Current status of oral anticoagulant reversal strategies: a review

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Abstract: Utilization of direct oral anticoagulants (DOAC) have steadily increased since their approval and are now recommended over warfarin for both stroke prevention in nonvalvular atrial fibrillation and treatment of venous thromboembolism (VTE). With increased DOAC use, the number of major bleeding events requiring medical intervention will continue to rise. Until 2015, warfarin maintained an advantage as the only oral anticoagulant with a specific reversal agent. Since then, idarucizumab has been approved for dabigatran reversal and recently, andexanet alfa was granted approval for the reversal of apixaban or rivaroxaban in patients with life-threatening or uncontrolled bleeding events. Due to the manufacturing practices required to yield these reversal therapies, they are available at high cost to hospital systems and as a result, have been met with resistance. Data exists describing both prothrombin complex concentrates (PCC) and andexanet alfa for DOAC reversal, however, without head-to-head comparison. Until future studies are available, current literature must be critically evaluated to aid in the clinical decision-making process of how to treat patients with life-threatening DOAC-related bleeding.

Keywords: Atrial fibrillation; direct oral anticoagulants (DOAC); oral anticoagulant reversal; venous thromboembolism (VTE); and exanet alfa; idarucizumab; factor Xa inhibitors; factor Xa inhibitors reversal; direct thrombin inhibitors; direct thrombin inhibitor reversal

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Introduction

Worldwide, there are approximately 3 million patients suffering with atrial fibrillation and 75,000 patients who are diagnosed with venous thromboembolism (VTE) annually (1). A major overlying goal of management of each condition is the reduction of thromboembolic (TE) events. Warfarin, the first oral anticoagulant, was approved for use by the FDA in 1954 and for over half a century remained the most widely used oral anticoagulant in practice (2). Direct-acting oral anticoagulants (DOAC) were first introduced to the market in 2010 with the FDA approval of dabigatran (3). Since that time, three other medications have been released that have received FDA approval for stroke prevention in atrial fibrillation and treatment and secondary prevention of deep venous thrombosis and pulmonary embolism: rivaroxaban (FDA approval July 2011), apixaban (FDA approval December 2012) and edoxaban (FDA approval January 2015). Apart from dabigatran, which acts as a direct thrombin inhibitor, the remaining DOACs are factor Xa inhibitors. As a class, DOACs have begun to be utilized with increased frequency (4), presumptively due to the fact that they do not require international normalized ratio (INR) monitoring (5), and offer similar efficacy while

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at the same time offering an improved safety profile (6-9). As of 2016, DOAC prescriptions exceeded those for warfarin in outpatient office visits for atrial fibrillation (4). Overall there was a 2.6% increase in oral anticoagulation prescriptions between 4th quarter of 2015 and 4th quarter in 2016. This equated to 4,210,000 prescriptions for DOACs in the US among which 1,073,550 (25.5%) were for dabigatran and the remainder for factor Xa inhibitors.

As DOAC use increases, the overall number of DOACrelated major and minor bleeding is increasing as well (10). Major bleeding events in nonvalvular atrial fibrillation patients on rivaroxaban were 3.6% per year and on apixaban were 2.13% per year in their respective landmark trials (11,12). Major bleeding or clinically relevant nonmajor bleeding rates in VTE patients on rivaroxaban was 8.1% and on apixaban was 4.3% during the 6-month therapy length (13,14). Unlike warfarin, which has readily available INR monitoring for direct measurement of the degree of anticoagulation and an established protocol for reversal, DOACs do not have reliable methods of laboratory monitoring available in clinical practice. Until recently, DOACs have not had targeted reversal strategies. Fortunately, several therapeutic strategies have been developed that can aid providers to manage bleeding events for those who take DOACs. Dabigatran can be reversed directly by idarucizumab in a specific and potent manner. Clinically, factor Xa inhibitors present a more challenging strategy. While a specific reversal agent is available to the factor Xa class in andexanet alfa, many utilize prothrombin complex concentrate (PCC) or activated prothrombin complex concentrate (aPCC) off-label for the management of DOAC-related bleeding. The goal of this review is to present the current available reversal strategies for DOACs in more detail and present the supporting evidence for their use.

Direct thrombin inhibitors

In October 2015, idarucizumab became the first specific reversal agent for dabigatran. Idarucizumab is a humanized monoclonal antibody that irreversibly binds dabigatran with a 350-fold greater affinity for dabigatran than that of thrombin (15). The utility of idarucizumab was studied in the RE-VERSE AD trial which assessed the effect of 5 g of intravenously administered idarucizumab in 503 patients taking dabigatran, classified in two groups: patients with uncontrolled bleeding (group A) and patients that were to undergo an urgent procedure (group B) (16). Idarucizumab immediately reversed the anticoagulant effect of dabigatran, with the nearly all (98.7%) patients having complete reversal of anticoagulation within four hours defined by the diluted thrombin time (dTT). Similar results were observed using the ecarin clotting time (ECT). The median time to complete bleeding cessation within group A in RE-VERSE AD was 2.5 hours in the arm that had experienced intracranial hemorrhage (ICH) and 1.6 hours in the arm that had gastrointestinal bleeding. In the group B, 93% of patients had normal hemostasis after the procedure. The major benefit of idarucizumab is its rapid reversal of dabigatran, without having any intrinsic procoagulant activity of its own. In addition, it is able to be dosed on future occasions without any loss of efficacy (17). After RE-VERSE AD was published, other studies conducted have validated the efficacy of anticoagulation reversal of idarucizumab as well (16,18). The current recommended dose is 5 g, given as two consecutive intravenous doses of 2.5 g. After 24 hours of administration, subtherapeutic levels of dabigatran are found in the blood stream due to redistribution of the drug (15). Cost remains a significant issue with idarucizumab, as annual costs of treating 10 to 20 patients can range from 34,825 to 69,650 respectively for administration of one dose (19). These costs increase significantly as a reported 20% of patients require a second dose for full effect as well (20).

Prior to idarucizumab, dabigatran-related major or clinically relevant bleeding was controlled with non-specific antagonists like PCC, aPCC or rFVIIa after conservative management had failed. An initial dose of 50 U/kg of PCC or aPCC or 90 µg/kg rFVIIa is recommended with additional doses if required (21-23). However, studies evaluating efficacy of PCC and aPCC for dabigatran reversal have shown mixed results (24-26). The limited efficacy combined with increased thrombotic risk, has restrained the use of these non-specific reversal agents.

Factor Xa inhibitors

Of the four oral factor Xa inhibitors on the market: rivaroxaban, apixaban, edoxaban and betrixaban, none are dialyzable and there is little utility for the use of activated charcoal to reduce systemic absorption outside of a two hour window from ingestion (5,27,28). Unlike the direct reversal provided by idarucizumab for dabigatran, factor Xa reversal remains a slightly more complex dilemma. Several current guidelines recommend and exanet alfa as the first line therapy for the management of life-threatening or uncontrolled bleeds for factor Xa inhibitors and the

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use of PCCs or aPCCs whenever and exanet alfa is not available (29-31).

A relatively novel agent, and exanet alfa received FDA approval for use in factor Xa-related life-threatening and uncontrollable bleeding in 2018 (32). Manufactured using Chinese hamster ovarian cells, it is a factor Xa "mimetic" that acts as a decoy receptor to competitively bind factor Xa inhibitors in a 1:1 ratio to prevent binding to native factor Xa (10). ANNEXA-A was the first randomized placebocontrol trial that studied the effect of IV bolus and IV bolus plus continuous infusion for 120 min of andexanet alfa. Healthy 50- to 75- year-old volunteers were given and exanet following pretreatment with apixaban 5 mg twice daily for 3.5 days. Efficacy was measured via changes in anti-factor Xa enzymatic activity, unbound inhibitor plasma concentration, and thrombin generation. The anti-factor Xa activity was reduced to a greater extent in IV bolus and examet alfa group as compared to the control group (94%±2% vs. 21%±9%; P<0.001). The group receiving IV infusion in addition to bolus also had similar reduction in anti-factor Xa activity as compared to control (92%±3% vs. $33\% \pm 6\%$, P<0.001). Within the and examet alfa-treated group, 100% of volunteers showed increased thrombin generation compared to 11% in control group. Unbound apixaban was reduced after IV bolus with continuous infusion compared to control (6.5 vs. 3.0 ng/mL; P<0.001). Similar to ANNEXA-A, ANNEXA-R trial studied the reversal of a rivaroxaban regimen of 20 mg daily for 4 days in healthy patients and had similar results. It similarly showed a >90% reduction of factor Xa activity versus placebo, and increased thrombin generation. ANNEXA-A and ANNEXA-R reported no TE or serious adverse events in these healthy patients while at the same time showed a measurable decrease in plasma activity of factor Xa inhibitors in all patients (33).

In hopes of analyzing the clinical utility of andexanet alfa, ANNEXA-4 was a multicenter, prospective study that evaluated the efficacy of andexanet alfa in management of acute life-threatening bleeding occurring in a critical area or organ, of which intracranial (64%) and gastrointestinal (26%) were most common. Patients were eligible if they received apixaban, rivaroxaban, edoxaban or enoxaparin within 18 hours of presentation. Of the 352 patients enrolled, the majority were previously receiving apixaban (55%) and rivaroxaban (36%). The cohort was elderly (mean age 77 years) and the most common indication for anticoagulation was atrial fibrillation (80%). Patients with more than 7 hours since last dose of rivaroxaban and all patients on apixaban received a 400 mg bolus followed by 480 mg infusion over 2 hours. Similarly, patients whose last dose of edoxaban, enoxaparin or rivaroxaban was less than 7 hours ago or if unknown received an 800 mg bolus followed by 960 mg infusion. Success was assessed by change in anti-factor Xa activity and hemostatic efficacy. Among patients on apixaban, anti-factor Xa activity reduced by 92% from 149.7 to 11.1 ng/mL while patients on rivaroxaban had reduction of 92% from 211.8 to 14.2 ng/mL. Good to excellent hemostatic efficacy was achieved in 83% patients on apixaban and 80% patients on rivaroxaban. Further analyses related to location of bleed revealed 85% patients with gastrointestinal bleed and 80% with intracranial bleed had either excellent or good hemostasis. Hemostatic efficacy for intracranial hemorrhage (ICH) was defined as hematoma volume increase of 0-20% (excellent), 20-35% (good) and >35% (poor). Although not evident in the overall cohort, anti-factor Xa activity reduction magnitude was a predictor of hemostatic efficacy in patients with ICH. Additionally, in patients with non-traumatic, single compartment intraparenchymal hemorrhage with <35% volume expansion from baseline to 1 hour, 98% had no additional hematoma expansion between 1-hour and 12-hour scans. All-cause mortality and TE rates at 30 days were 14% and 10%, respectively. However, in patients restarted on anticoagulation, the TE event rate was 0%, suggesting that TE events were likely resultant from the populations' propensity for thrombosis at baseline. ANNEXA-4 highlights the utility of a specific reversal agent by decreasing anti-factor Xa activity and establishing hemostatic efficacy, especially in patients with ICH. However, a lack of comparator is a significant limitation as the use of PCC off-label has become frequently utilized for emergent reversal.

When and exanet alfa is unavailable, PCCs or aPCCs are recommended as second line therapy for management of factor Xa-related bleeding (29). PCCs come in both 3 and 4 factor complexes that include the vitamin K dependent cofactors II, IX, and X. The 4-factor complexes include a higher concentration of factor VII as compared to 3-factor PCCs. The efficacy of PCC in reversing factor Xa inhibitors was first established via a randomized, placebocontrolled crossover trial involving 12 healthy male volunteers that were given rivaroxaban (25). Administration of a PCC dose of 50 U/kg normalized prothrombin time (PT) from 15.8 ± 1.3 to 12.8 ± 1.0 seconds compared to a baseline of 12.3 ± 0.7 seconds. PCC also normalized the changes in rivaroxaban-associated thrombin potential in

these healthy patients. The study reported no major serious adverse events. Subsequently, a prospective study assessed management of acute active major bleeding with 25 U/kg dose of PCC. In 84 patients who were on rivaroxaban or apixaban, Overall, ISTH-defined effective hemostasis was achieved in a total of 70% of patients, including 66.7% patients on rivaroxaban and 71.1% patients on apixaban. A total of 72.9% of patients with ICH were effectively managed. Three patients experienced a thrombotic event. The 30-day all-cause mortality was 32%; however, only one death could not be ruled out as unrelated to PCC (34). Similar results were reported in a retrospective observational study that evaluated PCC management of major bleeding in 31 patients on either rivaroxaban or apixaban treated with a higher PCC dose. A 50 U/kg dose of PCC was given to 16 patients (52%) while 12 patients (39%) received 25 U/kg PCC dose. The remaining 3 patients received alternative regimens that were undefined. Overall, effective hemostasis was achieved in 80.6% of patients, but comparisons between regimens demonstrated improved hemostasis without an increase in thrombotic events in the cohort that received 50 U/kg. No TE events were reported, and overall mortality was 16%, all related to severity of bleed (35). Finally, a retrospective trial of 18 patients on rivaroxaban or apixaban presenting with ICH showed that PCC was effective in only 33% patients (36). The study reported in-hospital mortality rate of 33%, although none were attributed to PCC. They reported one TE event. The data regarding PCCs is highly variable in regard to hemostatic efficacy and limited by small sample size and trial design. The above evidence shows that while PCCs may be beneficial to promote hemostasis, their effect remains imperfect and not uniform among patients.

Among healthy volunteers treated with factor Xa inhibitors, PCC and andexanet alfa have shown effective reversal of PT and factor xa activity without any increased risk of TE events (25,33). Although direct comparisons can't be made, among patients treated with factor Xa inhibitors and presenting with ICH, PCC has 33–72% efficacy whereas ANNEXA-4 trial estimated andexanet alfa efficacy at 80% (34,36-38). Amongst patients treated with factor Xa inhibitor presenting with gastrointestinal bleeding, effective management was achieved in 62% patients with PCC and in 85% patients with andexanet alfa (34,37,38). A meta-analysis of studies evaluating PCC reversal of factor Xa inhibitors reported 30-day TE event rate of 3% (39). While this was considerably lower than 30-day TE rate reported in ANNEXA-4 trial of 10% with andexanet alfa use, the patients in ANNEXA-4 trial restarted on anticoagulation had 0% TE event rate. A majority (68%) of these TE events occurred after 5 days from andexanet alfa administration suggesting that andexanet alfa may not play a role in creating hypercoagulable state (38). Despite the mechanism of action and relative quality of existing data compared to PCC, andexanet alfa has met resistance in favor of PCCs due to lack of comparator studies and cost. The price of PCC (Kcentra) is \$1.62/U while andexanet alfa is \$3,300/100 mg. Relative to the higher dosing for patients, PCC would be cheaper by over \$50,000 compared to andexanet alfa (35). Until more data is available many institutions are forced to make a difficult decision between continuing with current practices with an off-label therapy or change to a specific agent with a hefty price tag.

Compared to PCCs and andexanet alfa, aPCCs and rVIIa have sparse clinical data on their efficacy. The majority of the available information comes primarily from in vitro studies. Activated PCCs are made of the same components as 4-factor PCCs but contain the factor VIIa in an activated form (10). In vitro studies on 30 patients treated with apixaban showed that both aPCC and rVIIa were more effective than PCC (40). The lag time for thrombin generation was shortened by 39.4% and 48.9% by aPCC and rVIIa respectively while PCC did not affect it. Peak thrombin concentration was increased by 111.6%, 353% and 145.3% by PCC, aPCC and rVIIa, respectively. Clotting time was shortened by 14%, 58% and 41% by PCC, aPCC and rVIIa respectively. The study concluded that aPCC was a better reversal agent than PCC and rVIIa for apixaban-related coagulopathy. aPCC was more effective than PCC and rVIIa at reversing rivaroxaban inhibition of peak thrombin concentration in another in vitro study (41). Current guidelines for factor Xa reversal recommend aPCC use after PCC failure due to increased thrombotic complications (42). However, recent cases for reversing DOAC-related bleeding with aPCC reported good hemostasis with no increased risk of TE events (43-46).

Recent ex vivo studies on a novel antidote to DOACs, ciraparantag has showed some efficacy in reversing factor Xa inhibitors (47). Ciraparantag is a small, water soluble cation that binds to rivaroxaban, apixaban, edoxaban via hydrogen bonds and charge-charge interactions and completely reverses coagulopathy. It has the added benefit of binding similarly to dabigatran as well (48). Phase I trial on 80 healthy volunteers showed that ciraparantag reversed the edoxaban-induced prolonged whole blood clotting time 10–30 minutes after drug administration (49). It is currently undergoing

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Phase II trials and Phase III trials have been planned (50).

Conclusions

Since the emergence of DOACs and the significant increase in their use, there has become a greater need for management of bleeding attributed to their use. For direct thrombin inhibitors reversal and management of acute bleeding is clear. Idarucizumab provides a targeted and effective reversal of anticoagulation and allows for rapid return to hemostasis. The management of factor Xa inhibitors, however, is not as straightforward due to the emergence of routine off-label use of PCC. Andexanet alfa is a decoy receptor that prevents native factor Xa from binding to factor Xa inhibitors and is the recommended first line therapy for management of factor Xa inhibitor related bleeding. However, its broad utilization may be limited by its cost and the lack of comparator data with PCC. PCCs are recommended when and exanet alfa are not available and may be an effective modality for many patients; however, they do not provide uniform reversal of bleeding. Factor VIIa and aPCCs show promising *in-vitro* data but more clinical data is needed, and they remain recommended only when PCCs fail to control bleeding. Ciraparantag is a new molecular agent for factor Xa inhibitors and dabigatran that is undergoing further trials and may lead to more promising and clear directions in the future.

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Footnote

Conflicts of Interest: Dr. Cave discloses that he serves on the speaker's bureau for Portola Pharmaceuticals. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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