Ultra-Early Hemostatic Therapy for Acute Intracerebral Hemorrhage

An Updated Review

Michael Fortunato, BA, Galadu Subah, PHD,† Anish D. Thomas, MD,† Bridget Nolan, BS,† Monica Mureb, DO,† Anaz Uddin, MS,† Kiran Upadhyay, MD,‡ Jonathan V. Ogulnick, MD,§ Nitesh Damodara, MD,† Colleen Bond, PHARMD, BCPS,¶ Chirag D. Gandhi, MD,† Stephan A. Mayer, MD,† and Fawaz Al-Mufti, MD†*

Abstract: Intracerebral hemorrhage (ICH) is the second most common type of stroke, accounting for approximately 10–20% of all strokes, and is linked to severe neurological disability and death. Since the most accurate predictor of outcome in patients with ICH is hematoma volume, there is a great need for pharmacologic therapy that can reduce hematoma expansion and resultant mass effect and edema. This is especially critical within the ultra-early window of 3–4 hours after the presentation. Hemostatic therapies are exceptionally important for those patients taking antiplatelet or anticoagulant medications to reverse the effects of these medications and therefore prevent hematoma expansion. Furthermore, the recent publication of the 2023 Guideline for the Management of Patients with Aneurysmal Subarachnoid Hemorrhage by the American Heart Association/American Stroke Association, the first update to the guidelines since 2012, underscores the importance of optimizing anticoagulation reversal for this population. The purpose of this selective, nonsystematic review is to examine current literature regarding the use of hemostatic therapies in ICH, with particular attention paid to antiplatelet, anticoagulation, and antifibrinolytic therapies.

Key Words: reversal, intracerebral hemorrhage, antiplatelet, anticoagulation, fibrinolytic, hemostasis

(*Cardiology in Review* 2024;32: 194–202)

Intracerebral hemorrhage (ICH) is the second most common type of stroke, accounting for approximately 10–20% of all strokes, and is associated with severe neurological disability and death. In particular, the case fatality rate of ICH is very high, with approximately 40% of patients with an ICH dying within the first month and 54% dying within the first year. Additionally, only about 12–39% of survivors regain functional independence.[1]

An increasing array of agents for the reversal of anticoagulation have become available in recent years (Table 1). However, as antiplatelet and anticoagulant agents have gained popularity for a wide variety of pathologies, concern for ICH morbidity and mortality has also increased. Research has shown that hemostatic therapy, a pharmacological intervention that promotes hemostasis, given within the first 3–4 hours of presentation is crucial in the early management of ICH. Because the best predictor of outcomes after an ICH is the volume of the hematoma, this ultra-early pharmacological hemostatic therapy has the capability to reduce ICH volume and prevent hematoma expansion, which can substantially improve neurological outcomes. Hematoma growth has been shown to occur in about 38% of patients who obtain a CT within 3 hours of symptom onset and 16% of patients who are scanned between 3 and 6 hours. Progressive bleeding has been associated with contrast extravasation—also known as the "spot sign" on CT angiography—and poor outcomes are also common after early (less than 4 hours) surgical clot evacuation. Studies have shown that hematoma enlargement is expected in 10%, 17%, and 21% of patients after a 15-, 30-, and 45-minute delay in treatment after the 1-hour span, respectively. Ultra-early pharmacologic hemostatic therapy has proven to be beneficial in preventing hematoma expansion and preventing edema and mass effect.[2]

With the recent publication of the 2023 Guideline for the Management of Patients with Aneurysmal Subarachnoid Hemorrhage by the American Heart Association (AHA)/American Stroke Association, the first update to the guidelines since 2012, we present this timely review to discuss the most current available literature regarding the treatment of ICH associated with antiplatelet, anticoagulation, and antifibrinolytic therapy.[3] More specifically, we aim to explore the efficacy of ultra-early pharmacologic hemostatic therapy on patient prognosis, functional outcomes, and overall survival following spontaneous ICH.

REVERSAL OF ANTIPLATELET AGENTS

Evidence shows that there is high mortality associated with aspirin and clopidogrel in the elderly population who have had head trauma resulting in ICH. The presenting Glasgow Coma Scale (GCS) and initial grade of the CT scan are the most predictive of hemorrhage progression, neurological outcome, and death. Studies have shown that patients with a GCS of 14.2 ± 1.9 on initial evaluation have a better prognosis, whereas those with a GCS of 11.3 ± 4.9 have a worse prognosis. Given the severity of intracerebral bleeds, it is imperative to administer antiplatelet-reversing agents in a timely manner. There are several candidates that may prove to be beneficial in these emergency situations.[4]

Platelet Transfusion

The seminal Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH) trial was the first randomized trial that aimed to investigate the effects of platelet transfusion in acute ICH associated with the use of antiplatelet therapy. Researchers assessed the efficacy of platelet transfusion versus standard care after spontaneous cerebral hemorrhage and acute stroke. In this

From the *School of Medicine, New York Medical College, Valhalla, NY; †Department of Neurosurgery, Westchester Medical Center at New York Medical College, Valhalla, NY; ‡Department of Medicine, New York University Langone, Long Island, Mineola, NY; §Department of Neurology, Stony Brook University Hospital, Stony Brook, NY; and ¶Department of Pharmacy, Westchester Medical Center, Valhalla, NY.

Disclosure: The authors declare no conflict of interest.

Michael Fortunato and Galadu Subah are considered as co-first authors.

Correspondence: Fawaz Al-Mufti, MD, Department of Neurosurgery, Westchester Medical Center at New York Medical College, 100 Woods Road, Macy Pavilion 1331, Valhalla, NY 10595. E-mail: fawaz.al-mufti@wmchealth.org.

ISSN: 1061-5377/24/323-194202
DOI: 10.1097/CRD.0000000000000675

TABLE 1. Reversal of Anticoagulation Agents

Drug	Reversal Agent	Dosing			Half-Life	Comments
Antiplatelet (plavix/ brilinta)	Desmopressin	0.4 mcg/kg, dilute in 50 mL NS and infuse over 15–30 min			1–2 h	± platelet transfusion if patient requires urgent surgery
Warfarin (Coumadin)	Vitamin K 4F-PCC (KCentra)	10 mg IVPB INR = 1.5–3.9 INR 4–6 INR >6		25 IU/kg 35 IU/kg 50 IU/kg	22 min 6–72 h†	Administer concomitantly with 4F-PCC 4F-PCC is contraindicated in pts with HIT Maximum dose for 100 kg
Apixaban (Eliquis)	4F-PCC (KCentra)	25–50 units/kg			6–72 h†	
	Additional Restriction Criteria:* Factor Xa inactivated-zhzo (Andexxa) bolus + infusion	FXa inhibitor last dose	Timing of FXa inhibitor last dose before bleed		5–7 h	Dose-dependent on medication strength, and timing of last dose, see table below
			< 8 h or unknown	8–18 h		
		< or = 5 mg	Low dose	Low dose		
		> 5 mg or unknown	High dose			
Rivaroxaban (Xarelto)	4F-PCC (KCentra)	25–50 units/kg			6–72 h†	
	Additional Restriction Criteria:* Factor Xa inactivated-zhzo (Andexxa) bolus + infusion	FXa inhibitor last dose	Timing of FXa inhibitor last dose before bleed		5–7 h	Dose-dependent on medication strength, and timing of last dose, see table below
			<8 h or unknown	8–18 h		
			Low dose	Low dose		
		>10 mg or unknown	High dose			
Edoxaban (Savaysa)	4F-PCC (KCentra)	25–50 units/kg			6–72 h†	No FDA-approved antidote for the reversal
Dabigatran (Pradaxa)	Idarucizumab (Praxibind)	5 grams (Two vials of 2.5 grams) Administer each vial over 5–10 min			Biphasic: 45 min (initial) 4.4–8.1 h (terminal)	Consider dialysis for patients with renal failure
Unfractionated heparin (UFH)	Protamine sulfate	1 mg/100 units if UFH received in the previous 2.5 h			5 min	Max single dose of 50 mg: Protamine can cause paradoxical bleeding. Contraindicated if fish allergy
Low molecular weight heparin (LMWH)	Protamine sulfate	If LMWH within 8 h: 1 mg per 1 mg of enoxaparin If LMWH >8 h: 0.5 mg per 1 mg of enoxaparin			5 min	

*Andexanet alfa Restriction Criteria:

1. Factor Xa inactivated-zhzo (andexanet alfa, Andexxa) will be procured and restricted to using the non-formulary medication pathway.
2. Candidates for Factor Xa inactivated-zhzo (andexanet alfa, Andexxa) will meet the following criteria
   a. Reversal of oral factor Xa inhibitors limited to rivaroxaban and apixaban.
   b. Adult patients 18 years and older.
   c. No known history of atrial clot.
   d. No known deep vein thrombosis (DVT) or pulmonary embolism (PE) in the past 3 months.
   e. Type of bleed:
      i. Intracranial or intraspinal bleed, with all of the following.
         (1) ICH Score less than or equal to 3.
         (2) Glasgow coma scale (GCS) greater than or equal to 7.
         (3) Intracerebral hemorrhage volume less than 40 mL.
         (4) Life expectancy greater than 1 month.
      ii. Acute life-threatening bleed, as evidenced by:
         (1) Signs or symptoms of severe hemodynamic compromise - hemorrhagic shock.
         (2) Acute bleeding in a critical area or organ, such as pericardial, intracranial, or intraspinal.
3. Prescribe responsibilities.
   a. Patients identified as candidates based on the above criteria will have a paper Physician order sheet documenting approving attending physicians from Neurosurgery, Critical Care, Hematology, or Emergency Medicine and sent to the pharmacy for validation, preparation, and dispensation.

†The half-lives of the four coagulation factors contained within 4F-PCC differ widely: factor II has the longest (60–72 h), factor VII has the shortest (~6 h), and factor IX and factor X have half-lives between 6 and 24 h.

4F-PCC indicates 4-factor prothrombin complex concentrate; FDA, food and drug administration; FXa, factor Xa; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; IVPB, intravenous piggyback.

randomized, open-label phase III trial, adult patients were enrolled within 6 hours of symptom onset of supratentorial ICH. All patients were taking antiplatelet medication for at least 7 days before symptom onset and had a GCS of at least 8. These patients were randomly assigned to receive either standard care or standard care with a platelet transfusion. The primary outcome was death or dependence rated on the modified Rankin scale (mRS) at 3 months. The secondary outcome was survival at 3 months, poor outcomes—defined as mRS of 4–6—and median hemorrhage growth in mL after 24 hours on imaging. This study found that the odds of death or dependence at 3 months were higher in the platelet transfusion group than in the standard care group. This can be attributed to the fact that platelets have proinflammatory effects and transfusions may increase vascular permeability.[5]

However, the PATCH trial does have some limitations. Patients and investigators giving the treatment were not blinded to the allocation of treatment. Furthermore, most patients had taken aspirin and not $P2Y_{12}$ inhibitors, such as clopidogrel or ticagrelor, which have also been implicated in causing ICH. Another major limitation is the exclusion of patients with known cerebrovascular malformations, such as arteriovenous malformations (AVMs), limiting clinicians' ability to extrapolate the outcomes of this trial for this important subgroup. A retrospective study analyzing the charts of 191 patients with cerebral AVMs found that AVM size is a significant predictor of the risk of developing a hemorrhage. Several different variables, including age, sex, size of the AVM, type of initial hemorrhage, and the condition of the patients, were examined. The average yearly risk for developing a first hemorrhage in these patients was 2–3% annually, and bleeding occurred most frequently when patients were between the ages of 11 and 35 years. Furthermore, the risk of rebleeding was demonstrated to increase with age. Among the 93 patients who had a ruptured aneurysm, 6% developed a recurrent bleed within 1 year and had up to a 2% risk of rupture per year for the next 20 years.[6] Despite the risk of first-time and subsequent AVM rupture, patients with AVMs were excluded from the PATCH trial.

Desmopressin

Desmopressin (DDAVP) is an analog of the endogenous hormone vasopressin that increases serum concentrations of factor VIII, von Willebrand's factor, and tissue plasminogen activator (tPA) that has been shown to improve platelet activity in the setting of ICH.[7] A systematic review of 22 studies concerning the effects of desmopressin administration on hemostasis in patients on antiplatelet therapy who experienced either noncardiac surgery, ICH, or subarachnoid hemorrhage found that desmopressin increases platelet aggregation and improves bleeding time.[8] Patients receiving desmopressin after symptom onset also experienced minor adverse effects and small changes in hematoma volume. Gunther et al.[9] recently performed a retrospective cohort study of 52 patients who presented with alcohol use-associated intracranial bleeding and were treated with either DDAVP (n = 27) or not (n = 25). They found that the incidence of hyponatremia in the DDAVP-treated group was higher, but this number was not statistically significant, and thrombotic complications were likewise similar.[9] The authors concluded that while the use of DDAVP in this population was safe, it did not significantly reduce hematoma expansion.

Several other retrospective studies have similarly concluded that DDAVP use was safe but provided no benefit and was not associated with a decrease in hematoma expansion in patients with ICH.[10–12] One retrospective study reported a decrease in hematoma expansion, but this was limited to the first 24 hours of treatment as the researchers only looked at the first 24 hours as their primary endpoint.[13] A single-center, nonrandomized study of patients with spontaneous ICH on antiplatelet therapy who received combined desmopressin and platelet transfusion had results in line with the PATCH[9] trial: there was no benefit found with early platelet transfusion, and desmopressin failed to decrease hematoma expansion or improve functional outcome.[14] Finally, a meta-analysis of the use of desmopressin to reduce hematoma expansion in antiplatelet-associated ICH found that the literature did not support the routine use of desmopressin for this purpose.[15]

Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa) (eptacog alfa, NovoSeven, among others) promotes hemostasis through activation of the extrinsic coagulation cascade pathway. Preliminary studies seemed to indicate that rFVIIa was safe and effective for the reversal of aspirin and clopidogrel in the treatment of ICH.[16,17] However, the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, a multicenter, double-blind study, showed that while treatment with rFVIIa reduced hematoma growth, it failed to demonstrate improved outcomes in ICH patients.[18] According to new guidelines, rVIIa should not be administered to patients for the reversal of Vitamin K antagonists (VKAs). Rather, 4-factor prothrombin complex concentrate (4F-PCC) is favored in this case over rFVIIa because it has a lower risk of thrombotic events.[19]

REVERSAL OF DIRECT ORAL ANTICOAGULATION AGENTS

Direct oral anticoagulation agents (DOACs) are less likely than warfarin to cause ICH and are effective at secondary prevention of venous thromboembolism and ischemic stroke due to nonvalvular atrial fibrillation. Additionally, they carry more favorable food and drug interaction profiles and eliminate the need for routine laboratory follow-up. However, DOACs still pose a 0.23–0.50% annual risk of ICH. Given the fact that DOAC-induced ICH portends significant morbidity and mortality, the clinician caring for these patients should be aware of the available reversal agents to prevent and mitigate poor outcomes.[20]

Idarucizumab

Idarucizumab (Praxbind) is a monoclonal antibody fragment with a high affinity for dabigatran (Pradaxa). Idarucizumab can be considered a new therapeutic option for patients taking dabigatran and developing either ischemic stroke or ICH. A prospective study found that in emergency situations, 5 g of intravenous idarucizumab can be administered safely to rapidly reverse anticoagulation by dabigatran.[21] The 2017 publication of the results of the landmark Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial, a multicenter, open-label, single-arm prospective cohort study of dabigatran reversal, showed that idarucizumab could safely, effectively, and rapidly manage hemorrhages of all types, including ICH.[22] However, the authors did not detail the specific outcomes of ICH patients. Lu et al.[23] performed a systematic review of the use of idarucizumab for ICH and analyzed 9 articles involving 23 cases of dabigatran-associated ICH managed with idarucizumab. They concluded that idarucizumab is safe and effective for reversing dabigatran-induced anticoagulation in patients presenting specifically with ICH. However, they noted that the dearth of other critical data regarding the treatment of ICH patients, including recovery and long-term outcomes, limits the significance of these conclusions.[23]

Kermer et al.[24] described a case series of 120 patients on dabigatran in 61 stroke centers throughout Germany who received reversal with idarucizumab after presenting with signs of either an ischemic stroke or ICH. Of these patients, 80 had evidence of ischemic stroke and 40 had signs of intracranial bleeding, with 27 of these 40 patients having ICH.[24] In patients who received recombinant tPA (rtPA, alteplase) after idarucizumab, 78% demonstrated a

median improvement of 7 points on the National Institutes of Health Stroke Scale (NIHSS), and none had any bleeding complications. In patients with ICH, 3 out of 27 had hematoma growth, and a good outcome was reported with a median improvement of 4 points on the NIHSS and a mRS of 0–3 in 61% of patients. Six out of the 40 patients in the intracranial bleeding group died during hospitalization. The authors further concluded that idarucizumab prevented hematoma growth and improved clinical outcomes.

Andexanet Alfa

Andexanet alfa (Andexxa) is a recombinant modified variant of human factor Xa (FXa) that acts as a decoy receptor by binding free floating FXa inhibitors, sequestering them, and reducing their overall plasma concentration, thereby neutralizing the anticoagulation effect. Currently, andexanet alfa is approved for patients on rivaroxaban (Xarelto) or apixaban (Eliquis) when the anticoagulation reversal is needed to prevent life-threatening bleeds. However, this indication is on a limited basis, as it has not been shown to improve hemostasis.[25] It is also efficacious in treating patients with major acute gastrointestinal or cerebral bleeding associated with anti-FXa within 12 hours of administration.[26] Clinical trials have shown that andexanet alfa causes a median decline in anti-FXa activity of apixaban or rivaroxaban by at least 88% in a dose-dependent manner. As expected, adverse effects are due to thrombus formation.[27] The current dosing recommendations for andexanet alfa are described in Table 2.

Two Phase 3 studies were conducted to assess the efficacy and safety of oral FXa inhibitors in older, healthy adults treated with either apixaban (ANNEXA-A) or rivaroxaban (ANNEXA-R), with the primary endpoint being mean percentage change in anti-FXa activity from baseline.[25] Healthy volunteers (n = 145) were randomized into either the apixaban group receiving andexanet alfa (n = 48) versus placebo (n = 17) or the rivaroxaban group receiving andexanet alfa (n = 48) versus placebo (n = 17). Patients in both trials were noted to have an immediate decrease in anti-FXa activity from baseline to nadir within 2 minutes with an initial bolus, followed by suppressed anti-FXa activity for 2 hours following continuous infusion of andexanet alfa. ANNEXA-A patients treated with apixaban showed a 92% reduction in anti-FX activity ($P < 0.0001$), while ANNEXA-R patients treated with rivaroxaban had a 97% reduction in anti-FXa activity ($P < 0.0001$). The secondary endpoint of these trials was a change in thrombin generation from baseline, and in both cases, thrombin was restored within 2–5 minutes of bolus and maintained thrombin activity for 22 hours thereafter. The overall frequency of adverse events was nearly the same between the andexanet alfa-treated group and placebo, although 18% reported experiencing an infusion-related adverse reaction, mild to moderate in severity.

ANNEXA-4 was a multinational, prospective, single-arm, open-label study that looked at patients presenting with acute major bleeding within 18 hours of receiving an FXa inhibitor (n = 352).[28] All patients received a bolus of andexanet alfa, followed by a 2-hour infusion. The primary endpoints were percent change in anti-FXa activity and rate of excellent versus good hemostatic efficacy at 12 hours after the end of the infusion. The safety objectives in this study were the overall safety of andexanet alfa, including thrombotic events, antibody development to any of the components of andexanet alfa, and 30-day all-cause mortality. Bleeding was primarily intracranial (n = 226, 64%) but also gastrointestinal (n = 90, 26%). This study noted a 92% decrease in anti-FXa activity in both apixaban patients and rivaroxaban patients. Within 30 days, death occurred in 49 patients (14%) and thrombotic events occurred in 34 patients (10%), with no thrombotic events occurring after oral anticoagulation was restarted. The researchers concluded that although the reduction in anti-FXa activity was not predictive of overall hemostatic efficacy, it was modestly predictive in ICH patients.

Most recently, this past June 2023, AstraZeneca announced that they would be stopping their ANNEXA-I trial, a randomized, open-label, multicenter Phase 4 postmarketing trial for assessing the safety and efficacy of using andexanet alfa in patients over 18 years who present with ICH within 6 hours of symptom onset to baseline scan and within 15 hours of taking an oral FXa inhibitor, including apixaban or rivaroxaban. Patients were randomized to receive either andexanet alfa or usual care.[29,30] The reason for stopping the trial early was due to having met prespecified criteria for achieving superior hemostatic efficacy compared with usual care. The primary endpoint was the rate of effective hemostasis, defined as a change in baseline NIHSS score of +6 or less at 12 hours and a ≤35% increase in hematoma volume compared with the baseline scan. The researchers originally planned to enroll between 900 and 1200 patients in the study; however, the recommendation to stop early was made by the independent Data and Safety Monitoring Board after the planned interim assessment of 450 randomized patients with 1-month follow-up, which demonstrated superior reversal benefits of andexanet alfa earlier than researchers that initially predicted.

Smith et al.[31] demonstrated that of 8 patients who received andexanet alfa for ICH at their institution, 6 experienced "good" or "excellent" hemostasis as defined by the ANNEXA-4 trial. However, they found that 4 of 8 patients experienced thrombotic events within a median of 3 days of andexanet alfa administration.[31] Cullbreth et al.[32] reported a series of 15 patients who received andexanet alfa for ICH that demonstrated more equivocal results: 40% experienced inpatient mortality, but no patients experienced thrombotic events. It should be noted, however, that both of these studies were limited by small sample sizes and uncontrolled confounders, such as prior administration of PCC or fresh frozen plasma (FFP), which are discussed later in this article. Additionally, there are no randomized trials to date directly comparing the effectiveness of andexanet alfa versus 4F-PCC.

Fresh Frozen Plasma and Prothrombin Complex Concentrate

PCC and FFP have long been considered good options for preventing hematoma expansion in patients undergoing anticoagulation therapy. Patients treated with PCC have been shown to have a decreased mean prothrombin time and lower eight-graded reaction level scale progression compared with those treated with FFP. PCC has also been shown

TABLE 2. Dosing Recommendations for Factor Xa inactivated-zhzo (andexanet alfa, Andexxa)

Dose	Initial Intravenous Bolus	Intermittent Infusion after Bolus
Low dose	400 mg at a rate of 30 mg/min (rate 180 mL/h)	480 mg infusion at 4 mg/min for 120 min (rate: 24 mL/h)
High dose	800 mg at a rate of 30 mg/min (rate 180 mL/h)	960 mg infusion at 8 mg/min for 120 min (rate: 48 mL/hour)

to have protective effects when it comes to the incidence and extent of hematoma growth since it can rapidly reverse international normalized ratio, which is a predisposing factor for hematoma expansion.[33,34] Further studies in evaluating warfarin reversal have concluded that patients are more likely to achieve warfarin reversal when administered 4F-PCC (Kcentra) in comparison to 3F-PCC treatment.[35]

Though food and drug administration (FDA) approved for the urgent reversal of VKA-induced coagulopathy, 4F-PCC had been used for the reversal of oral FXa inhibitor-induced hemorrhage before the approval of andexanet alfa for that indication in May 2018. However, it is unclear how widespread this off-label usage is, as well as how efficacious it is compared to andexanet alfa. Barra et al.[36] found that 88.9% of their patients who were treated with andexanet alfa for ICH achieved good or excellent hemostasis, and 55.6% achieved a good functional outcome on discharge. This compares to only 60% and 9.1% in the PCC group, respectively.[36] However, this study was complicated by the fact that PCC patients had a larger hematoma volume on admission on average and a higher preadmission GCS. Cohen et al.[37] in their series, showed that in patients with ICH, mortality was significantly lower in the group who received andexanet alfa compared with PCC. Finally, Vestal et al.[38] demonstrated in their retrospective, single-center case series that hemostatic efficacy occurred in 64.7% of patients treated with andexanet alfa versus 54.8% of those treated with 4F-PCC, while those receiving 4F-PCC had higher rates of thromboembolic events than those treated with andexanet alfa (31.4% versus 14.3%, respectively).

Several other smaller cohort studies demonstrated the similarly dubious efficacy of 4F-PCC, with some concluding that its use offers uncertain clinical benefits and may instead pose a significant risk to patients.[39–41] One retrospective cohort study by Smith et al.[42] was more auspicious, with 80.6% of patients achieving adequate hemostasis and no patients experiencing thromboembolic events. They concluded that the prohibitive cost and availability of andexanet alfa warrants further exploration into the off-label use of 4F-PCC for anti-FXa reversal.[42] Zheng and Tormey[43], on the other hand, noted that while 4F-PCC was effective at reversing DOAC-induced coagulopathy, 16.7% experienced thromboembolic events within days to weeks following 4F-PCC administration.

Protamine Sulfate

Protamine sulfate is a specific reversal agent with FDA approval for neutralizing unfractionated heparin (UFH) Thus, through this mechanism, it acts as an antifactor Xa reversal agent. It is commonly administered for cardiothoracic surgery, invasive vascular procedures, dialysis, and acute ischemic stroke. It is also given for overdose of low molecular weight heparin (LMWH), although it is not FDA-approved for this purpose and the extent of reversal in this case is unclear. One meta-analysis validated the use of protamine sulfate for reducing the risk of hemorrhage after carotid recanalization.[44] However, there is little data validating its efficacy in treating ICH. A retrospective study analyzing 18 patients, 14 of whom were actively bleeding, determined that protamine is capable of partially reversing anti-Xa medications.[45] Ray and Keyrouz[46] recommend that, for symptomatic ICH due to UFH with supratherapeutic activated partial thromboplastin time, the UFH infusion should be stopped and intravenous (IV) protamine sulfate should be started at a ratio of 1 mg protamine per 100 units of UFH infused over the prior 3 hours. Vitals should be closely monitored during this time, and the infusion should be given slowly due to a small risk of hypotension with a rapid infusion, and activated partial thromboplastin time should be followed because the risk of hemorrhagic conversion extends to 48 hours after administration.

REVERSAL OF FIBRINOLYTIC THERAPY

Fibrinolysis with rtPA (alteplase) is currently the only pharmacotherapy approved by the FDA for treating acute ischemic stroke. Numerous clinical trials have shown that the benefits of thrombolysis outweigh the risks, as demonstrated by the recently expanded time window for IV rtPA from a time period of 3 hours to 4.5 hours from symptom onset. However, up to 7% of patients treated with IV rtPA develop the feared complication of ICH, which is associated with worse outcomes. Despite the fact that there are no established guidelines for treating fibrinolysis-induced ICH, the currently available treatment options are discussed here.[47]

Prothrombin Complex Concentrates, Platelets, and Cryoprecipitate

Cryoprecipitate is derived from FFP and contains fibrinogen, factor VIII, factor XIII, and von Willebrand factor. Although there is currently no evidence supporting the use of cryoprecipitate in alteplase-induced ICH, the AHA recommends its use in patients with hemorrhagic conversion from fibrinolytic therapy for ischemic stroke who are found to be hypofibrinogenemic. PCC, at the time of this article's writing, has been found to only be beneficial in patients on warfarin and is considered by the AHA to be the preferred adjuvant treatment for hemorrhagic conversion after receiving alteplase for acute ischemic stroke. However, its benefit in other patient populations is currently unclear. Finally, the administration of platelets to reverse fibrinolytic therapy only has a clear benefit in patients with thrombocytopenia, but otherwise is of unclear benefit. Given the high incidence, morbidity, and mortality of ICH following fibrinolysis for ischemic stroke, further studies to evaluate the efficacy of blood product replacement would be highly beneficial.[48]

Aminocaproic Acid and Tranexamic Acid

Aminocaproic acid and tranexamic acid (TXA) are synthetic derivatives of the amino acid lysine that have proven antifibrinolytic activity in humans. These compounds bind reversibly to plasminogen, blocking its activation by fibrin and preventing its conversion to plasmin. TXA has a longer half-life than aminocaproic acid and is much more potent. While these compounds inhibit fibrinolysis and act as effective clot stabilizers, their application is limited because they cannot activate coagulation, clot formation, or thrombin generation.[2] Several clinical trials have not validated the use of TXA for the treatment of ICH. The Tranexamic acid in patients with intracerebral hemorrhage trial, a multicenter, randomized, placebo-controlled phase 2 trial of 13 stroke centers throughout Australia, Finland, and Taiwan, enrolled 100 patients between 2013 and 2019 who were treated with either TXA (n = 50) or placebo (n = 50). The authors found no difference in the incidence of ICH expansion between groups, with 22 patients (44%) in the TXA treatment group and 26 patients (52%) in the placebo group experiencing ICH growth. They concluded that although treatment with TXA in ICH was safe, it did not reduce hematoma expansion.[49] The TXA for Hyperacute Primary IntraCerebral Hemorrhage (TICH-2) trial, an international, randomized, placebo-controlled, phase 3 trial, arrived at a similar conclusion.[50] Here, the authors enrolled 2325 patients between 2013 and 2017 who were treated with either TXA (n = 1161) or placebo (n = 1164). They found that, while TXA reduced early deaths (within 7 days of treatment) and serious adverse events, functional status did not significantly differ between the two groups at 90 days after treatment.

Most recently, the ultra-early TXA after subarachnoid hemorrhage (ULTRA) trial, conducted by Post et al.,[51] was a multicenter, randomized, controlled, open-label trial of 955 patients with CT-proven subarachnoid hemorrhage who were either treated with TXA (n = 480) or usual care (n = 475). They found that

treatment with TXA did not improve functional outcome at 6 months, as assessed by the mRS, and there was no significant difference in rebleeding before aneurysm treatment between the groups.[51] However, a notable limitation of this trial is that the median time from diagnosis to aneurysm treatment was 14 hours. This means that there might still be a role for TXA treatment in patients whose aneurysm securements are delayed by more than 14 hours, with some institutions delaying treatment for as long as 24 hours. Indeed, the 2023 Guidelines now recommend treatment within 24 hours, which leaves a number of patients who would fall beyond the range of the ULTRA trial.

Aprotinin and to Other Lysine Analogues

Aprotinin is a serine protease inhibitor that acts indirectly against kallikrein and inhibits factor XII formation. This compound was widely used during surgical procedures as it has the capability of slowing fibrinolysis. Although studies have shown that aprotinin may be a viable option when treating ICH, this drug was withdrawn from the global market because patients given aprotinin preoperatively are prone to develop fatal thrombotic and thromboembolic events.[2,52]

Aprotinin has been shown to act as an effective antithrombotic in decreasing massive postoperative bleeding. A prospective study investigating whether aprotinin is a better antithrombolytic than TXA and aminocaproic acid showed that while the risk of massive bleeding is lower with aprotinin, the mortality rate is much greater in comparison to other lysine analogs, and this study was terminated due to substantially poor outcomes in patients taking aprotinin.[53]

Factor VIIa

Factor VIIa plays an important role in initiating hemostasis when in its active form. Recombinant activated factor VII (rFVIIa) is frequently used to treat spontaneous bleeds during surgery in patients with hemophilia A or B, and in patients who have inhibitors of factors VIII and IX. The mechanism of rFVIIa allows the partial restoration of platelet surface thrombin generation, as it is capable of binding to the surface of activated platelets, generating FXa. Factor VIIa administration was initially shown to be advantageous in patients suffering from ICH.[2] However, more recent literature recommends against administering rVIIa in ICH in certain cases.[19]

Factor Xa

Dabigatran (Pradaxa) is a FXa inhibitor, a first-line anticoagulant prescribed to patients with atrial fibrillation. These new oral anticoagulants, dabigatran and rivaroxaban, have been proven to be more effective than warfarin, and many patients and clinicians prefer them because they eliminate the need for laboratory testing and have fewer drug-drug and food-drug interactions.[54] Dabigatran is equally effective in preventing venous thromboembolism and has a lower risk of bleeding compared with warfarin.[55] Idarucizumab has been shown to rapidly reverse bleeding associated with dabigatran within a few minutes.[21]

When treating ICH in patients taking direct thrombin inhibitors, the first step is to discontinue anticoagulation therapy. Furthermore, it is important to assess the ingested dosage before hemorrhage, renal function, and possible drug interactions. To stop bleeding, 50 g of activated charcoal was administered to patients who presented within 2 hours of symptom onset. Idarucizumab (2 doses of 5 g intravenously) should be given to patients without renal failure within 3–5 half-lives of the last direct thrombin inhibitors administration. In the event that idarucizumab is not available, patients can be given either 4F-PCC or undergo hemodialysis.[19]

Another common medication prescribed for the management of atrial fibrillation is rivaroxaban (Xarelto). A double-blind study identified 14,264 patients with nonvalvular atrial fibrillation who were at an increased risk of stroke. These patients received either warfarin or rivaroxaban. Results showed rivaroxaban and warfarin were comparable in preventing embolism and stroke. Additionally, there was no significant difference in major bleeding between warfarin and rivaroxaban. However, it is notable that intracranial bleeding and fatal bleeding occur less in patients who received rivaroxaban.[56]

NEXT GENERATION THERAPIES

Ciraparantag

PER977, or ciraparantag, has been shown in preliminary studies to bind and inhibit direct thrombin inhibitors, FXa inhibitors, and heparins. In a randomized, placebo-controlled trial in which 80 healthy volunteers were given a single therapeutic dose of edoxaban (60 mg), a single IV dose of ciraparantag (100–300 mg) normalized the patients' clotting time within 10 minutes without adverse effects. In contrast, it took 12–15 hours for clotting time to normalize in the placebo group. While it is still only under investigation as an antidote to anticoagulants, ciraparantag has shown great promise for this purpose in preliminary studies.[57,58] Ansell et al.[59] further demonstrated in a study of 2 randomized, placebo-controlled dose-ranging trials of patients aged 50–75 receiving either apixaban 10 mg orally twice daily for 3.5 days (study 1) or rivaroxaban 20 mg orally once daily for 3 days (study 2) that sustained reversal was achieved with 60 mg of ciraparantag for apixaban and 120 mg of ciraparantag for rivaroxaban. Additionally, all doses of ciraparantag were well-tolerated, and the only adverse effects consisted of mild, transient hot flashes or flushing.[59]

FXa^{I16L}

FXa^{I16L} is a zymogen-like variant of FXa more resistant to degradation than endogenous FXa that has been shown to rapidly restore hemostasis in mouse models in the presence of factor X inhibitors. FXa^{I16L} circulates as an inactive enzyme with an active site that is resistant to factor X inhibitors, as the leucine on position 16 is replaced with isoleucine. It becomes activated by factor V or factor Va on damaged cell surfaces. In addition to reversing rivaroxaban-induced anticoagulation, FXa^{I16L} was shown in mouse models to reverse the antithrombin activity of dabigatran. This mutant protein is a potentially impactful candidate to restore hemostasis and rapidly reverse the effects of DOACs. At the time of this article's writing, one Phase 1 dose-escalating study has been published regarding FXa^{I16L}, and it concluded that its use was safe, well-tolerated, and exhibited a pharmacologic effect when given in doses up to 5 μg/kg. However, the sample size was very small (49 volunteers) and only enrolled males. Nevertheless, these positive results support further studies into the use of FXa^{I16L} as a potential reversal agent.[60]

Bentracimab (PB2452)

Another agent to consider is bentracimab (PB2452), a recombinant human monoclonal antibody that binds ticagrelor and its circulating active metabolites, thereby rapidly reversing its antiplatelet effect. This agent is the newest reversal agent that has shown promise in the recent Bentracimab (PB2452) in Ticagrelor-treated Patients with Uncontrolled Major or Life-Threatening Bleeding or Requiring Urgent Surgery or Invasive Procedure (REVERSE-IT) trial, a multicenter, single-arm, open-label, phase 3 study. Unlike other antiplatelets, ticagrelor binds reversibly to $P2Y_{12}$, making it a suitable target for immediate reversal agents, like bentracimab. In 2019, the FDA granted a breakthrough therapy designation for bentracimab because it appeared safe and effective for the reversal of ticagrelor. The trial enrolled 150 patients across 23 sites in the United States and Europe who had taken ticagrelor in the previous 3 days, requiring urgent surgery or invasive procedures, or had a major bleeding event.[61] These patients were evaluated based on two primary efficacy outcomes: ticagrelor reversal based on $P2Y_{12}$ platelet

function assay to determine minimum percent inhibition of platelet reactivity units (PRUs) within 4 hours of treatment drug, and achievement of effective homeostasis using prespecified hemostatic efficacy criteria. The secondary outcome was the minimum percent inhibition of the platelet reactivity index. Interim study results showed a significant 135% reduction in inhibitor with bentracimab. PRU at multiple time points after the treatment drug was given increased from an average of 65 PRUs before treatment to 230 PRUs within 10 minutes and remained above 230 PRUs for 24 hours before it began to decline by 72 hours. The average platelet reactivity index increased from 30% before treatment to 90% after treatment within 10 minutes and remained above 90% for 12 hours before declining at the 24–72 hour mark. According to these results, bentracimab significantly restored platelet function for hemostasis based on two platelet assays at several points across time in patients receiving ticagrelor.[48] However, this study did not include a control group for ethical reasons. In the absence of a control group and the small sample size in the bleeding group, the extent of the true clinical benefit provided by bentracimab, especially in actively bleeding patients, cannot be assessed. In terms of the overall safety profile, there were no allergic or infusion-related reactions. P-selectin and mean platelet volumes all indicated low amounts of thrombotic events, with no evidence of rebound platelet hyperactivity.

DISCUSSION

ICH has very poor outcomes, especially if hematoma enlargement occurs. Patients receiving antiplatelet, anticoagulation, or antifibrinolytic treatment are at increased risk for developing ICH and subsequently having poor neurological outcomes. Although there are some reversal agents and therapies available, it is important to note that the literature available on these therapies is rather limited. The current therapeutic reversal options available are summarized in Figure 1 to help facilitate clinical decision-making.

The PATCH trial is noteworthy in that it was the first study aimed to investigate the effects of platelet transfusion in acute ICH after the use of antiplatelet therapy. However, this study did not include patients who had AVMs, despite their high likelihood of rupture and development of ICH.[5,6] Given the high prevalence of AVM rupture and risk for secondary bleeding, additional research in this area would be highly beneficial.

Aspirin and clopidogrel have been implicated in bleeding and increased mortality in the elderly. Studies have shown that desmopressin and recombinant factor VIIa are good candidates for decreasing prolonged bleeding time in patients undergoing antiplatelet therapy.[2,19] Furthermore, there are many pharmacological anticoagulation reversal agents, including idarucizumab, andexanet alfa, and protamine sulfate. These anticoagulant antidotes have been shown to restore thrombin generation by reducing antifactor Xa. FFP and PCC have also been demonstrated to be effective in reversing international normalized ratio. However, PCC has protective effects in terms of hematoma growth in comparison to FFP.[33,34]

In addition to existing therapies, there are a variety of emerging therapies targeted to reverse thrombin inhibitors, FXa inhibitors, antiplatelet agents, heparin, and DOACs. The importance of these reversal agents is paramount as the growing elderly population is increasingly prescribed anticoagulant and antiplatelet medications for a variety of underlying health conditions. More robust, longitudinal studies that include diverse patient populations will be required to prove the efficacy of both existing and emerging therapies in preventing hematoma expansion and improving outcomes in patients with ICH.

CONCLUSIONS

ICH is a sufficiently prevalent, morbid, and lethal condition such that medical therapy for its reversal is highly desirable. However,

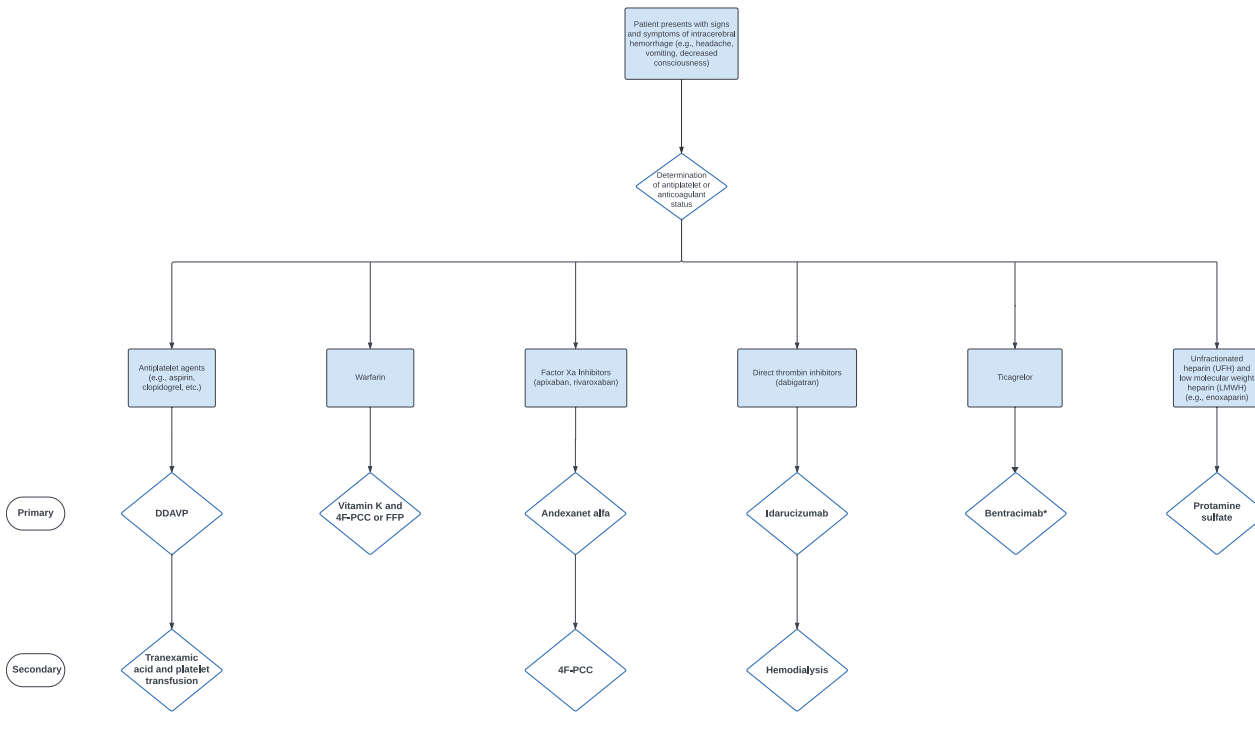

FIGURE 1. Algorithm for Selection of Anticoagulation Reversal Agents in the Clinical Setting.

appropriate therapy for ICH has remained elusive. Despite the fact that there are considerable options discussed in this review, more high-quality evidence is needed to validate their efficacy, although there are some promising preliminary results.

REFERENCES

1. van Asch CJ, Luitse MJ, Rinkel GJ, et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. 2010;9:167–176.
2. Mayer SA. Intracerebral hemorrhage: natural history and rationale of ultra-early hemostatic therapy. *Intensive Care Med*. 2002;28:S235–S240.
3. Hoh BL, Ko NU, Amin-Hanjani S, et al. 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association [published correction appears in Stroke. 2023 Dec;54(12):e516]. *Stroke*. 2023;54:e314–e370.
4. Ivascu FA, Howells GA, Junn FS, et al. Predictors of mortality in trauma patients with intracranial hemorrhage on preinjury aspirin or clopidogrel. *J Trauma*. 2008;65:785–788.
5. Baharoglu M, Cordonnier C, Salman R, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet*. 2016;387:2605–2613.
6. Graf CJ, Perret GE, Torner JC. Bleeding from cerebral arteriovenous malformations as part of their natural history. *J Neurosurg*. 1983;58:331–337.
7. Naidech AM, Maas MB, Levasseur-Franklin KE, et al. Desmopressin improves platelet activity in acute intracerebral hemorrhage. *Stroke*. 2014;45:2451–2453.
8. Andersen LK, Hvas AM, Hvas CL. Effect of desmopressin on platelet dysfunction during antiplatelet therapy: a systematic review. *Neurocrit Care*. 2021;34:1026–1046.
9. Gunther M, Witenko CJ, Prust M, et al. The safety and efficacy of desmopressin in patients with intracranial hemorrhage and a history of alcohol use. *J Intensive Care Med*. 2022;37:825–832.
10. McManus J, Ferreira J, Jones GM, et al. Effect of desmopressin acetate on acute spontaneous intracranial hemorrhage in patients on antiplatelet therapy. *J Neurol Sci*. 2022;434:120142.
11. Summers A, Singh J, Lai M, et al. A multicenter retrospective study evaluating the impact of desmopressin on hematoma expansion in patients with antiplatelet-associated intracranial hemorrhage. *Thromb Res*. 2023;222:96–101.
12. Schmidt KJ, Sager B, Zachariah J, et al. Cohort analysis of desmopressin effect on hematoma expansion in patients with spontaneous intracerebral hemorrhage and documented pre-ictus antiplatelet use. *J Clin Neurosci*. 2019;66:33–37.
13. Feldman EA, Meola G, Zyck S, et al. Retrospective assessment of desmopressin effectiveness and safety in patients with antiplatelet-associated intracranial hemorrhage. *Crit Care Med*. 2019;47:1759–1765.
14. Mengel A, Stefanou MI, Hadaschik KA, et al. Early administration of desmopressin and platelet transfusion for reducing hematoma expansion in patients with acute antiplatelet therapy associated intracerebral hemorrhage. *Crit Care Med*. 2020;48:1009–1017.
15. Loggini A, El Ammar F, Darzi AJ, et al. Effect of desmopressin on hematoma expansion in antiplatelet-associated intracerebral hemorrhage: a systematic review and meta-analysis. *J Clin Neurosci*. 2021;86:116–121.
16. Mayer SA, Brun NC, Broderick J, et al; Europe/AustralAsia NovoSeven ICH Trial Investigators. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke*. 2005;36:74–79.
17. Mayer SA, Brun NC, Begtrup K, et al; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777–785.
18. Mayer SA, Brun NC, Begtrup K, et al; FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358:2127–2137.
19. Frontera J, Lewin J, Rabinstein A, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Crit Care Med*. 2016;44:2251–2257.
20. Steiner T, Köhrmann M, Schellinger P, et al. Non-vitamin K oral anticoagulants associated bleeding and its antidotes. *J Stroke*. 2018;20:292–301.
21. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511–520.
22. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377:431–441.
23. Lu VM, Phan K, Rao PJ, et al. Dabigatran reversal by idarucizumab in the setting of intracranial hemorrhage: a systematic review of the literature. *Clin Neurol Neurosurg*. 2019;181:76–81.
24. Kermer P, Eschenfelder CC, Diener HC, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany-Updated series of 120 cases. *Int J Stroke*. 2020;15:609–618.
25. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the reversal of factor Xa inhibitor activity: Nejm. *N Engl J Med*. 2015;373:2413–2424. Available at: https://www.nejm.org/doi/full/10.1056/nejmoa1510991.
26. Connolly S, Milling T, Eikelboom J. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *J Vasc Surg*. 2017;65:279–280.
27. Reed M, Tadi P, Nicolas D. *Andexanet Alfa*. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 8, 2023.
28. Connolly SJ, Crowther M, Eikelboom JW, et al; ANNEXA-4 Investigators. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380:1326–1335.
29. ClinicalTrials.gov. *Trial of Andexanet Alfa in ICrH Patients Receiving an Oral FXa Inhibitor*. ClinicalTrials.gov website. Available at: https://clinicaltrials.gov/ct2/show/NCT03661528. Accessed October 29, 2023
30. AstraZeneca. *Andexxa Phase IV trial stopped early after achieving pre-specified criteria on haemostatic efficacy versus usual care*. Available at: https://www.astrazeneca.com/media-centre/press-releases/2023/andexxa-phase-iv-trial-stopped-early-after-achieving-pre-specified-criteria-on-haemostatic-efficacy-versus-usual-care.html. Accessed October 29, 2023.
31. Smith M, Beatty J, Keegan S, et al. A tertiary care center's experience with andexanet alfa for reversal of factor Xa inhibitor associated intracranial hemorrhage (P3.9-008). *Neurology*. 2019;92. Available at: https://www.neurology.org/doi/10.1212/WNL.92.15_supplement.P3.9-008.
32. Culbreth SE, Rimsans J, Sylvester K, et al. Andexanet alfa-the first 150 days. *Am J Hematol*. 2018;94:E21–E24.
33. Fredriksson K, Norrving B, Strömblad L. Emergency reversal of anticoagulation after intracerebral hemorrhage. *Stroke*. 1992;23:972–977.
34. Huttner H, Schellinger P, Hartmann M, et al. Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy. *Stroke*. 2006;37:1465–1470.
35. Al-Majzoub O, Rybak E, Reardon D, et al. Evaluation of warfarin reversal with 4-factor prothrombin complex concentrate compared to 3-factor prothrombin complex concentrate at a tertiary academic medical center. *J Emerg Med*. 2016;50:7–13.
36. Barra ME, Das AS, Hayes BD, et al. Evaluation of andexanet alfa and four-factor prothrombin complex concentrate (4F-PCC) for reversal of rivaroxaban- and apixaban-associated intracranial hemorrhages. *J Thromb Haemost*. 2020;18:1637–1647.
37. Cohen AT, Lewis M, Connor A, et al. 30 day mortality following Andexanet Alfa In Annexa-4 compared with Prothrombin Complex Concentrate (Pcc) therapy in the orange study for life threatening non-vitamin K Oral Anticoagulant (Noac) related bleeding. *J Am Coll Cardiol*. 2020;75:2242.
38. Vestal ML, Hodulik K, Mando-Vandrick J, et al. Andexanet alfa and four-factor prothrombin complex concentrate for reversal of apixaban and rivaroxaban in patients diagnosed with intracranial hemorrhage. *J Thromb Thrombolysis*. 2022;53:167–175.
39. Scharman CD, Shatzel JJ, Kim E, et al. Off-label use of 4-factor prothrombin complex concentrate is common despite little known benefit: a retrospective study. *Eur J Haematol*. 2018;101:349–353.
40. Cho BC, Jung YH, DeMario VM, et al. On-label compared to off-label four-factor prothrombin complex concentrate use: a retrospective, observational study. *Transfusion*. 2019;59:2678–2684.
41. Adkins BD, Shaim H, Abid A, et al. Four-factor prothrombin complex concentrate use for on-label versus off-label indications: a retrospective cohort study. *J Thromb Thrombolysis*. 2023;55:74–82.
42. Smith MN, Deloney L, Carter C, et al. Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4F-PCC) in patients with factor Xa inhibitor-related bleeding: a retrospective study. *J Thromb Thrombolysis*. 2019;48:250–255.
43. Zheng Y, Tormey CA. The use of 4F-PCC to correct direct oral anticoagulant-induced coagulopathy: an observational analysis. *Transfus Med*. 2020;30:304–307.
44. Pan Y, Zhao Z, Yang T, et al. A meta-analysis of using protamine for reducing the risk of hemorrhage during carotid recanalization: direct comparisons of post-operative complications. *Front Pharmacol*. 2022;13:796329.
45. van Veen JJ, Maclean RM, Hampton KK, et al. Protamine reversal of low molecular weight heparin. *Blood Coagul Fibrinolysis*. 2011;22:565–570.

46. Ray B, Keyrouz SG. Management of anticoagulant-related intracranial hemorrhage: an evidence-based review. *Crit Care*. 2014;18:223.
47. Goldstein JN, Marrero M, Masrur S, et al. Management of thrombolysis-associated symptomatic intracerebral hemorrhage. *Arch Neurol*. 2010;67:965–969.
48. Yaghi S, Willey JZ, Cucchiara B, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Quality of Care and Outcomes Research. Treatment and outcome of hemorrhagic transformation after intravenous alteplase in acute ischemic stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e343–e361.
49. Meretoja A, Yassi N, Wu TY, et al. Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST): a multicentre, randomised, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2020;19:980–987.
50. Sprigg N, Flaherty K, Appleton JP, et al; TICH-2 Investigators. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet*. 2018;391:2107–2115.
51. Post R, Germans MR, Tjerkstra MA, et al; ULTRA Investigators. Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA): a randomised controlled trial. *Lancet*. 2021;397:112–118.
52. Warnaar N, Mallett SV, Klinck JR, et al. Aprotinin and the risk of thrombotic complications after liver transplantation: a retrospective analysis of 1492 patients. *Liver Transpl*. 2009;15:747–753.
53. Fergusson DA, Hébert PC, Mazer CD, et al; BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med*. 2008;358:2319–2331.
54. Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol*. 2012;87:S141–S145.
55. Schulman S, Kakkar AK, Goldhaber SZ, et al; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129:764–772.
56. Pearson S, Troughton R, Richards AM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:2333–2335.
57. Ansell JE, Bakhru SH, Laulicht BE, et al. Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. *Thromb Haemost*. 2017;117:238–245.
58. Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med*. 2014;371:2141–2142.
59. Ansell J, Bakhru S, Laulicht BE, et al. Ciraparantag reverses the anticoagulant activity of apixaban and rivaroxaban in healthy elderly subjects. *Eur Heart J*. 2022;43:985–992.
60. Parsons-Rich D, Hua F, Li G, et al. Phase 1 dose-escalating study to evaluate the safety, pharmacokinetics, and pharmacodynamics of a recombinant factor Xa variant (FXa^{I16L}). *J Thromb Haemost*. 2017;15:931–937.
61. Bhatt DL, Pollack CV, Mazer CD, et al. Bentracimab for ticagrelor reversal in patients undergoing urgent surgery. *NEJM Evid*. 2022;1:EVIDoa2100047.