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A Review on the Reversal of the Old and New Anticoagulants

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ABSTRACT
It is not uncommon for providers in the emergency department to take care of patients who are taking anticoagulant therapy in the outpatient setting. However, the bigger challenge is caring for these patients when they present with bleeding that could be secondary to 1 or more of these medications. In recent years, this class of medications has expanded from warfarin to include direct thrombin inhibitors and Factor Xa inhibitors. As this class of medications has evolved, so has the approach to the reversal of these agents. Thus, it is imperative that providers in the emergency department be familiar not only with the anticoagulants that patients may be taking in the outpatient setting but also with their reversal agents. **Key words:** anticoagulation, apixaban, bleeding, dabigatran, direct thrombin inhibitor, edoxaban, enoxaparin, Factor Xa inhibitor, low-molecular-weight heparin, reversal, rivaroxaban, vitamin K antagonist, warfarin

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ORAL ANTICOAGULANTS are used for a variety of clinical indications commonly seen by providers in the emergency department (ED) including treatment and prevention of venous thromboembolism (VTE) and stroke prophylaxis in nonvalvular atrial fibrillation (NVAF; Siegal et al., 2015). Clinicians in the ED could be the diagnosticians for these conditions or be charged with treating patients for bleeding complications (Pollack, 2012).

For decades, the standard of care for any patient requiring oral anticoagulation was warfarin. However, warfarin is plagued

with many clinical challenges, which make long-term management and treatment difficult (e.g., profound interpatient variability, dietary restrictions, narrow therapeutic window, the need for continued laboratory monitoring, and a multitude of drug–drug interactions). Over the last 5 years, new oral anticoagulants have come to the market and have demonstrated advantages in terms of monitoring and clinical efficacy and are deemed to possess a similar, sometimes lower, risk of bleeding when compared with warfarin.

Different terminology has been used in regard to the new oral anticoagulants including new/novel oral anticoagulants (NOACs) and direct oral anticoagulants (DOACs). Barnes, Ageno, Ansell, and Kaatz (2015) conducted a web-based survey that revealed that consensus on a single term be reached and that the preferred term by the group be DOACs. The DOACs target two specific receptor sites and are divided into two classes: direct thrombin inhibitors (DTIs) and Factor Xa inhibitors. Selection of specific receptor targets is thought to help enhance the anticoagulant effect while limiting unnecessary interactions and bleeding complications. Refer to Figure 1 for an illustration depicting the mechanisms of action of each anticoagulant and reversal agent on the clotting cascade.

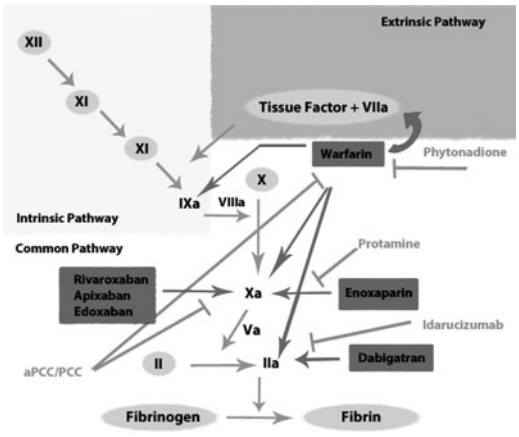

Figure 1. An overview of the mechanisms of action for the anticoagulants and the reversal agents currently available. aPCC = activated prothrombin complex concentrate; PCC = prothrombin complex concentrate.

However, unlike warfarin, providers are not able to monitor the DOACs for either efficacy or safety because there are no objective coagulation assays that dictate whether dose adjustments are warranted (Pollack, 2012). Similarly, agent-specific antidotes have only just come to market in the last year. Prior to this, providers were left trying to decipher different reversal strategies or apply their knowledge of warfarin-related bleeding to these new agents.

Life-threatening bleeding is an important concern for patients taking anticoagulants because the mortality and morbidity can be as high as 66% (Peacock, Gearhart, & Mills, 2012). Therefore, it is important for all ED practitioners to be knowledgeable about the use of these agents, their mechanism of action, clinical impact, and existing methods to mitigate bleeding complications.

ANTICOAGULANT REVIEW

Warfarin—Vitamin K Antagonist

Mechanism of Action

To understand warfarin's mechanism of action, one must first have an understanding of normal physiological coagulation. This process begins with vitamin K, which is essential for the synthesis of clotting Factors II, VII, IX, and X. In the liver, vitamin K is oxidized into vitamin K epoxide. Vitamin K epoxide is then recycled back to vitamin K by the enzyme vitamin K epoxide reductase (Ageno et al., 2012).

Warfarin inhibits the action of vitamin K epoxide reductase, leading to a reduction in the synthesis of the aforementioned clotting factors. However, the full anticoagulant effects will not be established until the preexisting clotting factors already in circulation have degraded naturally. This process normally takes 5–7 days. Warfarin also inhibits the production of coagulant proteins C and S, and because these proteins have shorter half-lives than the vitamin K-dependent clotting

factors, their degradation may result in a procoagulant effect upon warfarin initiation. As a result, warfarin must be started in combination with a parenteral agent with a rapid onset of action, such as a low-molecular-weight heparin (LMWH) or unfractionated heparin, for the treatment of a preformed thrombus (Ageno et al., 2012).

Indications

Warfarin has been available for more than 60 years and has been studied and utilized for a wide range of indications that require anticoagulation. Warfarin carries Food and Drug Administration (FDA) approval for several indications. Refer to Table 1 for a list of these indications (Ageno et al., 2012; Holbrook et al., 2012; Nishimura et al., 2014).

Risk of Bleeding

The risk of bleeding with warfarin is proportional to a patient's degree of anticoagulation. Intensity of anticoagulation can be

Table 1. Food and Drug Administration-approved indications for the anticoagulants

Anticoagulant	Food and Drug Administration-approved indications
Warfarin	Treatment and prevention of DVT and PE Prevention of stroke in the setting of atrial fibrillation Prevention of thrombotic complications in patients with prosthetic heart valves (Ageno et al., 2012; Holbrook et al., 2012; Nishimura et al., 2014)
Enoxaparin	Treatment and prevention of venous thromboembolism, including DVT and PE, in a variety of medical and surgical populations Acute coronary syndrome, including myocardial infarction (Amsterdam et al., 2014; Holbrook et al., 2012; Kearon et al., 2012; Noble, Peters, & Goa, 1995)
Dabigatran	Prophylaxis of thromboembolic disorder in patients with NVAF Treatment and prophylaxis of DVT and PE Prophylaxis of DVT and PE in hip repair surgery (Dabigatran [package insert], Boehringer Ingelheim Pharmaceuticals, 2015a)
Apixaban	Prevention of stroke and systemic embolism in patients with NVAF Prophylaxis of DVT in patients who have undergone hip or knee replacement surgery Treatment of DVT and PE Reduction in the risk of recurrent DVT and PE following initial therapy (Agnelli et al., 2013a, 2013b; Connolly et al., 2011; Granger et al., 2011; Lassen et al., 2009, Lassen, Gallus, et al., 2010, Lassen, Raskob, et al., 2010)
Edoxaban	Decrease the risk of stroke and systemic embolism in patients with NVAF Treatment of DVT and PE after the patient has been treated with a parenteral anticoagulant for 5–10 days (Giugliano et al., 2013; Hokusai-VTE Investigators, 2013)
Rivaroxaban	Prevention of VTE in patients who have had a major orthopedic surgery of the lower extremities (i.e., hip and knee replacements) Prevention of stroke and systemic embolism in patients with NVAF and at least one additional risk factor for stroke Treatment of DVT and PE (Bauersachs et al., 2010; EINSTEIN-PE Investigators, 2012; Executive Steering Committee, 2010)

Note. DVT = deep vein thrombosis; NVAF = nonvalvular atrial fibrillation; PE = pulmonary embolism.

directly measured by obtaining a patient's international normalized ratio (INR) while undergoing warfarin therapy. For most indications, an INR of 2–3 is sufficient whereas an INR of 2.5–3.5 is recommended for patients with a mechanical mitral valve or a mechanical aortic valve with certain risk factors. For patients with mechanical valves, it is important to know what type of valve the patient has, as the goal INR varies from one to another (Bristol-Myers Squibb Company, 2015).

Medications that interfere with warfarin's metabolism will also have effects on the degree of anticoagulation. For example, medications that inhibit warfarin's metabolism (i.e., amiodarone or metronidazole) can lead to increased systemic warfarin availability and supratherapeutic INRs, which can place that patient at a greater risk of bleeding. In contrast, medications that induce warfarin's metabolism (i.e., carbamazepine or rifampin) can reduce its anticoagulant effect, possibly leading to thrombus formation.

There are recent data comparing the bleeding risk of warfarin with dabigatran, rivaroxaban, and apixaban. A 2014 meta-analysis concluded that when used for stroke prevention among patients with atrial fibrillation, DOACs were associated with a greater incidence of gastrointestinal (GI) bleeding but a lesser instance of intracranial hemorrhage than that with warfarin (Ruff et al., 2014).

Enoxaparin—Low-Molecular-Weight Heparin

Mechanism of Action

Antithrombin is the major protein molecule responsible for inactivation of enzymes that propel the clotting cascade forward; it is an inhibitor of the clotting cascade. When an LMWH binds to antithrombin, it causes a conformational change, which enhances the inactivation of Factor Xa (Buckley & Sorkin, 1992; Garcia, Baglin, & Weitz, 2012). The end result is anticoagulation. This is the main mechanism, but because LMWH chains are heparin fragments, some may be long enough to inhibit thrombin as well. Unfractionated heparin shares this mechanism of action, but because the molecule is longer than an LMWH, it is able to inhibit thrombin to a greater extent (Garcia et al., 2012; Hirsh et al., 2001). Currently, there is no evidence linking the enhanced thrombin binding of heparin to better or worse clinical outcomes including bleeding complications (Hirsh et al., 2001). Even though there are two other LMWHs available in the United States (i.e., dalteparin and tinzaparin), our focus is on enoxaparin, as it is still the most commonly used.

Indications

Enoxaparin is prescribed on both inpatient and outpatient bases. Although therapeutic levels of anticoagulation can be achieved with enoxaparin alone, it is commonly prescribed as bridge therapy in combination with warfarin. It may take several days for a patient's INR to reach a therapeutic level; therefore, enoxaparin is used to provide a therapeutic level of anticoagulation until the INR is within goal range. A bridge with enoxaparin is continued for a minimum of 5 days and stopped when a patient has an INR within his or her therapeutic goal range for at least 24 hr (Kearon et al., 2012).

Risk of Bleeding

Major bleeding has been reported with an incidence of up to 4%, and the incidence of other hematological complications (e.g., hemorrhage and anemia) has been reported to be even higher. Enoxaparin is eliminated from the body through the kidneys and therefore significant renal impairment can lead to drug accumulation and inadvertent bleeding (Buckley & Sorkin, 1992; Hirsh et al., 2001; Lim, Dentali, Eikelboom, & Crowther, 2006). This can occur in patients who develop an acute kidney injury after the initiation with enoxaparin therapy if it is not dose adjusted to reflect the decrease in kidney function. Below a creatinine clearance of 30 ml/min, a dose reduction of 50% is recommended (Hirsh et al., 2001). Frequent monitoring of renal function while on this medication is necessary, especially in times of labile kidney function. Dose adjustments and anti-Xa

monitoring via anti-Xa levels, if available, are also employed to prevent an excess of enoxaparin being administered.

Direct Thrombin Inhibitors—Dabigatran

Mechanism of Action

Direct thrombin inhibitors work by inhibiting thrombin, a necessary component of the clotting cascade that converts fibrinogen to fibrin. This action helps prevent the formation of a clot. Currently, the DTIs available in the United States include argatroban, bivalirudin, desirudin, and dabigatran. Of the approved agents, dabigatran is the only oral DTI currently approved in the United States (Boehringer Ingelheim Pharmaceuticals, 2015a; GlaxoSmithKline, 2014; The Medicines Company, 2013; Valeant Pharmaceuticals, 2015).

Indications

Refer to Table 1 for a list of the FDA-approved indications for dabigatran.

Risk of Bleeding

The data about the risk of bleeding with dabigatran compared with other agents such as warfarin are somewhat conflicting. The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY; Connolly et al., 2009) trial showed that compared with warfarin, dabigatran dosed at 150 mg twice daily was associated with a lower rate of strokes and other systemic thromboses and similar rates of major bleeding in patients with NVAF. Among the types of bleeding, there was a difference with dabigatran, showing a higher rate of GI bleeding but a lower rate of intracerebral bleeding than that with warfarin (Connolly et al., 2009). In a retrospective cohort study with Medicare patients, dabigatran was associated with a reduced risk of stroke, intracranial hemorrhage, and death compared with warfarin but a higher rate of major GI bleeding (Graham et al., 2015). This increased risk of GI bleed was not replicated in either of the RE-COVER or RE-COVER II trials, which showed noninferiority when compared with warfarin in preventing stroke and a lower rate of bleeding (Schulman et al., 2009, 2014). In contrast to the bleeding risk, in a recent meta-analysis conducted, which included 11 trials and 40,000 patients, patients taking dabigatran were more likely to experience an acute myocardial infarction than those who were taking warfarin (Artang, Rome, Nielsen, & Vidaillet, 2013; Tornyos, Kehl, D'Ascenzo, & Komócsi, 2015).

Oral Factor Xa Inhibitors—Apixaban, Edoxaban, and Rivaroxaban

Mechanism of Action

The Factor Xa inhibitors work by inhibiting both free Factor Xa and prothrombinase activity without requiring a cofactor for activity. Because Factor Xa is located at the junction of the extrinsic and intrinsic pathways in the coagulation cascade, this factor's inhibition results in a decrease in thrombin production. Despite the decrease in production, these agents do not directly inhibit thrombin or platelet aggregation.

On the basis of the mechanism of action of these anticoagulants, the following laboratory values may be prolonged or supratherapeutic: prothrombin, INR, and activated partial thromboplastin time (aPTT; Miyares & Davis, 2012). Even though the Factor Xa inhibitors affect the aforementioned laboratory values, the laboratory values do not directly correlate to their therapeutic efficacy.

Indications

Apixaban received approval for use in the United States in 2012. Efficacy and safety data for the use of apixaban in the reduction of stroke and systemic embolism in patients with NVAF were derived from the results of the ARISTOTLE study (Granger et al., 2011). Results from this study revealed that apixaban was superior to warfarin in reducing the risk of stroke and systemic embolism and demonstrated a reduction in hemorrhagic conversion in patients with stroke compared with warfarin (Granger et al., 2011). The AVERROES trial (Connolly et al., 2011) was

conducted to compare apixaban with aspirin for prevention of stroke or systemic embolism in patients who were not considered candidates for treatment with warfarin. This trial was stopped early when the interim analysis demonstrated a significant reduction in stroke and systemic embolism in the apixaban group (Connolly et al., 2011).

Initially approved by the FDA in 2015 for use in the United States, edoxaban is currently indicated to decrease the risk of stroke and systemic embolism in patients with NVAF and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) after the patient has been treated with a parenteral anticoagulant for 5–10 days. However, there is a limitation to the use of edoxaban in patients with NVAF. In patients who have a creatinine clearance of greater than 95 ml/min, edoxaban should not be used because there is an increased risk of ischemic stroke when compared with warfarin.

Rivaroxaban received FDA approval in 2011 and has FDA-approved indications similar to those mentioned previously for apixaban. This anticoagulant can also be used for the prevention of recurrent DVT and PE. The data for the use of rivaroxaban for stroke prevention in NVAF can be found in ROCKET-AF, which demonstrated that rivaroxaban was noninferior to warfarin in the time to first occurrence of stroke, of any type, or noncentral nervous system systemic embolism (Executive Steering Committee, 2010). The EINSTEIN DVT and PE studies evaluated the use of rivaroxaban for the treatment of DVT and/or PE and for the risk of recurrence. Both studies found rivaroxaban to be noninferior to enoxaparin in combination with a vitamin K antagonist (VKA) in regard to the time to first occurrence of recurrent DVT or nonfatal or fatal PE (Bauersachs et al., 2010; EINSTEIN-PE Investigators, 2012).

Risk of Bleeding

As is true with the other oral anticoagulants, the use of the oral Factor Xa inhibitors does increase the risk for the occurrence of bleeding. There are mixed data regarding the Factor Xa inhibitors and the risk of GI bleeding. However, the increased risk of GI bleeding may be dose- and age-dependent. Compared with warfarin, the DOACs significantly increased GI bleeding (relative risk [RR] = 1.23; 95% confidence interval [CI] [1.03, 1.46]; p = 0.01). In regard to the Factor Xa inhibitors specifically, higher doses of edoxaban (RR = 1.22; 95% CI [1.01, 1.47]; p = 0.038) and rivaroxaban (RR = 1.46; 95% CI [1.2, 1.8]; $p < 0.001$) significantly increased GI bleeding whereas a null effect was detected with apixaban (Loffredo, Perri, & Violi, 2015). In contrast to these data, the DOACs have been shown to have a decreased risk of intracranial hemorrhage in comparison with warfarin.

REVERSAL AGENTS

Fresh Frozen Plasma

Fresh frozen plasma (FFP) is considered a form of factor replacement. It is the plasma acquired from a whole unit of blood and contains all coagulation factors including the vitamin K-dependent factors (i.e., II, VII, IX, X, and proteins C and S). The availability of FFP is nearly universal in the United States, and it has become the cornerstone of treatment of warfarin-related critical bleeding (Goldstein et al., 2006; Hall & Carson, 2012; Peacock et al., 2012).

There is little in the way of evidence to help suggest how much FFP is required for full reversal. The recommended dose of FFP is 10–20 ml/kg for life-threatening bleeding (an average of 4 units is typically required; Goldstein et al., 2006). However, the amount of factor replaced with each unit is not standardized and can take several liters of FFP to fully replete depleted coagulation factors. Therefore, full reversal may not be seen for several hours depending on the volume and rate of administration and degree of coagulopathy to be corrected (Goldstein et al., 2006; Hall & Carson, 2012).

The use of FFP is not without limitations. It requires thawing prior to administration; thus, there may be delays in acquisition

and administration. Also, because FFP is a pooled blood product, there is the inherent risk of transfusion-related infection. Ideally, providers should obtain appropriate blood-type compatibilities prior to FFP administration and this can further delay reversal. Finally, given the volume of FFP required, patients are at risk of volume overload, pulmonary edema, or transfusion-related acute lung injury (Goldstein et al., 2006; Hall & Carson, 2012). Careful monitoring for adverse events is essential.

Phytonadione (Vitamin K)

Phytonadione (vitamin K_1) is used to reverse the anticoagulant effects of warfarin. For patients requiring nonurgent reversal (i.e., those with minor bleeding or an INR greater than 10 without bleeding), 2.5 mg of oral phytonadione is recommended. Patients requiring urgent reversal, such as those with a life-threatening bleed or anticoagulated patients in need of emergency surgery, may receive 5–10 mg of intravenous phytonadione due to its more rapid onset of action. When given intravenously, it is imperative to keep the black box warning of this medication in mind, as fatalities have resulted from administration via this route. Reactions that have resulted typically manifested as hypersensitivity or anaphylaxis. Subcutaneous or intramuscular administration of phytonadione is not recommended because of unpredictable absorption and risk of hematoma formation (Cushman, Lim, & Zakai, 2014).

Protamine

Protamine has been used as a reversal agent for heparins for more than 30 years (Suryanarayan & Schulman, 2014). Enoxaparin, which is an LMWH, is used at lower doses than heparin for thromboprophylaxis and at higher doses for the treatment of VTE (van Veen et al., 2011). Protamine completely reverses the anticoagulant effects of unfractionated heparin but only partially reverses the anti-Xa effects of LMWH. The dose of protamine used to reverse enoxaparin depends on the time from last administration and dose given. If enoxaparin was administered within the last 8 hr, 1 mg of protamine will neutralize 1 mg of enoxaparin. If enoxaparin was administered within 8–12 hr, 0.5 mg of protamine will neutralize 1 mg of enoxaparin. If it has been more than 12 hr since the last dose of enoxaparin (assuming every 12-hr dosing) and the patient has normal renal function, protamine may not be necessary (Bang, Berstad, & Talstad, 1991; Lindblad, Borgstrom, Wakefield, Whitehouse, & Stanley, 1987; Wiernikowski, Chan, & Lo, 2007).

Protamine can be administered undiluted as a slow intravenous push over 5–10 min. It can also be diluted prior to administration in either saline or dextrose and administered over the same rate. There is a very small risk of anaphylaxis associated with protamine administration (1%), but this has mainly been observed during cardiac surgical procedures (Suryanarayan & Schulman, 2014).

Prothrombin Complex Concentrates

Anti-Inhibitor Coagulant Complex (FEIBA)

FEIBA (Factor VIII inhibitor bypassing activity) is an activated prothrombin complex concentrate (aPCC) containing activated Factor VII and inactivated Factors II, IX, and X. Currently, aPCC is FDA approved to prevent spontaneous bleeding episodes or prevention of bleeding associated with surgical intervention in patients with hemophilia A (Factor VIII deficiency) and hemophilia B (Factor IX deficiency); however, it has been used off-label for the emergent reversal of warfarin, dabigatran, and other oral anticoagulants (Awad & Cocchio, 2013).

Composed of multiple factors required for the clotting cascade, aPCC enhances the levels of activated and nonactivated factors to restore impaired thrombin generation independently of Factor VIII. In return, aPCC results in shortening of the aPTT and INR (Baxter Healthcare Corporation, 2015; CSL Behring, 2015). The use of aPCC is contraindicated in certain populations. Specifically, it should not be used in the presence of known

severe hypersensitivity reaction or anaphylactic reaction to the product, normal coagulation mechanisms, acute thrombosis or embolism, signs of disseminated intravascular coagulation (DIC), and bleeding episodes resulting from the deficiencies or absence of coagulation factors (Baxter Healthcare Corporation, 2015).

aPCC has a general dosing range of 50–100 units/kg. For anticoagulation reversal, doses vary depending upon the severity of bleeding, with emergent life-threatening bleeds receiving higher doses. The maximum daily dose should be no greater than 200 units/kg. FEIBA should be administered as an intravenous injection or infusion at a rate no greater than 2 units/kg/min. Also, vitamin K should be given along with FEIBA (Baxter Healthcare Corporation, 2015).

Notable adverse reactions include nausea, vomiting, diarrhea, dyspnea, chills, dizziness, tachycardia, pruritus, and rash (frequencies undefined). More serious adverse effects include thrombosis (venous and arterial), PE, angioedema, and myocardial infarction (Baxter Healthcare Corporation, 2015).

Because aPCC contains activated Factor VII and inactivated Factors II, IX, and X, it repletes the factors inhibited by warfarin therapy, offering a rapid and effective reversal agent. In a retrospective review conducted by Wójcik, Schymik, and Cure (2009), aPCC (in addition to vitamin K) was compared at fixed doses with FFP in patients taking warfarin with life-threatening bleeding. Patients received either 500 units of aPCC intravenously over 10 min or 1,000 units of aPCC intravenously over 15 min based upon INR of less than 5 or greater than 5, respectively. The primary endpoint for Wójcik et al. (2009) was INR normalization. When compared, 50.7% of patients receiving aPCC achieved an INR of less than 1.4 versus 33.3% of patients receiving FFP ($p = 0.017$). The median time from drug administration to a measured INR of less than 1.4 was 2 hr for aPCC and 25.2 hr for FFP, indicating a faster time to normalization with aPCC. There was no statistically significant difference in survival or hospital length of stay between the products. On the basis of these findings, Wójcik et al. (2009) suggest that aPCC is a safe and efficient alternative to FFP in the setting of urgent reversal for life-threatening bleeding due to warfarin therapy (Stewart & Pettit, 2013). These results were later duplicated by Stewart and Pettit (2013) using the same dosing protocol. Stewart and Pettit (2013) found a mean pretreatment INR of 3.56 and a post-dose INR of 1.22 after a single dose of aPCC. Also, 93% of patients had clinically controlled bleeding (Babilonia & Trujillo, 2014).

Rivaroxaban, apixaban, and edoxaban are Factor Xa inhibitors, and dabigatran is an oral DTI. By providing supplement Factors II and X, aPCC would be expected to reverse the effects of Factor Xa and DTIs. Numerous animal studies have been conducted to evaluate the ability of aPCC to reverse these newer agents. A study conducted by van Ryn, Ruehl, Priepke, Hauel, and Wienen (2008) evaluated the reduction in bleeding times in rat tails in vivo after receiving dabigatran (30 mg/kg), followed by aPCC (100 units/kg). Bleeding times were significantly increased from baseline after administration of dabigatran (from 171 to 495 s) but were completely reversed to baseline 5 min after the administration of the reversal agent (van Ryn et al., 2008). In an ex vivo study in healthy volunteers, patients were given a single 150-mg dose of dabigatran and blood samples were compared from baseline 2 hr after administration to assess peak concentrations (Perzborn et al., 2013). FEIBA (80 units/kg) was then administered. After administration, thrombin generation was observed to increase above baseline levels (Perzborn et al., 2013).

aPCC offers several advantages over FFP. Typically, large volumes of FFP are required for adequate reversal. There is also lack of knowledge regarding the volume of plasma necessary for full reversal of DOACs. aPCC offers a small-volume alternative that can be reconstituted and administered in a short amount of time (Awad & Cocchio, 2013; van Ryn et al., 2008). Although there are many benefits to the use of aPCC, there are also some noteworthy adverse effects including

an increased risk for thrombotic events. Patients with coronary heart disease, liver disease, DIC, or postoperative immobilization, elderly patients and neonates, and patients receiving greater than 200 units/kg/day are at the greatest risk for an adverse thrombotic event. aPCC is a pooled, human-derived product with the inherent risk of transmission of infectious agents such as viruses. To date, there have been no documented cases of transmission of infectious diseases via these pooled factor products (Baxter Healthcare Corporation, 2015). Even though the new reversal agents have been shown to be effective, they are associated with substantial costs. Refer to Table 2 for a list of the agents and their corresponding costs. It is important to keep in mind that this chart is not reflective of the total cost for reversal per patient, as the doses of these products are weight based in most instances.

PCC Human (Kcentra)

Kcentra (four-factor prothrombin complex concentrate [human]; 4F-PCC) is a blood coagulation factor replacement product that contains clotting Factors II, VII, IX, and X in the inactive form, as well as antithrombotic proteins C and S. On the basis of the factor composition, 4F-PCC is beneficial in patients who are deficient in Factors II, VII, IX, and X after receiving VKAs such as warfarin. Currently, 4F-PCC is FDA approved for use in treatment of acute major bleeding due to VKA or for urgent reversal of VKA for surgical procedures (CSL Behring, 2015). Although not currently indicated for reversal of DOACs, 4F-PCC has been used off-label for reversal of Factor Xa inhibitors.

The administration of 4F-PCC rapidly replenishes plasma levels of Factors II, VII, IX, and X, thereby overcoming the deficiency in these factors caused by warfarin. As a result, a rapid correction in INR is observed when 4F-PCC is administered. It is contraindicated in patients with known anaphylactic or severe reactions to 4F-PCC or any of its components, those with known heparin-induced thrombocytopenia, given their reaction to heparin because 4F-PCC contains heparin, and patients with known DIC (CSL Behring, 2015).

Dosing of 4F-PCC for VKA reversal is based upon the patient's INR and actual body weight. The recommended dosing for VKA reversal ranges from 25 to 50 units of Factor IX/kg because the dose is dependent upon the Factor IX component. 4F-PCC should always be administered along with vitamin K because 4F-PCC provides immediate replenishment of clotting factors, but vitamin K provides the ability of the liver to endogenously produce more clotting factors, producing a sustained response. The administration rate should not exceed 8.4 ml/min (~210 units/min). If the product is not prepared in the pharmacy and must be prepared at the bedside, the transfer device and the diluent are provided in each box of 4F-PCC. The contents of each package must be reconstituted before the final product can be drawn up in appropriate size syringes or placed in an empty bag if available. After reconstitution, the product must be administered within 4 hr (CSL Behring, 2015). Dosing for the reversal of Factor Xa inhibitors

Table 2. Costs of reversal agents

Reversal agent	Cost
Anti-inhibitor coagulant complex (FEIBA)	$903.93–$5,257.99
PCC human (Kcentra)	$775.00–$1,728.25
Coagulation Factor IX complex (Bebulin)	$544.50–$703.49
Factor IX complex (Profilnine)	$583.00–$1,912.24
Idarucizumab (Praxbind)	$3,500.00

Note. Cost varies on the basis of the size of product purchased; ranges are reflective of price per unit. PCC = prothrombin complex concentrate.

is based solely on patient weight, and INR has no role.

4F-PCC was evaluated in patients receiving VKA who required emergent replacement of vitamin K-dependent clotting factors. In this prospective trial, patients with acute major bleeds and an INR of 2 or greater were randomized to receive 4F-PCC or plasma. The doses of 4F-PCC administered were 25, 35, or 50 units/kg based upon INR and the nominal Factor IX content. 4F-PCC was administered in addition to vitamin K. When compared with plasma, 4F-PCC achieved effective hemostasis in 72.4% of patients versus 65.4% in those receiving plasma demonstrating noninferiority ($p = 0.50$). When comparing the ability to achieve an INR of 1.3 or less within 30 min after administration, 62.2% of subjects receiving 4F-PCC achieved the desired decrease versus 9.6% of subjects receiving plasma displaying superiority ($p < 0.02$).

4F-PCC was also evaluated in a similar randomized controlled trial in patients receiving VKA who required emergent reversal due to urgent surgical intervention or invasive procedure. 4F-PCC, using the aforementioned dosing strategy based on INR, was compared with plasma with regard to hemostatic efficacy and reduction in the INR of 1.3 or less in 30 min. Once again, 4F-PCC displayed noninferiority to plasma for hemostatic efficacy and superiority for achieving an INR of 1.3 or less within 30 min (CSL Behring, 2015).

In the setting of severe and life-threatening bleeding due to anticoagulation from DOACs, it is hypothesized that administering agents to provide excess coagulation factors would saturate DOAC binding sites, leaving unbound factors to restore hemostasis and allow for normal thrombus formation (Liotta, Levasseur-Franklin, & Naidech, 2015). Levi et al. (2014) conducted a study comparing the reversal effects of 3F- to 4F-PCCs in healthy volunteers receiving rivaroxaban. This study concluded that both 3F- and 4F-PCCs have the potential to partially reverse effects of rivaroxaban (Levi et al., 2014). In a study conducted by Eerenberg et al. (2011) evaluating reversal of effects of dabigatran and rivaroxaban in healthy human subjects, 4F-PCC failed to improve aPTT or thrombin time. The authors from this study did conclude that 4F-PCC did not effectively reverse effects of dabigatran (Eerenberg et al., 2011). Similarly, Marlu et al. (2012) evaluated PCC, Factor VII, and FEIBA for correction of the anticoagulant effects of rivaroxaban and dabigatran. In this study, PCC did not correct the altered lag time produced by dabigatran but was effective in correcting effects of rivaroxaban (Marlu et al., 2012).

A variety of side effects and adverse reactions from minor to serious have been attributed to the use of 4F-PCC. The most common adverse reactions are headache (1%–8%), nausea and vomiting (4%–6%), hypotension (5%–7%), and anemia (3%–6%). Among the most serious adverse reactions noted are stroke (1%–2%), PE (less than 2%), and DVT (1%) (CSL Behring, 2015). Patients with underlying disease states that require treatment with a VKA may be at increased risk of thrombotic events with 4F-PCC use due to induction of a procoagulant state (CSL Behring, 2015).

Coagulation Factor IX Complex (Bebulin)

Bebulin is a nonactive Factor IX complex that is extracted from human plasma pools and undergoes a process of nanofiltration and vapor heating to form a purified powder concentrate. It is supplied as a lyophilized powder, with the sterile water used for reconstitution, a transfer needle, and a filter needle used for reconstitution. Once reconstituted, the solution is administered at a rate tolerated by the patient, not to exceed 2 ml/min.

In addition to Factor IX, there is also Factor II, Factor X, and unappreciable amounts of Factor VII in the product. The amount of Factor VII is so small that this is considered to be a three-factor complex. Bebulin does contain a minimal amount of heparin, about 0.15 or fewer international units for every international unit of Factor IX, and therefore is contraindicated in patients with a heparin allergy (Baxter Healthcare Corporation, 2012). Bebulin carries an FDA indication for the treatment or prevention of bleeding in patients with hemophilia B, making its use in the

reversal of anticoagulants off-label. The data for the use of 4F-PCCs for reversal is much more robust, and it is not known whether or not 3F-PCCs will have the same effects as a 4F-PCC when used to reverse Factor Xa inhibitors (Kaatz et al., 2012). As such, Bebulin is unlikely to be chosen for reversal, with the approval of the 4F-PCC Kcentra. Upon administration of Bebulin, plasma levels of Factors IX, II, and X will be increased, replacing any deficient clotting factors (Baxter Healthcare Corporation, 2012; Peacock et al., 2012). Factor IX once activated flows down the intrinsic clotting pathway, activating Factors X to Xa. The end goal of the clotting cascade is that there is conversion of prothrombin to thrombin and the formation of a fibrin clot. Thus, the infusion of exogenous Factor IX is aimed at restoring hemostasis. Side effects such as dizziness, hypotension, urticaria, pyrexia, and chills have all been describe in the clinical trials with this agent for hemophilia and warrant monitoring for such in patients receiving Bebulin for reversal. More serious reactions reported include angioedema, nephrotic syndrome, and thromboembolic events (Baxter Healthcare Corporation, 2012).

Factor IX Complex (Profilnine)

Similar to Bebulin, Profilnine is another Factor IX complex available in the United States that is extracted from human plasma but is solvent detergent treated for purification. Despite the various purification processes these PCCs undergo, transmission for some diseases such as Creutzfeldt–Jakob disease or parvovirus B 19 infection is still possible, however slim (Grifols Biologicals, 2010). It is a three-factor complex and also contains Factors IX, II, and X. Factor VII is present but at very low levels. Both of these 3F-PCCs are dosed in units of Factor IX, and the amounts of the other factors given will vary even at the same Factor IX dose. Profilnine does not contain any heparin, and it is this fact that carves out a niche for its use for reversal. In the event that a patient has a heparin allergy, Profilnine is sometimes chosen when reversal with a PCC is desired. It may be given in combination with FFP or activated Factor VII to supplement the Factor VII concentration that is needed for complete warfarin reversal (Holland et al., 2009; Sarode et al., 2012). The mechanism is similar to the one described previously for PCCs, in that exogenous factors are given to increase the plasma levels, and its use for reversal is also off-label. Adverse reactions include chills, urticaria, nausea, pyrexia, headache, or tingling. Slowing the infusion, not to exceed 10 ml/min, may alleviate some of these. Serious adverse events are similar to those of Bebulin. Profilnine is available in three dosing size ranges: 500 international units (blue package), 1,000 international units (red package), and 1,500 international units (black package). As with all PCCs, because these are human-derived products, there will never be the exact same amount of Factor IX in every box. It comes packaged with the diluent needed for reconstitution as well as a transfer needle. Recommended dosing is similar to that of the 4F-PCCs, and doses used for reversal range from 12.5 to 50 units/kg. The optimum dose of 3F-PCCs for reversal is unknown.

Idarucizumab (Praxbind)

Idarucizumab is the first targeted reversal agent for the new oral anticoagulants approved in the United States. Idarucizumab is a monoclonal antibody fragment that is designed to bind dabigatran and has an affinity for binding that is 350 times that of thrombin, which leads to binding of both free dabigatran and thrombin-bound dabigatran. Efficacy of idarucizumab was demonstrated in the Reversal Effects of Idarucizumab in Active Dabigatran (REVERSE-AD) study. REVERSE-AD included patients taking dabigatran who presented with an acute bleeding event or need for emergent procedure or surgery. The majority of patients (64%) were taking a dose of 110 mg twice daily for atrial fibrillation (96%). The average creatinine clearance was 62 ml/min. Idarucizumab was administered intravenously as two 2.5-g infusions, no more than 15 min apart. Idarucizumab was effective at reversing effects of dabigatran within

minutes after the first of two infusions, as shown by normalization of coagulation laboratory parameters and decreased plasma concentrations of dabigatran in 88%–98% of patients. Of the patients who required an emergent procedure/surgery, normal intraoperative hemostasis was reported in 92% of patients. On the basis of these interim results from REVERSE-AD, idarucizumab was approved by the FDA in October 2015 for use in patients treated with dabigatran when reversal of anticoagulation is indicated for emergent procedures/surgery or when there is life-threatening/uncontrollable bleeding (Pollack et al., 2015).

Headache was the only adverse reaction that occurred in 5% or more of idarucizumab-treated healthy volunteers. However, patients who have received idarucizumab reported the following adverse reactions: hypokalemia, delirium, constipation, pyrexia, and pneumonia. As with the other reversal agents, there is the presence of thromboembolic risk when anticoagulation of these patients is reversed. Patients with increased coagulation parameters and signs and symptoms of bleeding may require an additional 5-g dose based on their prognosis. Of note, patients with hereditary fructose intolerance may be at an increased risk for adverse events due to the presence of sorbitol in the product (Boehringer Ingelheim Pharmaceuticals, 2015b).

Andexanet Alfa (Annexa)

As the use of Factor Xa inhibitors rises, the need for a targeted antidote increases. Andexanet is currently under clinical development and has completed Phase 3 studies. It is a modified Factor Xa decoy protein that is inactive but has the ability to bind both oral and injectable Factor Xa inhibitors. Andexanet has a high affinity and binds Factor Xa inhibitors in a 1:1 ratio (Siegal et al., 2015).

There are little published data on the efficacy of andexanet in this setting. However, there have been two randomized, placebo-controlled trials evaluating andexanet in healthy volunteers, Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Apixaban (ANNEXA-A) and Rivaroxaban (ANNEXA-R). Andexanet was evaluated in both studies as a bolus-only (Part 1) and a bolus plus infusion (Part 2). Thrombin generation was fully restored in those receiving andexanet within 5 min after administration of the bolus dose. It was determined that the dose of andexanet required to reverse effects of rivaroxaban is higher than that required to reverse those of apixaban. This is secondary to the higher initial plasma concentrations and the higher volume of distribution of rivaroxaban. The study investigators did not note any adverse events or development of neutralizing antibodies, which would diminish the efficacy or reversal potential (Ansell, 2016; Ebright & Mousa, 2015; Siegal et al., 2015).

Currently, there is a study actively recruiting patients to evaluate the ability of andexanet to reverse major bleeding with oral anticoagulants (ClinicalTrials.gov number, NCT02329327). Until further studies are conducted, it is unclear what dose is most effective for emergently reversing Factor Xa inhibitors for surgery or critical bleeding and whether that differs from data published from healthy volunteers. In addition, it is unclear whether sequestration of oral Factor Xa inhibitors will allow endogenous levels of Factor Xa to be restored to levels sufficient to produce hemostasis in critical bleeding. Unlike factor repletion, neutralization of Factor Xa inhibitors does not immediately replete endogenous Factor Xa and the complex and dynamic variables of coagulopathy, critical bleeding, and hemostasis are difficult to control for in randomized trials.

CONCLUSION

Because providers in the ED commonly encounter patients taking anticoagulants in the outpatient setting, they should be familiar with the different anticoagulants currently on the market and how to go about reversing the effects of these agents if needed because bleeding is one of the risks associated with

this class of medications. Given that what is kept in stock from hospital to hospital varies, it is imperative that providers be familiar with what reversal agents are available to them at their institution. With that being said, it is also essential for providers to develop guidelines or protocols specific to the reversal of effects of warfarin and the DOACs based on the agents that are readily available to them. Education on the preparation and administration of the reversal agents is critical as well because these medications should be given as quickly as possible.

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