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Contemporary Reversal of Oral Anticoagulation in Intracerebral Hemorrhage

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Intracerebral hemorrhage (ICH) accounts for ≈15% of all strokes and is associated with a high mortality rate and poor functional outcomes.[1] The mortality rate of patients with ICH remains high at ≈34% in the United States, despite declining incidence in the past 2 decades.[2,3] Oral anticoagulation is a common cause of ICH and will increase as the prevalence of atrial fibrillation is estimated to increase from 5.6 to 15.9 million by 2050 in an aging US population.[4] Coagulopathy is an independent risk factor for mortality and poor functional outcome with hematoma expansion occurring within 1 hour in 25% of patients and within 4 hours in 88% of patients.[1–3] One study identified that failure to reverse international normalized ratio (INR) within 2 hours was an independent predictor of mortality and morbidity.[4]

These data illustrate the importance of rapid and effective coagulopathy reversal. This article will review the current anticoagulation options for vitamin K antagonists (VKAs) or novel oral anticoagulants (NOACs) and the safety and efficacy of class-specific reversal of coagulopathy in patients with ICH. Andexanet alfa—the second NOAC-specific reversal agent after idarucizumab—was approved by the Food and Drug Administration early this year. We seek to evaluate the efficacy, safety, and cost of these new agents in comparison with older nonspecific reversal options.

Comparison of Efficacy and Safety Between NOACs and VKAs

There are 2 classes of NOACs, direct thrombin inhibitors, namely dabigatran, and factor Xa inhibitors (FXa-Is), including rivaroxaban, apixaban, edoxaban, and betrixaban. The use of NOACs has increased over warfarin as they do not require frequent monitoring of INR and have shorter half-lives with fewer drug and food interactions.[5] The rate of bleeding events with NOACs is 3% to 4% per year, which is lower than warfarin. All of the NOAC versus warfarin trials showed noninferiority to warfarin with the primary end point of stroke or systemic embolism (Table I in the online-only Data Supplement).[6–10]

A recent retrospective study of enterprise-wide patient data obtained by searching *International Classification of Diseases, Ninth Revision* or *Tenth Revision* code showed that patients taking NOAC had a higher rate of ischemic stroke compared with warfarin (odds ratio, 1.29; $P<0.001$).[11] The authors postulate that patients taking short half-life NOACs may be subtherapeutic because of noncompliance in taking medication regularly. Of note, other retrospective studies using 1:1 propensity score matching to balance patient characteristics confirmed the results from clinical trials and recent meta-analysis.[12,13]

The risk of ICH has been well established, but the outcome after ICH while on NOACs is a topic of current research. In a retrospective study of 161 patients, Tsivgoulis et al[14] found that NOAC-related spontaneous ICH had lower NIHSS scores and ICH volumes. Two more recent studies compared outcome metrics and mortality rates. The first study, CROMIS-2 (The Clinical Relevance of Microbleeds in Stroke study), included 500 patients with ICH and found that the rate of hematoma expansion and mortality was not significantly different between the NOAC and VKA groups. They also found no difference in good functional outcome (modified Rankin Scale, 0–2) at discharge.[15] The second study, J-ASPECT (Nationwide Survey of Acute Stroke Care Capacity for Proper Designation of Comprehensive Stroke Center in Japan), reported similar functional outcomes but an added mortality benefit in patients on NOACs.[16]

NOACs seem to have a better safety profile than VKAs and are becoming the preferred agents for oral anticoagulation. Although the reversal agents and protocols for VKA-related coagulopathy are well established, there are limited data on the management of NOAC-related coagulopathy. Because hematoma expansion occurs rapidly and is associated with worse outcomes, it is of the utmost importance to fully understand how to manage NOAC-related ICH as their use will continue to increase.

Reversal of VKA-Related Coagulopathy

Pharmacology

Warfarin inhibits VKOR (vitamin K oxide reductase) and the production of the reduced vitamin K—a cofactor for the carboxylation of factors II, VII, IX, and X (Figure 1).[17] It is metabolized by cytochrome P450 enzymes, and genetic variations in these enzymes contribute to variable metabolism of warfarin among individuals.[18] There are many common drugs

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that either inhibit or induce cytochrome P450 and, therefore, can affect the rate of warfarin metabolism.[19] The complex pharmacokinetics and drug interactions illustrate the difficulty in maintaining therapeutic INR with warfarin.

Reversal

Vitamin K

Vitamin K can be given oral, intravenously, or subcutaneous, but for patients with serious life-threatening bleeding, it is recommended to administer 10 mg IV as it reverses coagulopathy more quickly than oral.[20] The infusion of vitamin K should be slow given the risk of anaphylaxis. Subcutaneous vitamin K has less efficacy than both intravenous and oral and is not recommended.[21]

Because most hematoma expansion occurs within the first few hours of symptom onset and INR reversal in >2 hours is associated with higher mortality and morbidity, vitamin K administration alone is insufficient in the acute setting because INR normalization can take up to a day.[1–4,22] Therefore, it should be used as combination therapy along with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) to maintain normal INR and improve outcomes.[23]

Fresh Frozen Plasma

FFP is derived from whole blood and provides nonspecific repletion of clotting factor, but the majority of patients do not achieve INR reversal by 24 hours, and the reversal may take at least 30 hours.[24–26] Therefore, FFP is not an effective treatment for early reduction of hematoma expansion. Additionally, FFP requires high transfusion volumes and may increase the risk of heart failure, pulmonary edema, and other adverse events.[27] Various doses ranging from 5 to 30 mL/kg have been used to normalize INR and would result in ≤2.1 L of FFP transfusion in a 70-kg patient.[28]

Prothrombin Complex Concentrates

PCC contains vitamin K-dependent factors at levels of 25× higher than FFP. Comparisons of the efficacy and safety of FFP versus PCC for reversal of VKA-associated major bleeding favor PCC because of rapid INR correction, fewer complications from fluid overload, and no difference in the rate of thrombotic complications.[23,29–34] Frontera et al compared PCC with FFP for reversal of coumadin-related coagulopathy in patients with ICH. The mean dose of PCC was 48 IU/kg, and FFP was 12.5 mL/kg. They found significantly lower rates of hematoma expansion in PCC group (6% versus 52%; P=0.005). Multivariate analysis showed a lower risk of death or severe disability at 3 months in PCC group as compared with FFP alone.[23]

The INCH trial (International Normalized Ratio [INR] Normalization in Coumadin Associated Intracerebral Hemorrhage) compared FFP and PCC for reversal of VKA-associated ICH.[32] The dose of PCC was 30 IU/kg, and the dose of FFP was 20 mL/kg. PCC had a higher rate of reducing INR to <1.3 within 3 hours than FFP (67% versus 9%; P=0.0003) and, on average, reduced INR to goal in 40 minutes compared with >24 hours for FFP. PCC also had less hematoma expansion at both 3 and 24 hours.[32] Compared with the patients who received PCC after initial failure to normalize INR with FFP, the PCC-only group still had less hematoma expansion, indicating the importance of rapid reversal.[32] Eight and 5 patients died in the FFP and PCC groups, respectively. Five of the 8 deaths in the FFP group were related to hematoma expansion within 48 hours. None of the 5 deaths in the PCC group were related to hematoma expansion.[32] These results reaffirm that PCC is superior than FFP in lowering INR rapidly and reducing hematoma expansion without significant increase in thrombotic complications.[4,23,29–31,35] Although PCC is more expensive (Table 1), it has been shown to cost less overall because failure to normalize INR quickly and complications from FFP may result in prolonged hospital stays.[36]

Activated PCC (aPCC) is different from PCC in that it has activated factor VII. In patients with ICH, aPCC (20 U/kg) normalizes INR more quickly than FFP and results in a shorter time to neurosurgical intervention without significant increase

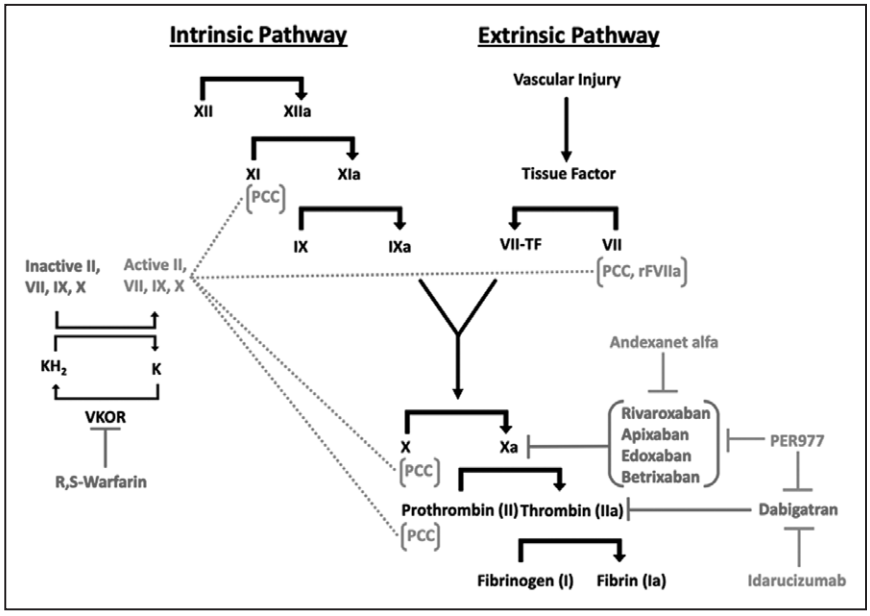

Figure 1. Oral anticoagulants and coagulopathy reversal. PCC indicates prothrombin complex concentrate; rFVIIa, recombinant FVIIa; VII-TF, VII-tissue factor; and VKOR, vitamin K oxide reductase.

Table 1. Costs of Approved Reversal Agents

	Dose	Total Cost*
4F-PCC	25–50 units per kg	$2748–$5495†
Idarucizumab	5 mg IV (2.5 mg q10×2)	$5495
Andexanet alfa	400 mg IV bolus; 480 mg IV infusion; if last dose of Xa-I >7 h	$24 750
	800 mg IV bolus; 960 mg IV infusion; if dose of Xa-I <7 h	$49 500

4F-PCC indicates 4 factor prothrombin complex concentrate.
*University of California, Irvine Medical Center (UCIMC), Department of Pharmacy.
†70-kg patient.

in risk of thrombotic complications.[37] Currently, there has been no study comparing aPCC with PCC.

Reversal of NOAC-Related Coagulopathy

Pharmacology

Dabigatran—a direct thrombin inhibitor, converted from the prodrug dabigatran etexilate in the blood—is a direct competitive inhibitor of thrombin, thus inhibiting production of fibrin.[38] It is 80% renally cleared with a half-life of 12 to 17 hours. FXa-Is are small molecules that bind and inhibit factor Xa, which converts prothrombin to thrombin (Figure 1).[39] FXa-Is also have short half-lives of 6 to 12 hours except for betrixaban, which is twice as long.[40] FXa-Is are all renally cleared with increased duration of anticoagulation effect in patients with renal disease.[41] So although they may not require routine INR monitoring like warfarin, it is important to monitor renal function. Furthermore, a recent retrospective study suggests that patients on NOACs may be chronically subtherapeutic and may need monitoring of thrombin time (TT), ecarin clotting time (ECT), or anti-factor Xa activity.[11,42,43]

Despite many advantages over warfarin, NOACs have drawbacks. They are transported by P-gp1 (P-glycoprotein 1), and all FXa-Is are metabolized by CYP3A4, except betrixaban, which has minimal CYP450 metabolism.[40,41] There are many inducers and inhibitors of the CYP450 and P-gp1 enzymes, and their effects in patients taking NOACs are an active area of research.[40] There are also ongoing investigations into the effect of enzyme polymorphisms on NOAC metabolism.[44]

A significant drawback of NOACs is that the typical coagulation tests (eg, prothrombin time [PT], activated partial thromboplastin time, and INR) do not accurately reflect the anticoagulant effect of NOACs. Studies recommend using TT and ECT for dabigatran because PT is not useful, and activated partial thromboplastin time is only useful in that values >90 seconds suggest a supratherapeutic dose.[45] Specific anti-Xa assays are the preferred tests to evaluate the anticoagulant effects of FXa-Is. However, these tests are not widely available and are infrequently used in clinical practice.[46] Until recently, the major drawback of NOACs was the lack of a reversal agent.

Reversal

Prothrombin Complex Concentrates

In vitro studies have shown that PCC can reverse NOACs anticoagulation.[47–50] In a trial of 12 healthy male subjects receiving either dabigatran or rivaroxaban, PCC (50 IU/kg) did not normalize activated partial thromboplastin time, ECT, or TT for the dabigatran group. However, PT and thrombin potential were normalized by the same dose of PCC in the rivaroxaban group.[42] An ex vivo study of 10 healthy men randomized to receive dabigatran or rivaroxaban showed that PCC and aPCC both increased thrombin generation.[43] A study of 35 healthy volunteers receiving supratherapeutic doses of rivaroxaban for 5 days followed by either 3F-PCC (3 factor prothrombin complex concentrate) or 4F-PCC (4 factor prothrombin complex concentrate; both at 50 IU/kg) reported a decrease of PT within 30 minutes for both groups.[51] A small 3-year crossover study with 15 patients taking apixaban and receiving 4F-PCC (50 IU/kg) showed that endogenous thrombin potential—a quantitative measure of the coagulation cascade's ability to generate thrombin—returned to baseline within 4 hours. Secondary end point analysis showed normalization of PT and INR.[52]

A trial published in 2017 (UPRATE [Unactivated Prothrombin Complex Concentrates for the Reversal of Anti-Factor Ten Inhibitors]) evaluated 4F-PCC for reversal of rivaroxaban and apixaban in 84 patients with major bleeding (70.2% ICH and 15.5% gastrointestinal bleed; Table 2).[53–55] The median dose of PCC administered was 26.7 units per kg, and the overall rate of hemostasis for patients on apixaban or rivaroxaban was 69.1% with a low overall thrombotic complication rate of 3.6%. The overall mortality rate for patients on apixaban or rivaroxaban in this study was 32% at 30-day follow-up.[53] Six deaths occurred in the 35 patients taking apixaban and 9 deaths in the 45 patients taking rivaroxaban. Although anti-factor Xa levels are the most reliable

Table 2. Comparisons of NOAC Reversal Agents[53–55]

	NOAC	Reversal Agent	N	Primary End Points	Reversal	Hemostasis Rate	Thrombotic Rate	Mortality Rate
UPRATE	Rivaroxaban, apixaban	4F-PCC	84	Hemostasis rate	…	69%	3.6% at 30 d	32% at 30 d
RE-VERSE AD	Dabigatran	Idarucizumab	301	Percentage reversal at 4 h	100%	…	6.3% at 90 d	19% at 90 d
ANNEXA-4 Interim Report	Rivaroxaban, apixaban	Andexanet alfa	67	Percentage change of anti-Xa activity and hemostasis at 12 h	89% after bolus	79% at 12 h	18% at 30 d	15% at 30 d

4F-PCC indicates 4 factor prothrombin complex concentrate; ANNEXA-4, Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors; NOAC, novel oral anticoagulants; RE-VERSE AD, Reversal Effects of Idarucizumab on Active Dabigatran; and UPRATE, Unactivated Prothrombin Complex Concentrates for the Reversal of Anti-Factor Ten Inhibitors.

pharmacological indicator of FXa-I reversal, they were not obtained in the study, and conclusions were drawn from qualitative assessments of hemostasis.[56]

In a multisite prospective study, Schulman et al[57] studied 4F-PCC in patients with major bleeding on FXa-I. The study enrolled 66 patients total and 36 patients with ICH, and efficacy of hemostasis in ICH was determined through assessment of serial computed tomographic scans or change in neurological status. The median dose of 4F-PCC administered was 26.4 IU/kg, and hemostatic efficacy was defined as good, moderate, and poor in 67%, 17%, and 17% of the ICH population, respectively. The study reported 5 serious thromboembolic events of which 4 occurred within 12 days after PCC administration but before resuming anticoagulation. This 8% thromboembolic event rate is higher than that reported by the UPRATE study.[53,57]

Similar to PCC, in vitro studies have also confirmed aPCC's ability to reverse NOAC coagulopathy.[47,48,50,58] An ex vivo study found that adding aPCC to the plasma of 8 patients on dabigatran reduced thrombin generation.[59] A case series of 5 patients showed no hematoma growth after aPCC (50 U/kg) and no thrombotic complications.[60] The largest study yet was a case series of 11 patients with ICH who received aPCC (20 U/kg) for FXa-I reversal, and it showed that 55% had a stable hematoma on repeat computed tomographic imaging. Mortality rate was 27%, and only 2 patients developed thrombotic complications.[61] Furthermore, one of the thrombotic complications was a deep vein thrombosis that was weeks after aPCC administration and likely unrelated. The other complication was an ischemic stroke that was later deemed to be secondary to high ICP and subsequent arterial occlusion rather than thrombosis.[61]

Idarucizumab

In 2015, idarucizumab—a monoclonal antibody that binds dabigatran—was approved for reversal of coagulopathy from direct thrombin inhibitors by the Food and Drug Administration. An interim analysis of the first 90 patients of the RE-VERSE AD trial (Reversal Effects of Idarucizumab on Active Dabigatran) led to approval of idarucizumab in many countries, and the full cohort analysis confirmed the efficacy.[54,62] A dose of 5 g idarucizumab divided into 2 doses of 2.5 g given intravenously ≤15 minutes apart was shown to reverse the effect of dabigatran for 88% to 98% of patients within just minutes (Table 2).[62] RE-VERSE AD enrolled patients with active bleeding or patients about to receive a procedure requiring anticoagulation reversal. Reversal was measured pharmacologically with TT and ECT. A reported 32.6% of the patients in this study had ICH. Idarucizumab was shown to reverse ECT and TT to normal levels within minutes with a median 100% reversal after 4 hours. The 6.3% thrombotic complication rate at 30 days was higher than the UPRATE trial.[53] However, the authors believed this rate was an overestimation as most thrombotic complications occurred on the order of days and weeks, all of which exceeded 45-minute half-life of idarucizumab.[54] All the thrombotic events that occurred within 72 hours were in patients not resumed on anticoagulation, which most likely were from an underlying prothrombotic state because pharmacological studies have shown that idarucizumab has no prothrombotic effects.[63] In the RE-VERSE AD trial, 22.9% of patients were restarted on anticoagulation in 72 hours, whereas the remaining 72.8% were restarted within 90 days.[54] Prompt resumption of anticoagulation is important to reduce thrombotic complications from the patient's underlying disease. These results are promising, but a randomized controlled trial is still needed.

The RE-VERSE AD trial had limitations. The dabigatran dose of 110 mg BID used for 62% of patients in the study was different from the US Food and Drug Administration–approved dose of 150 mg BID (75 mg BID in patients with renal failure).[54] Additionally, the last dose of dabigatran was 15 to 18 hours before reversal, which means that the majority of patients had trough concentrations of the drug at the time of idarucizumab administeration.[38] Another limitation of the study was the lack of objective measurement of clinical hemostasis in the ICH group.[54]

Dabigatran, idarucizumab, and the dabigatran-idarucizumab complex are all renally cleared.[64] Original pharmacokinetic studies were performed in young volunteers, so further studies are needed to understand the pharmacokinetics in the elderly and renally impaired patients because these factors are often comorbidities in patients taking NOACs.[38,65–67] Poor renal function results in less clearance of idarucizumab; however, this does not increase adverse effects.[63] Decreased clearance of reversal agent likely contributed to the immediate and 100% reversal.[63] This study validates the effectiveness of the 5-g IV dose for elderly and renally impaired patients from a pharmacological standpoint.[63]

Andexanet Alfa

Andexanet alfa is a promising specific reversal agent for FXa-Is. It is recombinant factor Xa that is enzymatically inactive but still binds FXa-I thus acting as a decoy target (Figure 1).[68] An interim analysis of the ANNEXA-4 trial (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors) analyzing 67 patients on rivaroxaban and apixaban with major bleeding was recently published (Table 2).[55] In this multicenter, prospective, open-label, single-group study, 42% of patients had ICH, and hemostatic efficacy was evaluated with serial computed tomographic scans. An andexanet alfa bolus of 400 mg during 15 to 30 minutes followed by an infusion of 480 mg for 2 hours achieved excellent or good hemostatic efficacy in 79% of all patients 12 hours after infusion. In patients with ICH, hemostatic efficacy was deemed excellent or good in 80% of cases. Hemostatic efficacy was deemed excellent if hematoma growth was <20% at 12 hours and good if <35% at 12 hours. The abovementioned dose was administered to the patients whose last dose of FXa-I had been >7 hours before the bleed. In the patients whose last dose of FXa-I had been within 7 hours of the bleed, the dose was doubled. Successful reversal was also measured by anti-factor Xa activity, which decreased to 89% and 93% of baseline for rivaroxaban and apixaban, respectively. The levels slowly increased after infusion with a total decrease of anti-factor Xa activity levels at 39% and 30% of baseline for rivaroxaban and apixaban, respectively. Thrombotic events occurred in 18% of patients, and 15% of patients died by the 30-day follow-up period. Deaths included 1 myocardial infarction, 1 pulmonary

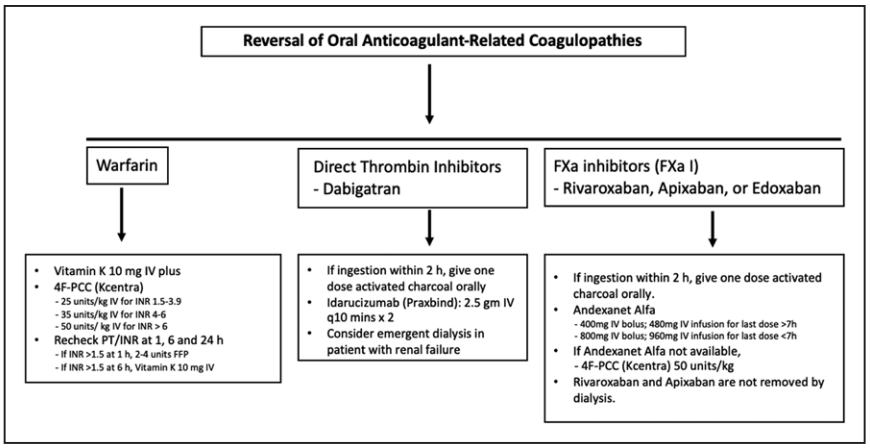

Figure 2. Current approaches for reversal of coagulopathy. 4F-PCC indicates 4 factor prothrombin complex concentrate; FFP, fresh frozen plasma; FXa-I, factor Xa inhibitor; INR, international normalized ratio; and PT, prothrombin time.

embolism, 5 strokes, and 7 deep vein thromboses for a total of 14 events in 12 patients. Anticoagulation was resumed in 27% of patients by 30 days.[55]

The ongoing ANNEXA-4 study has significant limitations. Exclusion criteria for this study includes any patients expected to undergo surgical intervention within 12 hours, ICH with GCS <7, ICH volume >60 mL, and an expected survival of <1 month.[55] Therefore, the study excluded many patients with severe ICH and worse prognoses. As such, the clinical efficacy of andexanet alfa needs to be validated in future studies. In addition, the anti-Xa factor activity reduction was short-lived, and anti-Xa levels increased 4 hours after completion of the infusion.[55] Many patients with ICH may need neurosurgical interventions (ie, ventriculostomy or hematoma evacuation), and a periprocedural rebound in coagulopathy may be dangerous.

PER977 (Ciraparatang)

PER977 (ciraparatang) was designed to bind to heparin and low-molecular-weight heparin but also has the ability to bind to FXa-Is and direct thrombin inhibitors, raising the exciting possibility of it being a universal reversal agent.[69] Edoxaban was the reversal target in a phase 1 trial, and PER977 reduced clotting times to 10% above baseline in <3 minutes. The authors examined fibrin strands with scanning electron microscopy before and after PER977 and demonstrated a 50% reduction of the strand thickness (250–125 nm; $P<0.001$) with restoration of normal strand width by 30 minutes. The doses used varied from 100 to 300 mg, and phase 2 studies are in progress. No prothrombotic adverse effects occurred, and laboratory values, as measured by prothrombin fragment 1.2 and D-dimer, did not indicate prothrombotic potential. The potential side effect includes perioral flushing.[70] Further studies will be important to further elucidate the frequency and severity of the potential side effects.

Comparison and Cost Analysis

Based on the current data, 4F-PCC is at least partially effective for FXa-I reversal.[53,57] A recent retrospective safety review of 43 patients who had FXa-I coagulopathy reversed with 4F-PCC reported a low complication rate of 2.3% (1 upper-extremity deep vein thrombosis).[71] Overall, the efficacy data are limited, but given the lack of readily available specific reversal agents and acceptable rate of thromboembolic complications, the Neurocritical Care Society guidelines currently recommend aPCC or PCC for FXa-I reversal.[28] However, the utility of PCC or aPCC for dabigatran reversal remains unanswered. See Table II in the online-only Data Supplement for a summary of current reversal options.

Currently, there has been no report on the efficacies of idarucizumab and andexanet alfa in comparison with 4F-PCC. REVERSE-AD evaluated pharmacological reversal but not clinical hemostasis. Meanwhile, UPRATE only evaluated clinical hemostasis and had no pharmacological markers, such as anti-Xa activity. Additionally, these studies had different definitions of clinical hemostasis and different study populations, most notably with ANNEXA-4 excluding more severe ICH (Table 2).[53–55]

Andexanet alfa seems to be expensive compared with 4F-PCC and idarucizumab (Table 1). For example, 4F-PCC costs ≈$5495 for a 20-IU/kg dose in a 70-kg patient. Idarucizumab is slightly more expensive than 4F-PCC. Given the lack of convincing data for 4F-PCC effectiveness in dabigatran reversal, idarucizumab use seems reasonable at this time. Andexanet alfa for reversal of coagulopathy from FXa-I may cost ≤$49 500 for patient taking the last dose of FXa-I within 7 hours. Preliminary data from ANNEXA-4 show that andexanet alfa is associated with a higher 30-day thrombotic complication rate (18% versus 3.6%) but a lower 30-day mortality rate (15% versus 32%) when compared with the results for 4F-PCC in UPRATE.[53,55] If future randomized trials can prove the mortality benefit of andexanet alfa over 4F-PCC, its cost may be justified. Currently, most medical centers do not have andexanet alfa and in the interim will continue to rely on 4F-PCC.[53–55]

Conclusions

The most common indication for OAT is stroke prevention in patients with atrial fibrillation, which affects millions of Americans and will increase in prevalence as the US population ages. Recent studies show that NOACs are associated with numerous advantages, including lower risk of bleeding and mortality, than VKAs. However, reversal of coagulopathy from NOACs remains a challenge in patients with ICH given the risk of rapid hematoma expansion. The data for idarucizumab and andexanet alfa seem promising, but these agents require cost-effectiveness analysis and direct comparisons

with 4F-PCC. New agents are still being discovered with the most recent PER977, showing the exciting potential to be a universal reversal agent. A current approach to reversal of coagulopathy is summarized in Figure 2.

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Disclosures

None.

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