a 5-10 day parenteral anticoagulation (LMWH or UFH) period prior to the initiation of oral treatment, and the FDA label requirements for each reflect this. In addition, all index studies were quite conservative with regards to the presence of hepatic and renal insufficiency, either requiring dose adjustment with impaired creatinine clearance, or excluding patients completely. Caution should be exercised when considering DOAC therapy for these patients. Although long-term therapy with LMWH has been recommended in consensus guidelines for cancer-associated thrombosis, new data are emerging that suggest that DOACs may be a reasonable alternative in a selected subpopulation of these patients.[17]

FIGURE 03 **DOACs Show Safety and Efficacy in Venous Thromboembolism Treatment**



Hazard ratios (HR) for recurrent VTE and VTE-related death and their 95% confidence intervals (CI) in phase 3 trials comparing NOACs with conventional therapy for acute VTE treatment.



Hazard ratios (HR) for major bleeding or major plus clinically relevant nonmajor bleeding (CRNB) and their 95% CI in phase 3 trials comparing NOACs with conventional therapy for acute VTE treatment.

Adapted with permission from Yeh et al. Blood. 2014;124:1020-1028

Repletion and Reversal Strategies

Vitamin K Antagonist Repletion

A patient who is therapeutically anticoagulated on a VKA has impaired physiologic activity at the multiple steps in the cascade that require participation of the vitamin K-dependent factors. Vitamin K administration merely allows the resumption of production of carboxylated Gla- domain and functionally active factors, and it takes hours to several days to re-establish physiologic levels. Although necessary, this is certainly not a sufficient response to management of ICH or other life-threatening hemorrhage. In fact, warfarin-related anticoagulation cannot be reversed. Instead, the levels of deficient factors must be repleted, and clinicians must not view vitamin K as a "reversal agent." Repletion can be accomplished in several ways. Traditionally, FFP was the direct repletion method of choice, but its use is limited by time requirements for thawing and cross-matching, concern for volume overload, and limited efficacy. The superior alternative for repleting vitamin K-dependent factors quickly is administration of PCC. The PCCs are pooled, virus-inactivated concentrates of human clotting factors. Four-factor PCCs (4F-PCCs) contain the vitamin K-dependent coagulation factors (II [prothrombin], VII, IX and X), as well as therapeutically effective concentrations of coagulation regulatory proteins (Proteins C and S). Three-factor PCCs (3FPCCs) do not contain Factor VII. In the past, some authorities recommended combining 3FPCCs with recombinant Factor VIIa (rFVIIa), though the need for this approach has not been specifically studied. The PCCs are indicated and most commonly used for warfarin reversal.[18] There are suggestive data that in warfarin-associated intracranial hemorrhage (ICH), PCCs reduce hematoma expansion more than FFP does,[19] and PCCs are preferentially recommended in professional society guidelines.[20]

Repletion of vitamin K-dependent factors in warfarin-associated hemorrhage and reversal of anticoagulation effect as in the case of DOAC treatment strategies discussed below should be reserved for life-threatening events, such as exsanguinating blood loss or bleeding into a critical space (primarily ICH). Two immediate concerns arise from precipitous removal of anticoagulation. The first is that patients who are therapeutically anticoagulated are treated for a good clinical reason, such as high risk of stroke associated with atrial fibrillation, previously demonstrated pathologic clot (e.g., venous thromboembolic disease), or mechanical heart valve (warfarin only). When anticoagulation "protection" is suddenly removed, these patients immediately return to their baseline prothrombotic state. It is important to

note that the patient should be left "unprotected" for as short a time as is clinically possible. The second concern is intuitive - a patient might receive more repletion than is needed. The "overshoot" thromboembolic complications are unusual after repletion, but are more common after PCC administration than with FFP. There is lower risk with FFP simply because less factor is being administered. Such events are still uncommon (5-10%) after use of PCCs and are dose-dependent. For this reason it is usually recommended that 4FPCC be given in two separate 25 IU/kg doses, with a clinical evaluation performed after the first infusion and consideration of omitting the second if the patient is stabilizing.[21]

Reversal of Direct Oral Anticoagulants

Reversal agents for the direct thrombin inhibitor, dabigatran, and the Factor Xa inhibitors, apixaban and rivaroxaban, are now approved in the United States. These agents are not hemostatic; rather, they reverse the effect of anticoagulants and are not dependent on repletion of factors, which is a critical distinction as compared to PCCs. In therapeutic anticoagulation with dabigatran, there is no deficiency of thrombin. Native thrombin is instead inhibited by the anticoagulant. Removing the effects of dabigatran frees up previously inhibited thrombin to participate meaningfully once again in coagulation. Likewise, patients treated with apixaban, betrixaban, edoxaban, or rivaroxaban have normal circulating levels of Factor Xa, but Xa function is inhibited by the therapy.

Dabigatran Reversal

Idarucizumab is a humanized monoclonal Fab fragment antibody to which dabigatran has 350 times higher affinity than to thrombin.[22] It has no intrinsic activity in the coagulation system and it provides immediate, complete, safe, and sustained reversal of the dabigatran effect. Idarucizumab is eliminated quickly, allowing early resumption of dabigatran therapy in clinically stable patients. The dose is 5 grams total, administered intravenously as two vials of 2.5 grams in rapid succession. Patients with very high dabigatran levels may show evidence of a recurrence of anticoagulation activity between 12 and 24 hours after reversal, due to drug re-entering the circulation from the extravascular space, but a repeat dose should probably only be given if there is also concomitant increased bleeding.

The safety and efficacy of idarucizumab as a reversal agent specifically for dabigatran was demonstrated in the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial of 503 patients, 301 of whom had serious or life-threatening hemorrhage.[23] The median maximum percentage reversal of dabigatran, on the basis of either the diluted thrombin time or the ecarin clotting time, was 100% (95% CI, 100 to 100). Nearly half of these patients had gastrointestinal bleeding and one-third presented with ICH. The median time to the cessation of bleeding was 2.5 hours, but this must be viewed in the context of multi-modal hemorrhage management. Idarucizumab (like andexanet alfa) is not a hemostatic agent. It merely neutralizes iatrogenic anticoagulation so that bleeding can be managed promptly, with mechanical and other pharmacologic means as appropriate and with support from transfusion of blood products as needed.[23]

At 90 days in RE-VERSE AD, thromboembolic events had occurred in 6.3% of the patients reversed for hemorrhage. Over 90% of these complications occurred in patients who did not have re-initiation of anticoagulant therapy. There were no serious adverse safety signals. Idarucizumab was also studied for, and approved for, reversal of dabigatran anticoagulation prior to an intervention that required clinically sufficient hemostasis.[23]

Factor Xa Inhibitor Reversal

Andexanet alfa, which is a class-specific reversal agent, is a decoy Factor Xa synthetic protein that lacks biologic activity in the coagulation cascade because of removal of the Gla- domain. It also has a mutation in the catalytic domain that removes its intrinsic procoagulant activity. The agent competitively binds to the Xa inhibitor and must be tailored to the molar concentration of the anticoagulant. The recommended dosing of andexanet alfa is based on the specific Factor Xa inhibitor, the dose of that Factor Xa inhibitor, and time since the patient's last dose.[24]

The bolus dose of andexanet is followed immediately with a 2-hour infusion. In the ANNEXA-A and ANNEXA-R healthy volunteer trials, the investigators described that after the infusions were stopped, anti-Factor Xa activity returned to levels that would be seen during normal metabolism of the Factor Xa inhibitors. While this phenomenon has been described as "rebound," it is actually an expected result of serum protease activity on the andexanet alfa molecule. It appears to be more pronounced with rivaroxaban by virtue of its increased volume of distribution (50L) compared to apixaban (15L). The driving theoretical hypothesis behind the bolus + 2 hour infusion strategy is that new clot formation and stabilization occurs during the initial 2 hours when there is a 90-92% reduction of anti-Factor Xa activity. Since DOACs have no fibrinolytic activity, the newly formed and stabilized clot is not subject to breakdown when the anti-Factor Xa activity returns as a result of the Factor Xa inhibitor being released from andexanet alfa as it is broken down by serum proteases.

In the years after DOAC approval (c. 2010) until the approval of andexanet alfa, PCCs served as a potential option for the management of life-threatening bleeding associated with anti-Factor Xa treatment. The PCCs reverse abnormal laboratory parameters (PT and endogenous thrombin potential) in human volunteers after taking high doses of rivaroxaban and apixaban.[25-27] However, giving high doses of prothrombin concentrates to patients who do not have deficient levels of Factor Xa or any of the other constituents of PCC is not an intuitive approach. In terms of clinical data, only a few small series have looked at the utility of PCCs in the treatment of DOAC-related major hemorrhage and thus none of the PCCs have regulatory approval for use in this scenario. In a retrospective cohort analysis of intracranial hematoma expansion, Gerner et al.[28] reported on 146 subjects with DOAC-related ICH; 103 were treated with PCCs and 43 received no PCCs. The primary outcome was hematoma enlargement (defined as volume increase of >33%) and secondary outcomes were in-hospital mortality, 3-month mortality and functional outcome at 3 months. No significant differences were seen between the two groups for the primary and secondary outcomes. Systolic blood pressure control (<160mmHg) at 4 hours post-admission was the only finding associated with a lower risk of hematoma expansion in DOAC-related ICH. Majeed et al.[29] found that PCC use resulted in effective hemostasis in 58/84 (69%) DOAC-related acute major bleeding subjects, 70% of whom had ICH. In the cohort with ineffective hemostasis (n=26), a similar percentage (61.5%) had ICH. In a prospective registry cohort study at nine Canadian hospitals, Schulman et al.[30] reported on 66 subjects with DOAC-related major bleeding (36 with ICH) who were treated with a fixed dose of 2,000 units of PCC. In the ICH subpopulation, 67% of treated subjects were described as having good hemostasis, 17% moderate and 17% poor/none. Of the 36 patients with ICH who had repeat brain imaging or died early, 31% died or had hematoma expansion of greater than 35%.

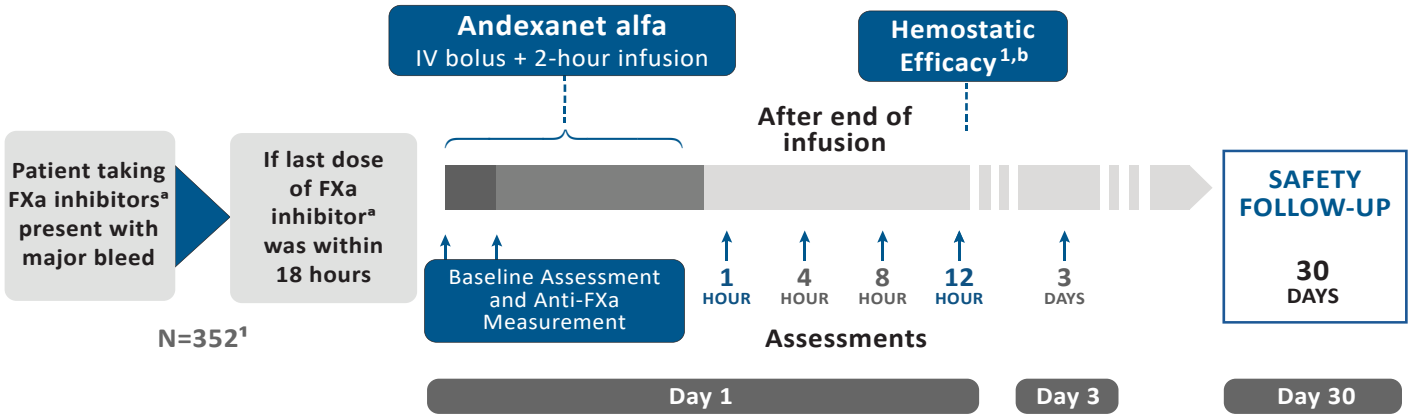
Since patients who are taking DOACs are doing so because they are at a high risk of thrombosis, removing the anticoagulant exposes them to their baseline thrombotic risk. Therefore, one would expect some thrombotic events in a subject population with major hemorrhage whose oral anticoagulant is discontinued abruptly. In the study by Schulman et al., 9/66 (14%) patients died by day 30 and 5/66 (8%) patients had a thromboembolic event.[30] In Majeed's study, mortality at 30 days was 32% and three (3.6%) subjects had thrombotic events. In a randomized comparison of 4F-PCCs versus FFP in VKA-associated major hemorrhage, Sarode et al. found thromboembolic adverse event rates of 7.8% for PCCs and 6.4% for FFP.[31] Overall, available studies suggest that thromboembolic rates of 3.6-10% are expected in this subject population and may vary depending on the severity of hemorrhage, baseline thromboembolic risk and comorbidities. Thus, treatment of anti-Factor Xa related bleeding may be associated with a risk of post-treatment thromboembolic complications. Importantly, treatment with the combination of a specific reversal agent AND PCCs would be expected to increase the risk of thrombotic complications. Therefore, if a patient will be treated with andexanet alfa or idarucizumab, PCCs should only be administered using extreme caution while balancing the risk versus benefit ratio in the patient with severe bleeding.

Full Study Report of ANNEXA-4

At the 2019 International Stroke Conference, Dr. TJ Milling presented the full study report of the ANNEXA-4 trial with simultaneous publication in the New England Journal of Medicine.[32] As directed by the FDA, this trial was designed as a multicenter, prospective, single arm, open label study with two co-primary outcomes: 1) the percent change from baseline anti-Factor Xa activity after andexanet alfa administration, and 2) the percentage of subjects with excellent or good hemostatic efficacy 12 hours after treatment as assessed by an independent adjudication committee based on pre-specified criteria. The clinical efficacy subgroup was selected based on confirmed major bleeding and a baseline anti-Factor Xa activity of greater than 75 ng/ml, suggesting a significant level of pretreatment anticoagulation.

Subjects were included in ANNEXA-4 if they presented with acute major bleeding and had taken their last dose of Factor Xa inhibitor within 18 hours of presentation (Figure 4). Acute major bleeding was defined as bleeding having one or more of the following features: potentially life-threatening bleeding with signs or symptoms of hemodynamic compromise (e.g., severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained); bleeding associated with a decrease in the hemoglobin level of at least 2 grams per deciliter (or a hemoglobin level of ≤8 grams per deciliter if no baseline hemoglobin level was available); or bleeding in a critical area or organ (e.g., retroperitoneal, intraarticular, pericardial, epidural, or intracranial bleeding or intramuscular bleeding with compartment syndrome).[32]

FIGURE 04 **Phase 3b/4 Confirmatory Study in Patients with Acute Major Bleeding**



Limitations of Use: Andexanet alfa has not been shown to be effective for, and is not indicated for, bleeding related to any FXa inhibitors other than apixaban or rivaroxaban

[a]Patients enrolled were taking apixaban, rivaroxaban, edoxaban, or enoxaparin

[b]The independent adjudication committee reviewed each case to determine hemostatic efficacy on the basis of predetermined criteria, to provide a rating of excellent or good (effective hemostasis) or poor/none (ineffective hemostasis).[1]

Accelerated approval of Andexanet alfa was based on percent change in anti-FXa activity, rather than hemostatic outcome.

1. Connolly SJ, et al. N Engl J Med. 2019; 380 (14): 1326-35.
2. Andexanet alfa [prescribing information]. South San Francisco, CA. Portola Pharmaceuticals Inc., 2018.

Key exclusion criteria were: planned surgery within 12 hours after andexanet treatment (with the exception of minimally invasive operations or procedures); intracranial hemorrhage in a patient with a Glasgow Coma Scale (GCS) <7 or an estimated hematoma volume of more than 60 cc; expected survival of less than 1 month; the occurrence of a thrombotic event within 2 weeks before enrollment; or use of any of the following agents within the previous 7 days: vitamin K antagonist, dabigatran, PCC, recombinant Factor VIIa, whole blood, or plasma.[32] While patients with GCS<7 and those with large hematoma volumes were excluded from ANNEXA 4, ultra-early risk stratification is very difficult in this patient population and different types of ICH may have different natural progressions. Other factors such comorbidities and pre-injury level of function may play a role in whether or not a patient may derive meaningful benefit from a reversal agent.

The ANNEXA-4 study findings were split into efficacy and safety populations. All patients who received andexanet alfa were included in the safety group and their adverse events were analyzed. Since no anti-Factor Xa assay is widely available for clinical use, investigators were unable to immediately measure anticoagulation activity at presentation. Therefore it was possible for subjects to be recruited appropriately, yet still have such low levels of anticoagulation that it would be wrong to consider them as part of an efficacy analysis. Therefore, as part of the study protocol, only patients with retrospective anti-Factor Xa levels of greater than 75 ng/ml were analyzed as part of the efficacy group. The lack of a widely available point-of-care anti-Factor Xa assay is a practical consideration for clinicians and researchers alike, but the design was methodologically rigorous.

The preliminary results of the ANNEXA-4 trial were released in 2016, but the full study report was not completed until 2019. Top line results show that the sites of bleeding were intracranial (64%), gastrointestinal (26%), or other (10%), and subjects had a mean age of 77 years. In patients taking apixaban and rivaroxaban, there was a 92% reduction of median anti-Factor Xa activity. Hemostatic efficacy was adjudicated as excellent or good in 204 (82%) of the 249 evaluable subjects at 12 hours. Death within 30 days occurred in 49 (14%) subjects and a thrombotic event in 34 (9.7%) subjects.

Since the release of the full study findings, much has been discussed about the trial methodology, results and next steps. In particular, the single arm design of the trial has received much scrutiny. Since previous healthy volunteer studies (ANNEXA-A and ANNEXA-R) found robust reduction of anti-Factor Xa activity and no thromboembolic adverse events with administration of andexanet alfa, it is reasonable to consider that the sponsor and regulatory bodies may have had ethical considerations in comparing andexanet alfa to a usual care arm when there were a wide variety of therapies being used, none of which were FDA approved for DOAC-related bleeding or had a strong mechanistic rationale and which may have been postulated to induce an iatrogenic prothombotic state. However, as part of the accelerated approval program, there are now plans for a Phase 3b/4 trial with a usual care comparator arm (ClinicalTrials.gov number NCT03661528).

The thromboembolic adverse event rate in ANNEXA-4 was 10% at 30 days. Although there are comparators in the literature using 4F-PCCs in VKA- and DOAC-related major bleeding, efforts to use the thromboembolic rates of these trials to advocate for a superior safety profile should be resisted because of the differences in adjudication, inclusion/exclusion criteria and sample size (Table 2). The predominant mechanism of action of andexanet alfa is competitive binding of the Factor Xa inhibitor molecule, but it also binds to tissue factor pathway inhibitor (TFPI). TFPI prevents unwanted anticoagulation, in essence halting the coagulation cascade. By binding to TFPI, andexanet alfa may have some intrinsic procoagulant activity, thus creating the potential for adverse events in certain subjects. However, in the Phase 2, placebo controlled, healthy volunteer ANNEXA-A and ANNEXA-R trials, no subject exposed to andexanet alfa had a thromboembolic event. Although 10% of subjects in ANNEXA-4 had a thromboembolic event, there were no thromboembolic events noted after resumption of oral anticoagulants.

TABLE 02 **Comparison with Other Studies on Management of Anticoagulant-Associated Bleeds**

Study (Ref.) characteristic or outcome	Sarode et al.[31] (N=104)	Sarode et al.[31] (N=98)	ANNEXA Full Study[32] Efficacy Population (N=254)	ANNEXA Full Study[32] Safety Population (N=352)	Majeed et al.[29] (N=84)	Schulman[30] (N=66)
Anticoagulant	Warfarin	Warfarin	Xa inhibitors		Xa inhibitors	Xa inhibitors
Reversal agent	Plasma	PCC	Adexanet alfa		PCC	PCC
Exclusion for poor prognosis	Expected survival < 3 days	Expected survival < 3 days	Expected survival < 1 month		DNR order given	DNR order given
Age, mean (SD)	69.8 (13.9)	69.8 (12.8)	77.1 (11.1)	77.4 (10.8)	75 (10.9)	76.9 (10.4)
Male sex	51 (49)	50 (51)	129 (51)	187 (53)	48 (57)	42 (67)
ICH	12 (12)	12 (12)	171 (67)	227 (64)	59 (70)	36 (55)
GI Bleed	64 (62)	63 (64)	62 (24)	90 (26)	13 (16)	16 (24)
Time last dose Xa inhibitor to REV, median (IQR)	NA	NA	(Mean ± SD) rivaroxaban: 12.3 ± 5.1 apixaban: 12.1 ± 4.6		12.5 (9-16)	16.9 (12-21)
Effectiveness assessment according to Sarode et al.[31] for CNS bleeds						
Excellent or Good	7 (58)	5 (42)	135 (80)		Not done	25 (76)†
Effectiveness assessment according to ISTH[39] criteria for CNS bleeds						
Excellent or Good	Not done	Not done	Not done		43 (73)	25 (69)
Safety outcomes during 30 days						
Thromboembolism	7 (6)	8 (8)	34 (10)		3 (4)	5 (8)
Death	5 (5)	6 (6)	49 (14)		27 (32)	9 (14)

† Only patients with repeat tomography (n=30) or with large CNS bleeds resulting in early death (n=3) were included in this analysis.
Results are in *n* (%).
Adapted with permission from Schulman et al. Thromb Haemost 2018;118(05): 842-851

Although ANNEXA-4 represents the largest dataset of DOAC-related major hemorrhage subjects, practical considerations not directly addressed by the study have arisen since its accelerated approval by the FDA in August 2018. There are little data about intraoperative use, of re-dosing, or extended infusion. Although trauma patients with major hemorrhage were enrolled in ANNEXA-4, they were a small fraction of the overall cohort and require more targeted study. Since the use of thromboelastography (TEG) has been more commonly adopted in the care of patients with hemorrhage, its use to guide the administration of a reversal agent, particularly in patients with renal dysfunction, is a subject for future investigation.

Cost considerations have played a large role in the discussion of the clinically utility of andexanet alfa. Although target-specific reversal therapy with andexanet alfa has been rigorously studied, received accelerated FDA approval, and been incorporated into professional society guidelines, some have questioned its use in comparison to a non-targeted, less rigorously studied, non-approved but less expensive option of 4F-PCCs.

Conclusion

The DOACs continue to be increasingly prescribed for AF and VTE indications and there is ongoing study and expansion of the indications for treatment to other disease states, such as coronary artery disease, peripheral arterial disease, and VTE treatment in cancer-associated thrombosis. As these therapies become more widely used, more patients will present with hemorrhagic adverse events. Whereas most are minor and can be managed conservatively, major hemorrhages should be managed with target-specific, agency-approved and guideline-recommended therapies. Although many unanswered questions related to the treatment of patients with DOAC-related major hemorrhage remain, it is clear that the decision to deploy repletion and reversal strategies should involve multiple stakeholders, including emergency physicians, hospitalists, intensivists, surgeons, hospital pharmacists, and the patients and their families.

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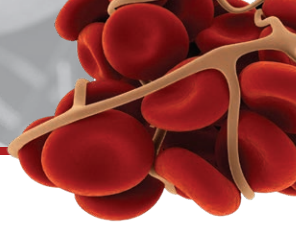

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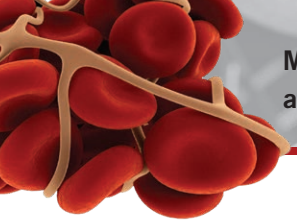

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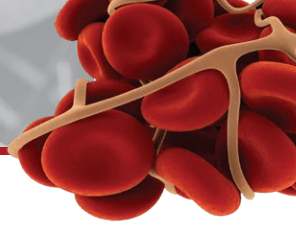

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1. Betrixaban is the only oral anticoagulant that is indicated for the prevention of venous thromboembolism (VTE) in medically hospitalized patients.

   A. True
   B. False

2. Anticoagulation decreases the annual risk of stroke by approximately:

   A. 10%
   B. 25%
   C. 66%
   D. 95%

3. Which coagulation protein is absent in three factor prothrombin complex concentrate in comparison to four factor prothrombin complex concentrate?

   A. Factor II
   B. Factor VII
   C. Factor IX
   D. Factor X

4. In the Full Study Report of ANNEXA-4, how large was the reduction in anti-Factor Xa activity that was noted after andexanet alfa bolus administration?

   A. 20%
   B. 40%
   C. 60%
   D. 90%

5. In the ANNEXA-4 trial, the majority of patients enrolled had which of the following types of acute major hemorrhage:

   A. Gastrointestinal
   B. Retroperitoneal
   C. Epistaxis
   D. Intracranial

(Answer sheet next page)

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CME ANSWER SHEET

(circle correct answer)

1.	**a**	**b**		
2.	**a**	**b**	**c**	**d**
3.	**a**	**b**	**c**	**d**
4.	**a**	**b**	**c**	**d**
5.	**a**	**b**	**c**	**d**

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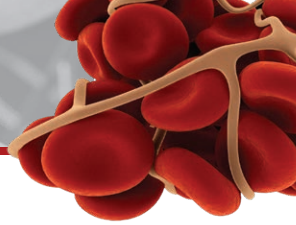

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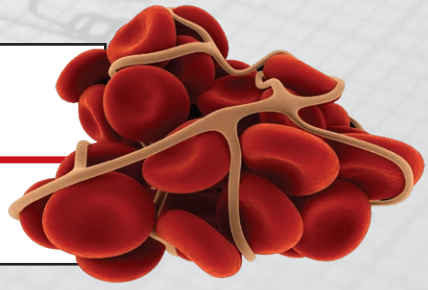

Management of Life-Threatening Bleeding in the Anticoagulated Patient in the Emergency Setting and the Impact of ANNEXA-4 on the Treatment of Patients Taking Factor Xa Inhibitors

AUGUST 2019