International Journal for Pharmaceutical Research Scholars (IJPRS)

V-5, I-2, 2016 ISSN No: 2277 - 7873

REVIEW ARTICLE

Review of Urgent Reversal Therapies for Oral Anticoagulation

John J. Mondin II*[1], Marintha R. Short[2], G. Shawn King[2], Patrick D. Ratliff[2]

[1]*Clear Lake Regional Medical Center, Webster, Texas*

[2]*KentuckyOne Health – Saint Joseph Hospital, Lexington, Kentucky.*

Manuscript No: IJPRS/V5/I2/00100, Received On: 24/06/2016, Accepted On: 02/07/2016

ABSTRACT

Anticoagulation has proven to be one of the most essential breakthroughs in cardiology in the last 100 years. The first major oral anticoagulant, warfarin, is a 4-hydroxycourmarin first synthesized in the 1940s for use as a rodenticide. It was not until 1954 that warfarin was finally approved by the FDA for use in patients requiring systemic anticoagulation. For over 55 years, warfarin was the only oral anticoagulant available in the United States until the approval of dabigatran in 2010, ushering in the era of the direct oral anticoagulants. This article will review modalities of anticoagulation reversal including activated charcoal, hemodialysis, blood-derived products, and medications currently available as well as in development.

KEYWORDS

Warfarin, Dabigatran, Rivaroxaban, Apixaban, Edoxaban, Reversal, Idarucizumab, Andexanet Alfa, Ciraparantag

INTRODUCTION

Anticoagulation has proven to be one of the most essential breakthroughs in cardiology in the last 100 years. The widespread use of oral anticoagulants as maintenance therapies for patients who have experienced a venous thrombomembolism, are at risk of a stroke from atrial fibrillation, or have hypercoagulable states have all been clinically shown to decrease morbidity and mortality. The first major oral anticoagulant, warfarin, is a 4-hydroxycourmarin first synthesized in the 1940s for use as a rodenticide. It was not until 1954 that warfarin was finally approved by the FDA for use in patients requiring systemic anticoagulation. For over 55 years, warfarin was the only oral anticoagulant available in the United States until the approval of dabigatran in 2010, ushering in the era of the direct oral anticoagulants.

***Address for Correspondence:**
John J. Mondin II,
Pharm. D., BCPS,
Clear Lake Regional Medical Center, Webster, Texas.
E-Mail Id: pcppharmd14@gmail.com

The problem with anticoagulation comes with the need for effective and quick reversal, especially in patients requiring surgery or has major bleeding. This purpose of this article is to review the currently available and future treatments to reverse therapeutic anticoagulation.

Activated Charcoal

Activated charcoal has shown to be beneficial for acute reversal of dabigatran following administration; its lipophilic nature should cause dabigatran to bind to the surface of charcoal and subsequently decrease the amount of drug absorbed and should be administered as quickly as possible (within 2-3 hours)[1]. Apixaban has slower uptake by the GI tract, making activated charcoal a possible reversal modality. According to apixaban prescribing information, administration following a 20 mg dose showed a reduction of AUC by 27-50% in 2-6 hours.[2] Rivaroxaban's rapid absorption makes it a poor candidate for charcoal administration and gastric

lavage, although prescribing information states that charcoal can be considered.[3] Edoxaban or warfarin prescribing information does not address activated charcoal[2-3]. Based on the low absorption of betrixaban by the GI tract, activated charcoal and gastric lavage could be possible methods of decreasing exposure in the instance of an overdose or accidental ingestion.

Hemodialysis

Hemodialysis is believed to only show benefit in dabigatran due to its low protein binding capacity; however, data supporting this reversal method is rather limited. Using a high-flux dialyzer, blood flow rate of 200 mL/min, and dialysate flow rate of 700 mL/min, approximately 49% of dabigatran can be cleared from plasma over a 4-hour dialysis session. With the same dialysate flow rate, approximately 59% can be cleared by increasing the blood flow rate to 400 mL/min, with no appreciable increase in clearance observed at higher blood flow rates. Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen.[4] The effect of dialysis on dabigatran plasma concentration would be expected to vary based on patient specific characteristics. Measurement of aPTT or ECT may help guide therapy.[5] A smaller case series (n = 5) in patients on dabigatran undergoing CVVHDF or HD showed a reduction in dabigatran plasma levels by 52-77%, but a rebound of up to 87% within 2 hours after HD was observed. CVVHDF was able to reduce levels of dabigatran by about 81% following 30 hours of CRRT. The authors recommend prolonged HD or HD followed by CRRT with HD parameters of a blood flow rate at 350-400 mL/min and dialysate flow rate at 800 mL/min.[6]

While it seems dialysis would serve as a potential reversal strategy, it presents with a host of problems making it a last line therapy. The largest concerns are prompt vascular access in a patient with hemorrhagic diathesis, machine availability, time required to initiate dialysis, and hemodynamic stability – if these four factors work harmoniously and agent-specific reversal is not readily available, hemodialysis would be a decent alternative.[1] Prescribing information for all other agents mentioned clearly state that dialysis will be unsuccessful or will not contribute significantly to reversal of anticoagulant effects.

Blood-Derived Products

Fresh Frozen Plasma (FFP)

Fresh frozen plasma is the fluid component of human blood that has been drawn, centrifuged, separated, and frozen within 8 hours. One unit of FFP is equivalent to the amount of plasma extracted from one unit of whole blood and contains all of the clotting factors at physiologic concentrations (including antithrombin and von Willebrand factor). FFP is usually prescribed in patients requiring rapid repletion of clotting factors as a result of coagulopathy, but it must be crossmatched to the patient's blood type and usually contains around 200 mL of volume. This large volume presents a problem for patients with congestive heart failure and elevated INR upon presentation, compounded with varying amounts of clotting factors, time required to thaw, potential transmission of viral illness, and risk of transfusion-related acute lung injury (TRALI).[7] FFP has utility in reversing warfarin, but does not show efficacy in reversing DOAC.[8] Moreover, FFP is usually coadministered with phytonadione since monotherapy is usually insufficient due to lingering concentrations of warfarin.

Phytonadione (Vitamin K1)

Phytonadione, or vitamin K1, is a fat-soluble vitamin responsible for gamma-carboxylation of vitamin K-dependent clotting factors. Phytonadione is available in oral and injectable forms, and is dosed from 1 to 10 mg depending on bleeding and INR. The injectable formulation may be administered intravenously through a slow IV infusion or subcutaneously. In the event of emergent reversal, the IV formulation should be chosen and infused over at least 20 minutes in 50 mL of intravenous fluid to reduce the risk for anaphylactoid reactions due to polyethoxylated castor oil that is used as a preservative. If the intravenous route is chosen in lieu of oral therapy, the INR should be expected to normalize

within 24 hours. After oral administration, the INR should begin to fall within 2 hours and return to normal within 24 hours if a large dose is given to a patient with normal hepatic function. When administered subcutaneously, the absorption of phytonadione is sporadic and appears to be less effective than oral administration. At 24 hours, 5 mg of oral and 1 mg of intravenous phytonadione can be expected to produce similar decreases of the INR. Additional vitamin K products are available, menaquinone (vitamin K_2) and menadione (vitamin K_3), but are not widely used nor have they been evaluated in clinical trials for reversal of VKA therapy.

When oral phytonadione is administered along with suspension of warfarin therapy, approximately 1.4 days are required for an INR in the range of 6 to 10 to fall to less than 4.0.[9] Dose and route of administration of phytonadione are dependent upon presence of bleeding and INR upon presentation. ACCP recommends that patients whose INR is 4.5 to 10 upon presentation with no signs of clinically-relevant bleeding that VKA therapy be withheld and the patient be closely monitored. There is no data currently demonstrating benefit in administering phytonadione in these patients. In patients whose INR is above 10, ACCP recommends that patients receive oral phytonadione with no specified dose. In the event a patient presents with an INR of at least 4.5 and bleeding associated with VKA therapy, ACCP recommends the utilization of intravenous phytonadione to emergently normalize INR.[10]

For surgical patients, urgency of intervention and time are key factors that determine route of administration and dose. Oral administration is preferred for patients undergoing elective surgery that can be delayed 24-36 hours and an INR of less than 3.0. For urgent procedures that can be delayed for 6 to 12 hours, one dose of 10 mg IV may be administered to counteract the effects of warfarin. Rapid reversal in the event of an emergent situation is automatic grounds for 10 mg IV, but other options (e.g. prothrombin complex concentrates, FFP, etc.) should be considered.[11]

Prothrombin Complex Concentrates

Under certain circumstances, the options previously mentioned for reversal have major drawbacks (e.g. slow onset of action, large fluid volume, hemodynamic stability, etc.) In patients who require urgent reversal of anticoagulation, but are unable to tolerate or wait for aforementioned agents to act should be considered for prothrombin complex concentrates (PCC). PCC is a highly purified and concentrated formulation of clotting factors prepared from pooled plasma. Comparatively, PCC is about 25 times more concentrated than FFP. Additional benefits of PCC include standardization of concentrations of factors compared to FFP, quick preparation time, diminished risk of TRALI and transfusion associated circulation overload (TACO), and no need to cross match to the patient's blood type.

Although all available PCC on the market have variations in their compositions, they are able to be grouped as 3-factor PCC and 4-factor PCC. All PCC contain FII, FIX, and FX. The added factor in 4-factor PCC is FVII, which provides a more reliable reduction in INR, but has a half life of around six hours.[12] In the United States, there are three PCC currently approved, only Kcentra® (4-factor PCC) carries approval for urgent reversal of drug-acquired coagulation factor deficiency for patients taking warfarin[13], Bebulin VH®[14], and Profilnine SD®[15] carry labeling for use in patients with FIX deficiency due to hemophilia B, but have been used off label to treat patients with elevated INR. Dosing of these agents are weight-based using units of Factor IX activity. Kcentra® and Bebulin VH® carry contraindications for patients with a history of heparin-induced thrombocytopenia or hypersensitivity to heparin since both agents contain a small amount of heparin.

Aside from warfarin, the utility of PCC has been examined with DOAC anecdotally. When tested on adult males given dabigatran treated with 4-factor PCC, reversal in ECT, aPTT, TT, or endogenous thrombin potential lag time was not observed. In the same study, patients were also treated with rivaroxaban 20 mg. The

investigators found that 4-factor PCC led to a normalization of PT in those treated with rivaroxaban.[8] A small study of six patients taking apixaban along with 4-factor PCC showed normalization of coagulation parameters, as well as two case reports (one with 3-factor PCC and one with 4-factor PCC).[16-18] Edoxaban was tested in a phase I, single-center study on 110 patients who received a dose of 60 mg and were treated with 4-factor PCC, which showed complete reversal of coagulation parameters in a dose-dependent manner.[19] The limited amount of evidence suggests that 4-factor PCC has a place in acute reversal of FXa inhibitors, but a conclusive recommendation cannot be made. The usual dose of PCC administered to reverse FXa inhibitors has been a one-time dose of 25 IU of FIX per kg, and repeated as necessary.

Table 1: Dosing of Kcentra (prothrombin complex concentrate [human]) for warfarin reversal[13]

Pre-Treatment INR	Dose of Kcentra (units of FIX / kg)	Maximum dose (units of FIX)
2 – <4	25	2500
4 – <6	35	3500
> 6	50	5000

Activated PCC

Unlike PCC, anti-inhibitor coagulant complex (FEIBA®) and recombinant Factor VIIa (rFVIIa, Novoseven®) are activated clotting factors, or in FEIBA's case, an activated prothrombin complex concentrate. Both agents have a labeled indication for hemophilia A and B, and rFVIIa carries and additional indication for patients with a congenital deficiency of FVII.[20-21] FEIBA® has been evaluated for reversal of dabigatran[22], rivaroxaban[23], and apixaban[24]. There is currently published clinical data on its utility in reversing edoxaban. Dosing of FEIBA® recommends 50-100 IU/kg IV every 6 to 12 hours, not exceeding a maximum daily dose of 200 IU/kg.[12]

Novoseven® is recombinant activated FVIIa, and is able to quickly increase the generation of thrombin via binding to activated platelets in an effort to form a stable platelet plug. Despite its labeled indications, a 2010 multi-center review showed that up to 92% of rFVIIa is used for off-label indications for the reversal of anticoagulation, trauma, liver failure, and platelet dysfunction.[25] The data surrounding rFVIIa is rather concerning for its high potential for thrombotic events and should be used carefully.

Synthetic Reversal Agents

Idarucizumab

Idarucizumab is the first reversal agent to gain approval for use in the United States. It is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran and its metabolites with higher affinity than the binding affinity of dabigatran to thrombin. Neutralizing the anticoagulant effect specific only to dabigatran, it does not work for the reversal of any other agent. It is dosed as a 5-gram infusion, divided into two 2.5-gram vials to be given within 15 minutes intravenously. It is the only proven medication to reverse dabigatran-sensitive laboratory values (diluted thrombin time, ecarin clotting time) with a median maximal reversal of 100%[26]. RE-VERSE AD demonstrated that idarucizumab was effective in achieving hemostasis in 11.4 hours in patients experiencing serious bleeding and 33 hours in patients requiring invasive intervention[27].

Reversal Agents in Clinical Development

Andexanet alfa

Andexanet alfa is a reversal agent currently undergoing phase III trials for use in the emergent reversal of rivaroxaban, apixaban, and edoxaban[28]. It is specific to only direct and indirect FXa inhibitors; therefore, it cannot be used to reverse dabigatran, warfarin, or other agents with antithrombotic properties. In phase II trials, intravenous andexanet yielded a "dose-dependent rapid and reproducible reversal of anticoagulant effects" in patients who received apixaban, edoxaban, enoxaparin, and rivaroxaban by measured anti-FXa levels, unbound FXa

Table 2: Utility of reversal agents with different oral anticoagulants

Reversal Agent	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Platelets	No	No	No	No	No
FFP	Yes	No	No	No	No
Cryoprecipitate	No	No	No	No	No
3-factor PCC	No	Consider	Consider	Consider	Consider
4-factor PCC	Yes	Consider	Consider	Consider	Consider
FEIBA	No	Consider	Consider	Consider	Consider
RFVIIa	No	Consider	Consider	Consider	Consider
Activated Charcoal	No	Yes	Recommend	Recommend	Recommend
Hemodialysis	No	Yes	No	No	No
Vitamin K	Yes	No	No	No	No
Idarucizumab	No	Yes	No	No	No
Andexanet alfa	No	No	Yes	Yes	Yes
Ciraparantag	No	Yes	Yes	Yes	Yes

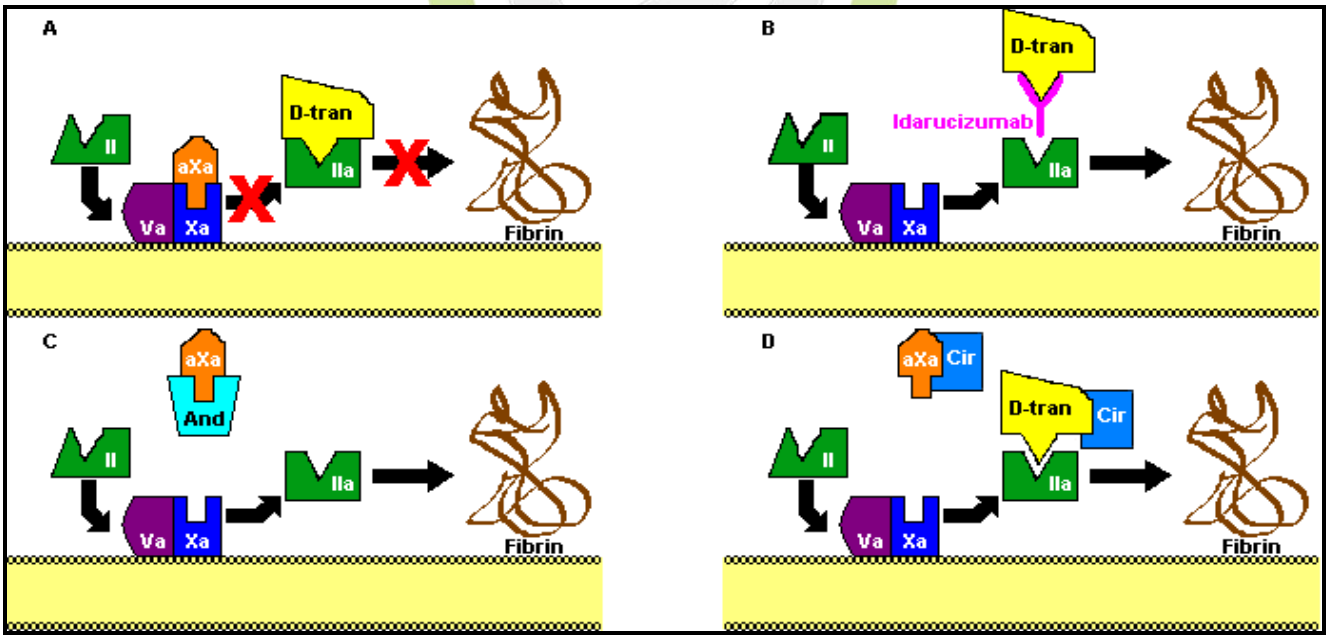

Figure 1: Mechanism of DOAC and their antidotes. (A) The prothrombinase complex. Dabigatran (D-tran) and FXa inhibitors (aXa) directly inhibit thrombin and FXa, respectively. (B) Idarucizumab is a humanized antibody fragment that binds to dabigatran, preventing it from binding to FIIa. (C) Andexanet alfa (And) is a modified inactive recombinant FXa that binds FXa inhibitors, allowing native FXa to restore normal coagulation. (D) Small synthetic molecule ciraparantag (Cir) competitively binds the DOACs, restoring normal coagulation.

Table 3: Basic characteristics of DOAC-specific reversal agents[30]

Agent	Idarucizumab	Andexanet alfa	Ciraparantag
Status	**Commercially available**	Phase III trials	Phase II trials
Structure	Humanized antibody fragment	Recombinant human FXa, catalytically inactive	Synthetic small molecule
Mechanism of action	Non-competitive binding to dabigatran with 350x greater affinity than FIIa	Complete and dose-dependent reversal of FXa	Binds to heparins, oral FXa and FIIa inhibitors through hydrogen bonding
Agents able to be reversed	Dabigatran only	Rivaroxaban, apixaban, edoxaban, betrixaban, enoxaparin, fondaparinux	Heparin, LMWH, fondaparinux, dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban

concentrations, and thrombin generation restoration. Andexanet alfa is a recombinant protein that is a structural analogue to FXa and has been devoid of all anticoagulant activity.[29]

The ANNEXA-A and ANNEXA-R studies evaluated the efficacy and safety of andexanet alfa. Patients were administered apixaban 5 mg twice daily or rivaroxaban 20 mg once daily and randomized to either a slow IV bolus or a bolus plus infusion. A decrease in anti-FXa activity was observed within 2 to 5 minutes and persisted for approximately two hours before returning to baseline in both the apixaban and rivaroxaban arms. When followed by an infusion, anti-FXa activity persisted throughout the infusion and for approximately 1 to 2 hours following. All patients who received the full infusion of andexanet alfa saw an 80% or greater decrease in anti-FXa activity with no serious or adverse events.[28] Andexanet alfa is now undergoing further investigation in a phase 3b-4 study, ANNEXA-4, to evaluate safety of in patients taking rivaroxaban, apixaban, edoxaban, and enoxaparin.

Ciraparantag

The newest and most promising reversal agent, ciraparantag (aripizine or PER977) appears to have the ability to negate the anticoagulant effect of unfractionated heparin, low molecular weight heparins, fondaparinux, dabigatran, rivaroxaban, apixaban, and edoxaban. Ciraparantag is a small, synthetic, water-soluble molecule that directly inhibits most oral and parenteral anticoagulants with the exception of warfarin. It does not appear to have affinity for plasma proteins or common cardiovascular, antiepileptic, or anesthetic medications.[1] The first *in vivo* human study was conducted in 180 patients who were given edoxaban 60 mg as a single dose followed by ciraparantag 100 mg or 300 mg. Following administration of ciraparantag, therapeutic anticoagulation was immediately reversed anticoagulation and the effect was maintained for over 24 hours with no further intervention or evident prothrombotic effects[29]. Based on early studies, the widespread utility of ciraparantag holds promise and potential as a universal reversal agent for non-warfarin anticoagulants.

CONCLUSION

Several factors are important when addressing patient-specific reversal strategies. Most strategies for reversal of anticoagulation in the United States are used anecdotally and off-label, but have been proven to be effective and supported by mountains of patient cases with good outcomes. Each of the strategies listed in this article has been shown to reverse oral anticoagulation effectively, and should be considered based on the patient's current clinical situation. While older methods of reversal are still viable options for reversal (e.g. transfusion, fresh frozen plasma, vitamin K), newer and agent-specific reversal strategies will likely begin to take precedence and likely become first-line choices for reversal of therapeutic anticoagulation. Special attention should be made when using specific reversal agents, as misuse may delay patient recovery and potentially impact survivability. It is important that patients are fully aware of the risk associated with anticoagulation once therapy is started; conversely, it is more important for the patient's health care team to adequately evaluate the patient to select the most optimal agent and that patients be aware of potential lack of reversal for certain agents.

REFERENCES

1. Crowther, M., & Crowther, M. A. (2015). Antidotes for Novel Oral Anticoagulants Current Status and Future Potential. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *35*(8), 1736-1745.
2. Eliquis [package insert]. (2015). Princeton, NJ: Bristol-Meyers Squibb, Inc.
3. Xarelto [package insert]. (2014). Gurabo, PR: Janssen Pharmaceuticals, Inc.
4. Winkle, R. A., Mead, R. H., Engel, G., Kong, M. H., & Patrawala, R. A. (2014). Peri-procedural interrupted oral anticoagulation for atrial fibrillation ablation: comparison of aspirin, warfarin, dabigatran, and rivaroxaban. *Europace*, euu196.
5. Pradaxa [package insert]. (2016). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.
6. Singh, T., Maw, T. T., Henry, B. L., Pastor-Soler, N. M., Unruh, M. L., Hallows, K. R., & Nolin, T. D. (2013). Extracorporeal therapy for dabigatran removal in the treatment of acute bleeding: a single center experience. *Clinical Journal of the American Society of Nephrology*, *8*(9), 1533-1539.
7. Jackson II, L. R., & Becker, R. C. (2014). Novel oral anticoagulants: pharmacology, coagulation measures, and considerations for reversal. *Journal of Thrombosis and Thrombolysis*, *37*(3), 380-391.
8. Gehrie, E., & Tormey, C. (2015). Novel oral anticoagulants: efficacy, laboratory measurement, and approaches to emergent reversal. *Archives of Pathology and Laboratory Medicine*, *139*(5), 687-692.
9. Ageno, W., Gallus, A. S., Wittkowsky, A., Crowther, M., Hylek, E. M., & Palareti, G. (2012). Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *CHEST Journal*, *141*(2_suppl), e44S-e88S.
10. Holbrook, A., Schulman, S., Witt, D. M., Vandvik, P. O., Fish, J., Kovacs, M. J., & Guyatt, G. H. (2012). Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest Journal*, *141*(2_suppl), e152S-e184S.
11. Khadzhynov D, Wagner F, Formella S. (2013). *Thromb Haemost*, 109(4), 596-605.
12. Schlitt, A., Jámbor, C., Spannagl, M., Gogarten, W., Schilling, T., & Zwissler, B. (2013). The perioperative management of treatment with anticoagulants and platelet aggregation inhibitors. *Dtsch Arztebl International*, *110*(31-32), 525-532.

13. Kcentra [package insert]. (2014). Kankakee, IL: CSL Behring, LLC.

14. Bebulin VH [package insert]. (2012). Westlake Village, CA: Baxter Healthcare Corporation.

15. Profilnine SD [package insert]. (2004). Los Angeles, CA: Alpha Therapeutic Corporation.

16. Cheung, Y. W., Barco, S., Hutten, B. A., Meijers, J. C. M., Middeldorp, S., & Coppens, M. (2015). In vivo increase in thrombin generation by four-factor prothrombin complex concentrate in apixaban-treated healthy volunteers. *Journal of Thrombosis and Haemostasis*, *13*(10), 1799-1805.

17. Denetclaw, T. H., Tam, J., Arias, V., Kim, R., & Martin, C. (2015). Case Report Apixaban-Associated Gluteal Artery Extravasation Reversed With PCC3 Without FFP. *Journal of Pharmacy Practice*, 0897190015613231.

18. Durie, R., Kohute, M., Fernandez, C., & Knight, M. (2016). Prothrombin complex concentrate for the management of severe traumatic bleeding in a patient anticoagulated with apixaban. *Journal of Clinical Pharmacy and Therapeutics*, *41*(1), 92-93.

19. Zahir, H., Brown, K. S., Vandell, A. G., Desai, M., Maa, J. F., Dishy, V., & Grosso, M. A. (2015). Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation*, *131*(1), 82-90.

20. FEIBA-NF [package insert]. (2011). Westlake Village, CA: Baxter Healthcare Corporation.

21. Novoseven [package insert]. (2006). Princeton, NJ: Novo Nordisk, Inc.

22. Van Ryn, J., Ruehl, D., Priepke, H., Hauel, N., & Wienen, W. (2008, June). Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran, by recombinant factor VIIa or activated prothrombin complex concentrate. In *haematologica-the hematology journal* (vol. 93, pp. 148-148). Via giuseppe belli 4, 27100 pavia, italy: ferrata storti foundation.

23. Marlu, R., Hodaj, E., Paris, A., Albaladejo, P., Crackowski, J. L., & Pernod, G. (2012). Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. *Thromb Haemost*, *108*(2), 217-224.

24. Escolar, G., Fernandez-Gallego, V., Arellano-Rodrigo, E., Roquer, J., Reverter, J. C., Sanz, V. V., & Galan, A. M. (2013). Reversal of apixaban induced alterations in hemostasis by different coagulation factor concentrates: significance of studies in vitro with circulating human blood. *PloS one*, *8*(11), e78696.

25. Beshay, J. E., Morgan, H., Madden, C., Yu, W., & Sarode, R. (2010). Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients: a review. *Journal of Neurosurgery*, *112*(2), 307-318.

26. Praxbind [package insert]. (2015). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.

27. Pollack Jr, C. V., Reilly, P. A., Eikelboom, J., Glund, S., Verhamme, P., Bernstein, R. A., & Kreuzer, J. (2015). Idarucizumab for dabigatran reversal. *New England Journal of Medicine*, *373*(6), 511-520.

28. Siegal, D. M., Curnutte, J. T., Connolly, S. J., Lu, G., Conley, P. B., Wiens, B. L., & Mar, F. A. (2015). Andexanet alfa for the reversal of factor Xa inhibitor activity. *New England Journal of Medicine*, *373*(25), 2413-2424.

29. Ansell, J. E. (2016). Universal, class-specific and drug-specific reversal agents for the new oral anticoagulants. *Journal of Thrombosis and Thrombolysis*, *41*(2), 248-252.

30. Enriquez, A., Lip, G. Y., & Baranchuk, A. (2015). Anticoagulation reversal in the era of the non-vitamin K oral anticoagulants. *Europace*, euv030.

