Drug Evaluation

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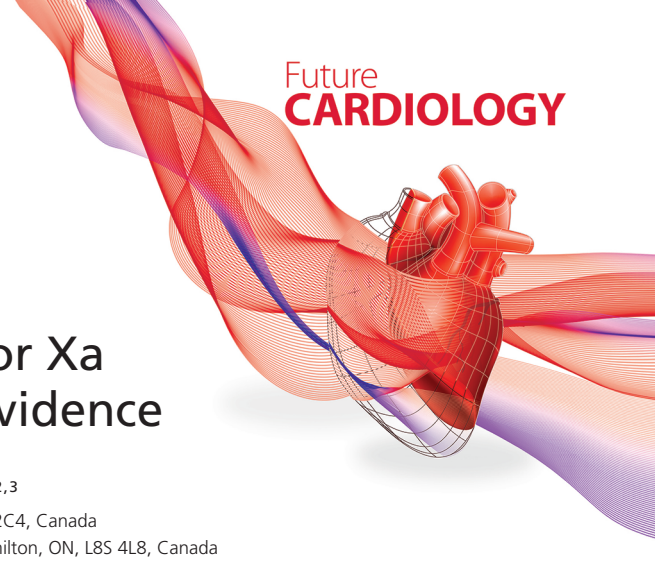

Andexanet alfa for reversal of factor Xa inhibitors: a critical review of the evidence

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Direct oral anticoagulants are associated with lower rates of bleeding than vitamin K antagonists, but life-threatening bleeding still occurs. Andexanet alfa is a catalytically inactive recombinant modified human factor Xa molecule that reverses the anticoagulant effect of direct and indirect acting factor Xa inhibitors. In the ANNEXA-4 study, treatment with andexanet was associated with a 92% reduction in median anti-Xa activity levels and excellent or good hemostasis in 82% of patients presenting with serious bleeding while receiving apixaban or rivaroxaban. In this review, we discuss the burden of bleeding in anticoagulated patients and the need for reversal agents, review the mechanism of action of andexanet and critically evaluate the evidence for its efficacy and safety.

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Randomized controlled trials have established the efficacy and safety of direct oral anticoagulants (DOACs) for prevention and treatment of venous thromboembolism, stroke prevention in atrial fibrillation and prevention of major adverse cardiovascular events in patients with atherosclerotic vascular disease [1–4]. One of the most important advantages of DOACs over vitamin K antagonist (VKA) is a lower risk of life-threatening bleeding, particularly intracranial hemorrhage (ICH) [5]. In randomized trials, the outcomes after major bleeding were similar in patients receiving DOACs and those receiving VKAs despite availability of VKA reversal strategies (e.g., vitamin K, prothrombin complex concentrates [PCC]) but not DOAC reversal agents [6,7]. Nevertheless, the case-fatality rates after DOAC-related major bleeding and intracranial bleeding remain high at 10–20% and 40%, respectively [6,8]. It is possible that the availability of specific reversal agents for the DOACs will improve clinical outcomes after bleeding.

The first reversal agent for DOACs approved for clinical use was idarucizumab, a humanized antibody fragment that fully reverses the anticoagulant effect of dabigatran within minutes [9–12]. More recently, the ANNEXA-4 study demonstrated that andexanet alfa, a recombinant modified human factor Xa (FXa) molecule, reverses the anticoagulant effect of direct and indirect FXa inhibitors [13]. Andexanet was recently approved in the USA and Europe for the reversal of apixaban and rivaroxaban in patients who present with life-threatening bleeding [14,15].

In this review, we discuss the burden of bleeding in anticoagulated patients and the need for reversal agents, review the mechanism of action of andexanet and critically evaluate the evidence for its efficacy and safety.

Burden of bleeding

Although DOACs are safer than VKAs, bleeding during DOAC therapy remains a major cause of disability and mortality and increases healthcare costs [16]. VKAs are still the most common anticoagulant associated with emergency department visits, but among older adults the hospitalization rate for bleeding is similar between VKAs and DOACs [17]. In the USA, FXa inhibitor-associated bleeding is estimated to be responsible for 117,000 hospitalizations and 2000 bleeding-related deaths per month [16]. These hospitalizations last on average 5.3 days

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and cost $28,059 USD [18]. Furthermore, patients hospitalized with major bleeding have higher mean total all-cause healthcare costs over the subsequent year compared with those who did not experience major bleeding, at $58,169 and $41,241 USD, respectively [18].

In a large multicenter observational cohort of patients bleeding on anticoagulation, in hospital mortality was lower in DOAC-treated patients compared with VKA-treated patients (adjusted relative risk 0.66; 95% CI: 0.49–0.89) but no difference was noted in 30-day mortality (adjusted relative risk 0.79; 95% CI: 0.61–1.03) [19]. In the randomized trials, comparing an oral direct FXa inhibitor (apixaban, rivaroxaban and edoxaban) with VKA for prevention of stroke and systemic embolism in atrial fibrillation, the annual risk of major bleeding was 1.6–3.6% for FXa inhibitors and 3.1–3.4% for VKA, with similar case fatality rates [3,6,7,20,21]. In the ARISTOTLE trial, the 30-day mortality rate after a nonintracranial major bleed was 8.9% in the apixaban arm compared with 9.5% in the VKA arm, and after an intracranial bleed was 45.3% compared with 42.3%, respectively [6]. In the ROCKET-AF trial, the 30-day mortality rate after a major bleed was 20.4% in the rivaroxaban arm compared with 26.1% in the VKA arm [7]. In the ENGAGE-TIMI trial, for edoxaban 60 mg once daily, edoxaban 30 mg once daily and VKA, the 30-day mortality rates were 2.2, 4.2 and 4.3% of extra-cranial major bleeds, and 39, 29 and 32% of intracranial bleeds, respectively [22].

Patients who experienced major bleeding in the ARISTOTLE and ROCKET-AF trials were managed with interruption of anticoagulation, intravenous fluids and blood transfusion as required, and in rare cases with the use of nonspecific hemostatic agents, including antifibrinolytic drugs and PCC [6,7]. In ARISTOTLE, the frequency of blood transfusion was similar in the apixaban and VKA groups for all major bleeds (37.8 vs 37.0%) and gastrointestinal bleeds (48.9 vs 52.6%) [6]. Adjunctive treatments vitamin K, thrombin, PCC, factor IX or factor VII were used in 10.4% of patients with major bleeds [6]. In the ROCKET-AF trial, red blood cell transfusion was administered to 40.8% of patients with major bleeds on rivaroxaban compared with 35.2% of those on VKA [7]. Other adjunctive treatments administered within 24 h to rivaroxaban- and warfarin-treated patients included vitamin K (7.4 vs 13.2%), epsilon-aminocaproic acid (0.5 vs 0.7%), tranexamic acid (0.5 vs 2.7%), PCC (0.9 vs 2.2%), recombinant factor VIIa (0 vs 0.2%), factor VIII (0.2 vs 0.2%) and factor IX (0 vs 0.7%) [7].

These data highlight that despite the safety advantages of the DOACs over VKA, bleeding in patients treated with an oral direct FXa inhibitor is common and a major cause of morbidity and mortality. The availability of an agent that can rapidly and completely reverse their anticoagulant effect could help to optimize management and potentially improve outcomes.

Andexanet alfa

Andexanet alfa (Andexxa® in the USA, Ondexxya® in Europe) is a recombinant-modified human FXa protein that lacks procoagulant or anticoagulant activity [23]. A mutation in the serine residue disrupting the catalytic triad prevents it from cleaving prothrombin and thereby generating thrombin, whereas a deletion of the membrane binding γ-carboxyglutamic acid domain prevents it from binding to factor Va and acting as a competitive inhibitor of the prothrombinase complex [23]. Andexanet alfa binds FXa inhibitors in the plasma, thereby freeing endogenous FXa to resume its normal function in hemostasis [23]. Andexanet also binds to pentasaccharide-activated antithrombin, thereby reversing the anticoagulant effect of indirect FXa inhibitors such as unfractionated heparin, low molecular weight heparin and fondaparinux [23].

In addition to reversing the anticoagulant effect of drugs that target FXa, andexanet binds to tissue factor pathway inhibitor (TFPI), an endogenous naturally occurring anticoagulant that normally circulates in very low concentrations in plasma [24]. TFPI binds reversibly to FXa, and the resulting TFPI–FXa complex inhibits the tissue factor–factor VIIa complex, which plays a key role in activation of the tissue factor pathway leading to thrombin generation [25]. When andexanet alfa binds to TFPI, circulating TFPI concentrations are reduced, which may lead to increased thrombin generation [26].

Pharmacokinetics

Andexanet is available in 200 mg vials of a lyophilized powder requiring reconstitution [27]. Once reconstituted, it is stable at room temperature for up to 8 h, or up to 24 h, if stored at 2–8°C [27]. It is administered intravenously as a bolus over 15–30 min followed by a 2-h infusion [13,24]. The recommended dose of andexanet is based on the FXa inhibitor to be reversed and the amount and timing of the last dose [13,27]. Andexanet reduces anti-FXa activity within 2–5 min of bolus administration [24,28]. Anti-FXa activity remains suppressed during continuous infusion

Table 1. The effect of an andexanet bolus on coagulation parameters and active drug levels in healthy volunteers.

Coagulation parameters and active drug levels	Apixaban			Rivaroxaban		
	Andexanet	Placebo	p-value	Andexanet	Placebo	p-value
Anti-FXa activity reduction (%)	94	21	<0.001	92	18	<0.001
Thrombin generation restoration (%)	100	11	<0.001	96	7	<0.001
Unbound drug concentration reduction (ng/ml)	9.3	1.9	<0.001	23.4	4.2	<0.001

FXa: Factor Xa.

and for up to 2 h after stopping the drug [24,28]. Andexanet alfa has a pharmacodynamic half-life of 1 h, although the mechanism of andexanet clearance is unknown [24,29].

Pharmacodynamics

The ANNEXA-A and ANNEXA-R studies evaluated the pharmacodynamic effects of andexanet on laboratory coagulation tests, anti-FXa activity (the most accurate and reliable measure of the anticoagulant activity of FXa inhibitors), unbound FXa inhibitor concentration and thrombin generation (Table 1) [24]. In these studies, healthy older volunteer subjects received andexanet or placebo after dosing of apixaban or rivaroxaban to steady-state [24]. Andexanet reduced apixaban anti-FXa activity by 94% and rivaroxaban anti-FXa activity by 92%, compared with 21 and 18% reductions, respectively, after placebo [24]. Andexanet restored thrombin generation, measured as the change in endogenous thrombin potential, in 100% of subjects receiving apixaban and 96% of those receiving rivaroxaban, compared with 11 and 7% receiving placebo ($p < 0.001$) [24]. These changes were accompanied by significantly greater reductions in blood levels of unbound (active) apixaban and rivaroxaban with andexanet compared with placebo, and the effects persisted during continuous infusion [24].

Despite andexanet's short half-life, temporary correction of hemostasis appears to be sufficient to control bleeding. In the ANNEXA-A and -R studies, even with rising anti-FXa activity after cessation of andexanet, thrombin generation was maintained and remained within one standard deviation of the baseline mean for at least 22 h post-andexanet [24].

Phase III evaluation in FXa inhibitor-treated patients with major bleeding

ANNEXA-4 was a multicenter, prospective, single arm cohort study of andexanet alfa for patients anticoagulated with apixaban, rivaroxaban, edoxaban or enoxaparin who presented with acute major bleeding. Results from the first 67 patients were reported in 2016, and from the full cohort of 352 patients in 2019 [13,30]. Patients were eligible for inclusion if they presented with major bleeding within 18 h of the last dose of FXa inhibitor [13]. Exclusion criteria included planned surgery within 12 h of andexanet administration (except for minimally invasive procedures), ICH accompanied by a Glasgow Coma Scale <7 or estimated hematoma volume >60 ml, expected survival <1 month, thrombotic event within 2 weeks prior to presentation, or use within the previous week of a VKA, dabigatran, PCC, recombinant factor VIIa, whole blood or plasma [13].

Eligible, consenting patients received a bolus of andexanet over 15–30 min followed by a 2-h infusion [13]. The dose of andexanet was determined by the FXa inhibitor and the amount and timing of the last dose [13]. The coprimary outcomes were the percent change in anti-FXa activity post-andexanet and the percentage of patients with good or excellent hemostatic efficacy at 12 h, which was independently evaluated by a blinded adjudication committee based on prespecified criteria from Sarode *et al.* [13,31,32]. The main safety outcomes were thrombotic events, mortality and the development of antibodies to andexanet or endogenous factor X or FXa at 30 days [13].

Baseline characteristics of patients in the efficacy and safety population are presented in Table 2. The majority of patients presented with ICH (64%) followed by gastrointestinal bleeding (28%) [13]. Patients with baseline anti-FXa activity ≥75 ng/ml (or >0.25 IU/ml for enoxaparin) and confirmed major bleeding at presentation were included in the efficacy analysis (n = 254) [13]. In the apixaban group, the median anti-FXa activity post-andexanet bolus was reduced by 92% (95% CI: 91–93), from 149.7 to 11.1 ng/ml [13]. In the rivaroxaban group, the median anti-FXa activity post-andexanet bolus was reduced by 92% (95% CI: 88–94), from 211.8 to 14.2 ng/ml [13]. Of those who could be evaluated, hemostasis was achieved in 82% (204/209), adjudicated as excellent in 69% (171/249) and good in 13% (33/249) [13]. In patients with intracranial or gastrointestinal bleeding, hemostasis was adjudicated as good or excellent in 80% (95% CI: 74–86) and 85% (95% CI: 76–94), respectively [13]. Reduction in anti-FXa

Table 2. Baseline characteristics of patients in ANNEXA-4 study.

Characteristics	Safety population (n = 352)	Efficacy population (n = 254)
Mean age, years (SD)	77 (11)	77 (11)
Male sex	187 (53)	129 (51)
Medical comorbidities		
– Myocardial infarction	48 (14)	36 (14)
– Stroke	69 (20)	57 (22)
Primary indication for anticoagulation†		
– Atrial fibrillation	280 (80)	201 (79)
– Venous thromboembolism ‡	61 (17)	46 (18)
– Other	11 (3)	7 (3)
Factor Xa inhibitor		
– Apixaban §	194 (55)	134 (53)
– Rivaroxaban	128 (36)	100 (39)
– Edoxaban	10 (3)	4 (2)
– Enoxaparin	20 (6)	16 (6)
Site of bleeding		
– Intracranial	227 (64)	171 (67)
– Gastrointestinal	90 (26)	62 (24)
– Other	35 (10)	21 (8)

Data shown as n (%) unless otherwise stated.
†Some patients had more than one primary indication for anticoagulation.
‡Includes prevention and treatment of deep vein thrombosis and pulmonary embolism.
§One patient who reported receiving apixaban, had a high concentration of rivaroxaban in their plasma.
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SD: Standard deviation.

activity was not predictive of hemostatic efficacy overall but was modestly predictive in patients with ICH (area under the receiver-operator curve [ROC] 0.64, 95% CI: 0.53–0.74).

All 352 patients who received andexanet in ANNEXA-4 were included in the safety analysis [13]. In total, 10% (34/352) of patients had thrombotic events which occurred within 5 days (n = 11), between days 6 and 14 (n = 11) and between days 15 and 30 (n = 12) after andexanet administration [13]. The thrombotic events included 14 ischemic strokes, 13 deep vein thromboses, seven myocardial infarctions and five pulmonary emboli [13]. Within 30 days of enrollment, 14% (49/352) of the cohort died of cardiovascular causes (10%, n = 35), noncardiovascular causes (3%, n = 12) and unknown causes (1%, n = 2) [13]. No antibodies were detected to factor X or FXa, and no neutralizing antibodies were detected to andexanet [13].

Critical evaluation

Hemostatic efficacy

Assessing the effect of treatments on clinical hemostasis is challenging because most types of bleeding cannot be directly visualized and without direct visualization the exact timing of bleeding cessation is unclear [13,32]. Surrogate markers of hemostasis such as laboratory tests of coagulation or thrombin generation may not correlate well with clinical hemostatic efficacy because bleeding is also a consequence of injury to a blood vessel [13]. In ANNEXA-4, there was a significant relationship between the change in anti-FXa activity and hemostatic efficacy only in the subgroup of patients with intracranial bleeding in whom hemostatic efficacy was evaluated using the measurement of hematoma volume on serial imaging with computed tomography or magnetic resonance imaging [13].

Hemostatic efficacy was adjudicated by an independent committee using prespecified criteria for different bleed types [13]. Without a control group for comparison, it is not possible to reliably determine the contribution of anticoagulant reversal to achieving hemostasis and clinical outcomes. ANNEXA-4 did not include a control or placebo group because withholding a specific reversal agent from a patient with serious (potentially life-threatening) bleeding was considered unethical [13].

In the absence of specific reversal agents, PCCs have been used in patients treated with FXa inhibitors who experience serious bleeding [33]. PCCs are plasma-derived concentrates of vitamin K-dependent coagulation factors available in formulations containing factor VII (4-factor PCC) or without factor VII (3-factor PCC) [34]. Evidence

regarding the effectiveness and safety of PCCs when used for the management of major bleeding in patients anticoagulated with oral FXa inhibitors is restricted to small observational studies lacking control groups [33]. The results of a systematic review and meta-analysis of observational studies indicate that PCCs were associated with hemostasis in 69% of patients (95% CI: 61–76) in studies using the International Society of Thrombosis and Hemostasis definition for effective hemostasis, and in 77% of patients (95% CI: 63–92) in studies using alternative definitions for effective hemostasis [33,35]. The variable hemostatic efficacy reported with PCC could reflect heterogeneous definitions of effective hemostasis, different composition of bleeding sites or the challenges determining clinical hemostasis, as discussed above [33].

Thrombosis risk

Reversal of anticoagulation in bleeding patients could be expected to increase the risk of thromboembolic events in patients with elevated baseline thrombotic risk. In ANNEXA-A, ANNEXA-R and earlier Phase I and II studies, a transient increase in D-dimer and prothrombin fragments 1+2 was observed after administration of andexanet, lasting for 24–72 h [24,28]. In ANNEXA-A and -R, the highest increase in D-dimer and prothrombin fragments were observed in subjects receiving the highest doses of andexanet, particularly in those who received andexanet after pretreatment with a FXa inhibitor [28]. These effects were hypothesized to be due to the binding of andexanet to TFPI which normally downregulates the activity of the tissue factor pathway of coagulation [24,28]. Despite these transient changes in surrogate markers, no thrombotic events were observed in animal model or healthy volunteer studies [24,28,36–42]. Furthermore, in bleeding animal models, andexanet alone had no effect on blood loss in animals that did not receive a FXa inhibitor [23]. However, the interaction of andexanet with TFPI and transient increases in D-dimer and prothrombin fragments have raised concerns about the risk of thrombosis in patients treated with andexanet for bleeding [24,28]. In ANNEXA-4, the 30-day rate of thrombotic events was 10% (n = 34) [13]. The majority of these events (n = 26, 76%) occurred in patients who had not yet restarted any anticoagulation and all of the events occurred in patients who had not restarted oral anticoagulation [13]. Although not directly comparable, the rate of thrombotic events seen in ANNEXA-4 are not dissimilar to those reported in the REVERSE-AD study and in studies evaluating the use of PCCs in patients treated with FXa inhibitors or warfarin [12,31,43,44].

Nonthrombotic risks

In healthy volunteers who received andexanet, adverse events were minor and included mild to moderate infusion reactions not associated with hemodynamic changes or respiratory compromise that resolved without intervention or with reduction in dose of andexanet [24,28]. Apart from pneumonia in one patient, unlikely related to andexanet, the only serious adverse events reported in these studies was a spontaneous abortion, considered possibly or probably related to andexanet [24,28,37–42]. In a pooled analysis of FXa inhibitor-treated healthy volunteers who received andexanet or placebo, the frequency of adverse reactions in those who received andexanet (54%, 120/223) and those who received placebo (57%, 54/94) was similar [27]. In the andexanet group, 18% (39/223) had infusion reactions [27]. In ANNEXA-4, two patients had nonsevere infusion reactions [13].

In ANNEXA-A and ANNEXA-R, non-neutralizing antibodies against andexanet occurred in 2% (1/44) of healthy volunteers who received placebo compared with 17% (17/101) who received andexanet; two of the participants had the antibodies prior to administration of the study drug [24]. No neutralizing antibodies to factor X, FXa or andexanet developed in the Phase I and II trials, ANNEXA-A, ANNEXA-R or ANNEXA-4 [13,24,28].

Unresolved issues

Although preclinical and human volunteer studies demonstrate that andexanet reverses the anticoagulant effect of other direct and indirect FXa inhibitors (enoxaparin, edoxaban, betrixaban and fondaparinux), the data for patients who bleed during treatment with these agents are limited [23,24,28,37–42,45]. The ANNEXA-4 extension study that is currently ongoing in Japan is evaluating the use of andexanet for reversal of rivaroxaban, apixaban and edoxaban in bleeding patients, whereas the extension study in Germany is evaluating its use specifically in enoxaparin and edoxaban patients.

There remain several patient populations in whom andexanet has not been fully assessed. Andexanet has not been assessed for reversal of FXa inhibitors in patients who require urgent surgery and is not approved for use in this setting. The ANNEXA-4 study focused predominantly on patients with ICHs, but excluded the most serious types including those with associated Glasgow Comas Scale less than 7 or estimated hematoma volume greater than 60 ml, who would be expected to receive andexanet in attempt to improve their outcomes [13]. Other patients for

Table 3. Andexanet dosing by drug as per US Food and Drug Administration.

FXa inhibitor	FXa inhibitor last dose	<8 hours or unknown	≥8 hours
Apixaban	≤5 mg	Low Dose	Low dose
	>5 mg or unknown	High Dose	
Rivaroxaban	≤10 mg	Low Dose	
	>10 mg or unknown	High Dose	

Low Dose: 400 mg at a target rate of 30 mg/min bolus then 4 mg/min for up to 120 min infusion.
High Dose: 800 mg at a target rate of 30 mg/min bolus then 8 mg/min for up to 120 min infusion.
FXa: Factor Xa.

whom data are lacking include those with recent thrombotic events, as well as those also treated with a PCC or recombinant factor VIIa [13].

The role of anti-FXa activity testing in the management of patients treated with a DOAC who present with bleeding has not been clearly defined. Although specific DOAC-calibrated anti-Xa activity assays are the most reliable and accurate tests for measuring FXa inhibitor levels, they are not always available and in the USA, no tests have been approved by the US FDA [46]. Notably, andexanet dosing in the ANNEXA-4 trial was based on the drug and time of its last administration rather than laboratory testing of drug levels [13,27].

The acquisition cost of andexanet will have implications for hospitals and health systems and would appear to warrant institutional protocols to promote its judicious use. In the USA, the acquisition cost of a 200 mg vial is $5500 [47]. Using FDA-recommended dosing, the total cost of the low and high dose andexanet reversals would be $27,500 and $49,500, respectively [27]. The high cost of andexanet highlights the importance of its judicious-protocolized use for the management of patients with bleeding on FXa inhibitors. Some cost reduction may be available through the manufacturer's New Technology Add-On Payment program [48]. Comparatively, the acquisition cost in the USA of a 5-g kit of idarucizumab required for reversal is $3500 to $4200 USD [47,49]. The cost of treatment with a PCC based on an average wholesale price of $1.62 USD per unit, and a fixed dose of 2000 units for a reversal of apixaban or rivaroxaban would be approximately $3240 USD [43,44,47,50].

Regulatory affairs & postmarketing

On 3 May 2018, andexanet was granted accelerated approval in the USA, with the stipulation of re-assessment of approval after the completion of the Phase IV trial, a Phase 4 randomized trial of ANDEXXA in acute intracranial hemorrhage in patients receiving oral factor Xa inhibitors (ClinicalTrials.gov number, NCT03661528) pending completion in 2023 [14]. On 26 April 2019, andexanet was granted conditional approval in Europe, again with the requirement of postmarketing studies [15].

In the USA and Europe, andexanet is approved for reversal of life threatening or uncontrolled bleeding for patients anticoagulated with apixaban or rivaroxaban [15,27]. The package insert for andexanet in the USA contains a black box warning for arterial and venous thromboembolic events, including myocardial infarction and ischemic stroke, cardiac arrest and sudden death and advises resumption of anticoagulation as soon as medically possible [27]. Table 3 summarizes FDA-recommended dosing.

Data on the postmarketing use of andexanet are limited [14,15]. An online survey conducted between September and December 2018 by the Anticoagulation Forum, a multidisciplinary organization of North American healthcare professionals with a focus on improving the quality of care of those on anticoagulation, found of the 53 responding hospitals, 41 had not yet included andexanet in their formulary [47]. However, this survey may not reflect current usage as it predates approval of the Generation 2 manufacturing process, which has enabled more widespread distribution.

A center in the USA described the limitations and challenges they experienced after 150 days and 15 patients managed with andexanet [51]. In their cohort of rivaroxaban- and apixaban-treated patients, the mean age of patients was 82 years, and 93% presented with an intracranial bleed [51]. The mean time from order placement to bedside delivery of andexanet was 43 min, and from order to bolus administration was 66 min [51]. No thrombotic events were observed and inpatient mortality observed in 6/15 (40%) of patients [51]. Five of the six (83%) of deaths occurred within 4 days of presentation and were attributed to their initial bleed and one was due to infection at 13 days [51]. The majority would not have been eligible for inclusion in ANNEXA-4 because of recent thrombosis, planned surgery or concomitant PCC use [51]. Several challenges were identified including logistical challenges of

patient transfer for treatment, determining whether PCC had been given, drug preparation time and requests for nonapproved indications [51].

In one case report, intraoperative-unfractionated heparin was ineffective after administration of andexanet for reversal of rivaroxaban [52]. This emphasizes the uncertainty regarding the pre-operative safety and efficacy of andexanet, which is not approved or recommended for use in this setting [27].

Current guidance from the Anticoagulation Forum suggests the use of reversal agents in DOAC-associated major bleeding when there is a reasonable expectation that clinically relevant DOAC plasma levels are present and the bleeding is life-threatening, into a critical organ, or is unresponsive to maximal supportive measures [47]. If reversal is indicated, the Anticoagulation Forum suggests that andexanet should be administered for the management of apixaban or rivaroxaban associated major bleeding. Off label use in patients with edoxaban or betrixaban associated major bleeding was also suggested [47]

Conclusion

With their convenience of use and improved safety profile, DOACs have largely replaced VKA as the first-line oral anticoagulant of choice for patients with atrial fibrillation or venous thromboembolism [1–5]. Although DOACs reduce the risk of serious bleeding compared with VKA, bleeding complications remain major contributors to patient morbidity and mortality and can be difficult to manage [5–7,17]. Andexanet alfa is a catalytically inactive recombinant-modified human FXa protein that binds to and sequesters FXa inhibitors, thereby restoring the normal hemostatic function of endogenous FXa [23]. Andexanet rapidly reverses anti-FXa activity, restores thrombin generation and decreases the concentration of unbound (active) FXa inhibitor drugs [24,28]. In patients anticoagulated with FXa inhibitors with major bleeding, andexanet treatment is associated with hemostasis in the majority of treated patients (82%) [13]. Although the rates of thrombosis (10%) and death (14%) seen after discontinuation and reversal of DOACs are likely influenced by underlying thrombotic tendency and pre-existing comorbidities, these findings emphasize that bleeding complications are not trivial [13]. In the absence of a control group, it is difficult to draw definitive conclusions about the benefits and harm of andexanet but reversal of anti-FXa activity appears to predict hemostatic efficacy in patients with ICH. Unresolved questions include the use of andexanet in reversing FXa inhibitors for urgent surgery, its efficacy and safety in FXa inhibitors other than apixaban or rivaroxaban, and its use in patients excluded from the studies. When a reversal agent is indicated, the Anticoagulation Forum suggests andexanet for the management of oral FXa inhibitor-associated bleeding, however cautions that its use in edoxaban or betrixaban-associated bleeding is off label [47].

Executive summary

Burden of bleeding

- Although safer than vitamin K antagonists, direct oral anticoagulant-associated bleeding is common and associated with substantial morbidity and mortality.
- Prior to the availability of reversal agents, management of direct oral anticoagulant-associated bleeding was supportive and involved interruption of anticoagulation, intravenous fluids, blood transfusions and selective use of prohemostatic agents including antifibrinolytic agents and prothrombin complex concentrates.

Andexanet alfa

- Andexanet alfa is a recombinant-modified human factor Xa (FXa) protein that reverses the anticoagulant effect of FXa inhibitors.
- The ANNEXA-4 study showed that in patients treated with apixaban or rivaroxaban who presented with major bleeding, an intravenous bolus and infusion of andexanet was associated with a 92% reduction in median anti-Xa activity levels, excellent or good hemostasis in 82% and a 10% rate of thromboembolic events at 30 days.

Key unresolved issues

- The contribution of andexanet to hemostasis and clinical outcomes is uncertain without a randomized clinical trial.
- Andexanet has not been evaluated for use in patients treated with FXa inhibitors who require urgent surgery.

Regulatory affairs & postmarketing

- Andexanet is approved for use in the USA and Europe for reversal of life threatening or uncontrolled bleeding in apixaban- or rivaroxaban-treated patients.
- There are limited postmarketing data on andexanet but challenges associated with its use may include limited drug access and the need to transfer patients to alternative centers to receive treatment, drug preparation time and requests for off-label indications.

Financial & competing interests disclosures

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Company review disclosure

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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