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Faculty Perspectives™

Advancing Anticoagulation Safety: Focus on Factor Xa Reversal

Patient Burden, Unmet Needs, and Professional Guidelines

WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS[1]

See full prescribing information for complete boxed warning

Treatment with ANDEXXA has been associated with serious and life threatening adverse events, including:

- **Arterial and venous thromboembolic events**
- **Ischemic events, including myocardial infarction and ischemic stroke**
- **Cardiac arrest**
- **Sudden deaths**

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.

INDICATION

ANDEXXA (coagulation factor Xa (recombinant), inactivated-zhzo) is a recombinant modified human factor Xa (FXa) protein indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies that demonstrate an improvement in hemostasis in patients.

Limitations of Use

ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban or rivaroxaban.

Faculty Perspectives™

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Advancing Anticoagulation Safety: Focus on Factor Xa Reversal

Patient Burden, Unmet Needs, and Professional Guidelines

A new frontier in anticoagulation was ushered in with the introduction of novel oral anticoagulants, also known as non–vitamin K antagonist oral anticoagulants (NOACs). The first of these agents, dabigatran, is a direct thrombin inhibitor that was approved by the US Food and Drug Administration (FDA) in 2010. The approval of dabigatran was followed closely by the introduction of direct factor Xa inhibitors: rivaroxaban was approved by the FDA in 2011, apixaban in 2012, edoxaban in 2015, and betrixaban in 2017. Collectively, these agents are now commonly referred to as direct oral anticoagulants (DOACs). These medications have revolutionized the prevention and treatment of thromboembolism in its various manifestations, including reduction of stroke risk in patients with nonvalvular atrial fibrillation and treatment of pulmonary embolism with those agents that are approved for this indication. Rivaroxaban in combination with aspirin has received an additional FDA indication to reduce the risk for major cardiovascular events—including cardiovascular death, myocardial infarction, and stroke—in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).[2]

DOACs are widely recognized as having a superior safety profile and similar or superior efficacy to vitamin K antagonists (VKAs).[3] These agents have several advantages over VKAs such as warfarin, with the most notable being the lack of need for laboratory monitoring. Other advantages include the lack of interactions with food, few strong drug interactions, a rapid onset of action, and predictable drug levels.[4] These characteristics also render DOACs preferable anticoagulants to VKAs during perioperative management.[5]

Because of the clinical advantages associated with DOAC therapy, the use of these agents has been steadily on the rise. A large US study found that by 2017, in patients newly started on oral anticoagulation for atrial fibrillation, 78.9% were initiated on DOACs compared with only 21.1% who were initiated on warfarin.[6] According to the apixaban manufacturer's annual report, in 2018, new prescriptions for apixaban outnumbered new prescriptions for warfarin in the United States.[7]

Although DOACs have a superior safety profile compared with VKAs, major bleeding remains a serious risk associated with these agents. In clinical trials of DOACs for the treatment of nonvalvular atrial fibrillation, major bleeding occurred at a rate of 1.4 to 3.6 per 100 person-years, or 1.4% to 3.6% per year.[8] In addition to the risk for major bleeding linked to the use of these agents, patients treated with DOACs can present with the need for an urgent, unplanned surgical procedure. The need for emergency surgery or an unplanned surgical intervention can necessitate the reversal of anticoagulation.[5]

Because of the clinical advantages associated with DOAC therapy, the use of these agents has been steadily on the rise.

Recommendations for reversing anticoagulation with warfarin have been well-established for many years. VKAs such as warfarin work by inhibiting the synthesis of vitamin K–dependent clotting factors, which include factors II, VII, IX, and X, and the anticoagulant proteins C and S.[9] Products historically used to reverse anticoagulation with warfarin or other VKAs include vitamin K, fresh frozen plasma, and such other blood-based products as prothrombin complex concentrate (PCC). These products specifically target and replenish the coagulation factors depleted by VKAs. DOACs, however, exhibit different mechanisms of action than VKAs. The mechanism of action of dabigatran is the direct inhibition of thrombin, whereas the other DOACs work by selective inhibition of factor Xa.[10] Nonspecific treatments for reversal of the effects of DOACs had been in use for serious bleeding events,

when needed, because no specific therapies had been available.

The newer generation of biologic agents designed to reverse the effects of DOACs are unique, however, in that they specifically target and bind the DOAC medication, rapidly reversing and inactivating the drug. Idarucizumab, which was approved by the FDA in October 2015, is indicated for the reversal of the anticoagulant effects of the direct thrombin inhibitor dabigatran.[11] In May 2018, andexanet alfa, the first specific reversal agent for the factor Xa inhibitors rivaroxaban and apixaban, was initially approved under the FDA's Accelerated Approval pathway.[12] In conjunction with this approval, national guidelines and recommendations concerning DOAC reversal have been updated to include treatment with specific reversal agents.

GI bleeding is the most frequently reported major bleed associated with the use of DOACs.

The focus of this article will be on the reversal of factor Xa inhibitors—specifically rivaroxaban and apixaban—as a significant clinical advancement in anticoagulation safety. Clinicians, hospital executives, pharmacists, and other key stakeholders should be aware of the most appropriate and effective treatment options available to reverse major bleeding in patients treated with rivaroxaban and apixaban. Furthermore, all major stakeholders need to ensure that patients and clinicians have access to those therapies that support the best clinical outcomes.

Burden of Illness

The incidence of major bleeding is significantly reduced with DOACs compared with VKAs.[13] Nevertheless, patients who present with a DOAC-related major bleed require access to prompt and appropriate therapy, in view of the morbidity, mortality, and healthcare costs associated with these bleeding events.

Overview of Major Bleeding

The 2017 American College of Cardiology (ACC) Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants provides a useful definition of major bleeding. The authors define a major bleed as bleeding that is associated with hemodynamic compromise, occurs in an anatomically critical site (eg, intracranial), results in a decrease in hemoglobin of ≥2 g/dL, or requires transfusion of ≥2 units of packed red blood cells.[14] Major bleeding or hemorrhage includes intracranial (including intracerebral) hemorrhage (ICH), other critical site bleeding, and gastrointestinal (GI) bleeds.[15]

Major bleeding remains the leading complication associated with the use of oral anticoagulant therapy.[16] Anticoagulants, including DOACs, were the leading cause of drug-related adverse events prompting emergency department visits in the United States from 2013 to 2014.[17] Phase 3 clinical trials of DOACs reported that major bleeding occurred in 1.4% to 3.6% of patients randomized to treatment with a DOAC.[8] A published analysis of the MarketScan Commercial and Medicare databases from January 1, 2015, through December 31, 2015, projected that of approximately 2.9 million US patients treated with factor Xa inhibitors in 2015, nearly 85,000 had been hospitalized for major bleeding.[18]

A real-world comparison of approximately 60,000 US patients treated with DOACs showed that inpatient major bleeding occurred in 1.4% to 2.1% of the participants within 1 to 2 years of initiation of therapy.[19] A Truven Health Analytics DOAC Market Data Report indicated that in 2017, there were approximately 149,000 hospitalizations for a major bleed in the United States in patients on factor Xa inhibitors, along with an estimated 25,400 deaths associated with the use of apixaban and rivaroxaban.[20] Truven Health Analytics estimated that in 2018, approximately 408 US patients were hospitalized each day for an apixaban-related or a rivaroxaban-related bleeding event.[21] It was also estimated that approximately 70 patients would die each day following hospitalization for apixaban-related or rivaroxaban-related bleeds.[21]

The location of major bleeding is most commonly in the GI tract, followed by intracranial bleeding sites and then various other sites. In the ROCKET AF trial of rivaroxaban for the treatment of nonvalvular atrial fibrillation, the proportion of major bleeds was 56% for GI-related bleeding and 14% for ICH.[2] In the ARISTOTLE trial of apixaban for the treatment of nonvalvular atrial fibrillation, the proportion of major bleeding was 39% for GI-related bleeds and 16% for ICH.[22] The UK ORANGE study, published in 2018, evaluated patients hospitalized for major bleeding while on an anticoagulant. Results of the study reported that of 401 patients treated with DOACs, the proportion of major bleeds was 44% for GI bleeding, 37% for intracranial bleeding (including 23% for intracerebral), and 18% for other types of bleeds.[16] The proportion of major bleeds per site in a 2016 to 2018 Andexxa Hospital Chart Audit conducted by Outcomes are shown in the **Figure**.[23]

In addition, patients hospitalized for a major bleeding event often experience other costly complications. Such

events may include admission to an intensive care unit (ICU) or development of such comorbidities as acute respiratory distress syndrome, hemorrhagic stroke, cardiac arrest, sepsis, or pneumonia.[16]

Intracranial and Intracerebral Hemorrhage

ICH is a feared, often fatal complication of anticoagulant therapy. Approximately 1 in 6 initial hospital admissions for ICH are related to anticoagulation.[24] ICH encompasses several types of bleeds, including subdural hemorrhage, subarachnoid hemorrhage, and intracerebral bleed. Although all of these are serious in nature, intracerebral hemorrhage is the most clinically significant and devastating complication. Intracerebral hemorrhage is associated with a substantial risk for permanent neurologic disability and death.[25] Many clinical studies, however, do not specifically differentiate between the various types of ICH in their data analysis. As discussed earlier in this article, in the UK ORANGE study, among patients treated with DOACs, of the 37% of reported bleeds that were intracranial in location, 23% were intracerebral bleeds. In other words, the majority of ICHs were, in fact, intracerebral bleeds. Furthermore, the rate of intracerebral DOAC bleeds was not found to differ significantly from the 22% bleed rate reported with warfarin therapy.[16]

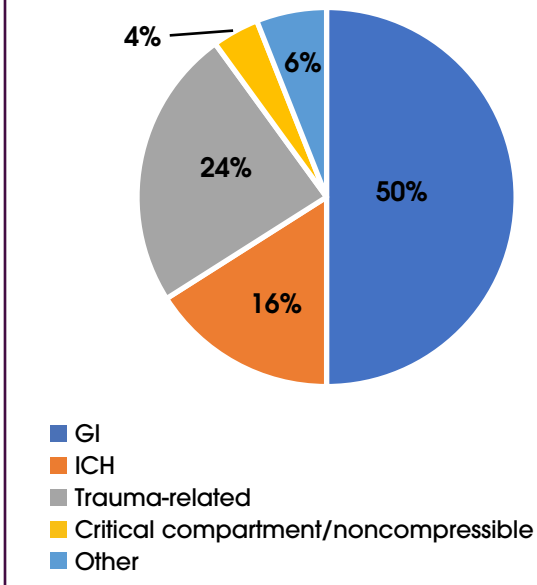
In phase 3 clinical trials, the annual risk for ICH has been reported as 0.23% to 0.5% in patients using DOACs. The RE-LY trial reported the annual incidence of ICH with dabigatran as 0.23% to 0.30% per year.[26] The ARISTOTLE trial found an annual incidence of ICH of 0.33% per year with apixaban.[27] The ROCKET-AF trial reported a rate of 0.5 per 100 patient-years with rivaroxaban.[28] The ENGAGE AF-TIMI 48 trial reported rates of ICH of 0.26% with low-dose edoxaban and 0.39% with high-dose edoxaban.[29]

Mortality is high in patients with ICH. In 2001, Qureshi and colleagues reported that the mortality rate ranged from 23% to 58% within 6 months following spontaneous ICH.[30] The ROCKET-AF trial, published in 2014, demonstrated a mortality rate following ICH of 43% within 30 days and 51% by 90 days after the event in patients treated with either warfarin or rivaroxaban.[25] In patients treated with rivaroxaban, the 90-day mortality rate following ICH was 48%.[25] In this trial, no significant difference in mortality from ICH was reported with rivaroxaban compared with warfarin.[25] The ARISTOTLE trial demonstrated a 30-day mortality following ICH of 45% in apixaban-treated patients.[31]

Other studies have also shown no difference in mortality rates between DOAC-related ICH and warfarin-related ICH.[32]

Furthermore, in-hospital mortality rates of patients with ICH are higher among those who had been on anticoagulation—either DOAC or warfarin—compared with those who had not.[33] A study of more than 141,000 patients with ICH across 1662 US hospitals found that the in-hospital mortality rate of ICH in those who had been on DOACs was 26.5%, compared with 32.6% in those who had been treated with warfarin and 22.5% in those who had not been on oral anticoagulation therapy.[33] At the time of this study, there was no specific reversal agent available for factor Xa inhibitors, which the authors cited as a "major concern."[33] They went on to conclude the following: "Immediate management is necessary for patients with life-threatening bleeding including ICH, and appropriate reversal agents should be administered."[33]

Figure. Proportion of Major Bleeds by Site[23]



GI indicates gastrointestinal; ICH, intracranial hemorrhage.

Gastrointestinal Bleeding

GI bleeding is the most frequently reported major bleed associated with the use of DOACs. In the UK ORANGE study, researchers found that the GI tract was the most common site of major bleeding among the 401 patients treated with DOACs at the time of hospital admission.[16] Randomized clinical trials showed that GI bleeds account for 39% and 56% of all major bleeds in patients treated with apixaban and rivaroxaban, respectively.[2,22] A 2017 study by Milling and colleagues found that 52% of all acute major bleeding associ-

Table 1. Specific Anticoagulation Reversal Agents[5]

Class	Vitamin K Antagonists	Direct Thrombin Inhibitors	Factor Xa Inhibitors
Drug(s)	Warfarin	Dabigatran	Rivaroxaban and Apixaban
Reversal Agent	4-Factor Prothrombin Complex Concentrate	Idarucizumab	Andexanet Alfa

ated with factor Xa inhibitors were GI bleeds.[15] The authors of the study noted that the patients "had a high mortality rate despite aggressive management in the absence of a specific reversal agent."[15] In this study, the mortality rate for a major bleed from a GI source was 14%.[15]

Although many GI bleeds are not major bleeds, reversal of oral anticoagulation is recommended in a life-threatening or critical site bleed, or in those situations in which bleeding cannot be controlled.[14]

Bleeding at Other Critical Sites

Critical site bleeds are defined as bleeds that compromise the function of an organ. In addition to ICH and other central nervous system bleeds, such as intraocular or spinal hemorrhage, other critical site bleeds include thoracic, intra-abdominal, retroperitoneal, intra-articular, and intramuscular bleeds. Examples of critical thoracic bleeding are pericardial tamponade; airway bleeding, including posterior epistaxis; and hemothorax.[14] Critical site bleeds may cause severe disability and require surgical interventions to control the bleeding.[14] As illustrated in the Figure, a 2016 to 2018 Andexxa Hospital Chart Audit reported that the proportion of critical compartment/noncompressible bleeds was 4%.[23]

Patients with major bleeding from DOACs require the use of significant healthcare resources, including complex care in ICU settings with numerous physician specialty consultations.[15] The burden of major bleeding will likely increase as greater numbers of patients are initiated on DOAC therapy.[15]

Specific Approved Agents

Although reversal strategies for warfarin have been widely publicized for many years, reversal agents for the newer DOACs became available more recently (**Table 1**).[5] Andexanet alfa was approved by the FDA in May 2018 as the first specific reversal agent for the factor Xa inhibitors rivaroxaban and apixaban.[12] Other FDA-approved, specific reversal agents include 4-factor PCC (4F-PCC) and idarucizumab. The FDA approved 4F-PCC in April 2013 for reversal of the effects of the VKA warfarin. Idarucizumab was approved in October 2015 as a reversal agent for the direct thrombin inhibitor dabigatran.[11] The clinical importance of each of these reversal agents rests on their ability to promptly return the patient to his or her native pre-anticoagulated state. Vitamin K can also be used to reverse the effects of warfarin, although its action is slower than that of 4F-PCC.[10] Agents used in the nonspecific reversal of anticoagulants include fresh frozen plasma and other blood products. The use of fresh frozen plasma, however, is not recommended for the reversal of rivaroxaban or apixaban.

Joint Commission Sentinel Event Alert: Issue 61

In July 2019, The Joint Commission published a Sentinel Event Alert titled "Managing the Risks of Direct Oral Anticoagulants."[34] The Alert, which was released in response to an increase in reported adverse events associated with DOACs, was intended to provide guidance on the safe use and management of these agents for all healthcare providers and healthcare organization leaders across all settings.[34] The Alert notes that serious and potentially lethal consequences of DOAC use can be avoided with appropriate and timely treatment. In addition, the Alert highlights the fact that DOACs present different risks than heparin and warfarin and have different reversal mechanisms.[34] A reversal mechanism that works with one DOAC may not work with another.[34]

The Alert outlines 6 specific recommendations. Clinician awareness regarding appropriate interventions for each DOAC is repeatedly emphasized, as well as the importance of clinician awareness with respect to variations in patient presentation and appropriate reversal agents.[34] Among the suggested actions was a recommendation that organizations use or create evidence-based protocols and apply practice guidelines for reversal of the effects of specific anticoagulants, as well as the management of associated bleeding events.[34]

Another key point made in the Alert is the fact that hospitals and critical access hospitals should stock blood products and the reversal agents needed for each type of anticoagulant.[34] The Alert refers often to The Joint Commission's National Patient Safety Goal 03.05.01 regarding anticoagulant therapy: "Reduce the likelihood of patient harm associated with the use of anticoagulant therapy."[34] Finally, the Alert

lists additional resources, including the 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants.[34]

Unmet Needs

The need for a rapid and specific reversal agent for factor Xa inhibitors has been well-recognized. That need was unmet until the initial approval of andexanet alfa in May 2018, however, and broad commercial availability of the agent in 2019.

Some of the drivers of that need include the rapid growth and widespread adoption of factor Xa inhibitors, the economic costs and projections regarding factor Xa–related bleeds, and the lack of truly suitable alternatives for DOAC anticoagulation reversal. Another concern for those caring for patients with intracerebral hemorrhage is a 2018 study that demonstrated the lack of effect of 4F-PCC on the prevention of hematoma enlargement in patients with intracerebral hemorrhage.[35]

Rapid Growth and Widespread Adoption of the Factor Xa inhibitors Rivaroxaban and Apixaban

All data suggest that prescriptions for DOACs have increased dramatically since the introduction of these agents to the market. An analysis of Medicare Part D claims for DOACs showed that claims for these medications rose from 15.4% of total claims for oral anticoagulants in 2013 to 31.0% of total claims by 2015.[36] By 2017 in the United States alone, an estimated 6.8 million prescriptions were written for rivaroxaban[37] and approximately 8.6 million were written for apixaban.[38]

Even among less affluent individuals, prescriptions for DOACs have been found to outnumber those for warfarin. A study of Medicare and Medicaid patients in the District of Columbia demonstrated that in 2016, among prescriptions for Medicaid patients, DOACs outnumbered those for warfarin (5198 vs 3402, respectively).[39] Among Medicare patients, DOAC prescriptions also outnumbered those for warfarin (15,066 vs 11,219, respectively).[39]

A large study from the Johns Hopkins Bloomberg School of Public Health, published in 2018, evaluated a total of 112,187 patients receiving oral anticoagulants for nonvalvular atrial fibrillation. The results of the study showed that in 2010, of patients newly started on oral anticoagulants, more than 90% were initiated on warfarin and fewer than 10% were initiated on DOAC therapy. By the first quarter of 2017, however, only 21.1% of patients were initiated on warfarin and 78.9% were initiated on DOACs.[6]

Sales figures tell a similar story. In the United States, rivaroxaban sales increased almost 6% from 2017 to 2018.[40] Sales of apixaban increased 32% over that same time period.[7] In 2018 in the United States, new prescriptions for apixaban alone outnumbered new prescriptions for warfarin.[7]

Other drivers for growth in DOAC market share are the recent updates across several well-respected professional societies that now endorse the use of DOACs over warfarin.[3,5,41] Further catalysts for growth include expanded rivaroxaban indications for chronic CAD and PAD,[2] as well as the loss of market exclusivity for apixaban[42,43] in December 2019 and for rivaroxaban[44] anticipated in August 2024. In addition to growth of market share, the eligible patient population may be expanding, as baby boomers age and require treatment for such comorbidities as atrial fibrillation and venous thromboembolism.

An understanding of recent advancements in DOAC reversal strategies is vital for reducing the substantial morbidity, mortality, and poor long-term clinical outcomes among DOAC-treated patients who develop major bleeding.

Economic Costs and Projections Regarding Factor Xa–Related Bleeds

In patients treated with factor Xa inhibitors, major bleeding events are a clinically significant cause of mortality and hospitalization in the absence of a specific reversal agent, as evidenced by the results of the Truven Health Analytics study.[20] From 2011 to 2014, the top 20% of hospital payments for bleeding in patients treated with factor Xa inhibitors averaged $153,000 for ICH, $108,000 for bleeding at another critical site, $96,000 for major trauma, and $59,000 for GI bleeding with hemodynamic instability.[45] An Optum database shows that approximately 2.5% of patients treated with factor Xa inhibitor were hospitalized with a bleeding event and approximately 5.5% were readmitted within 90 days.[46] Bleeding admissions are expected to rise by 30% each year as factor Xa inhibitor use increases.

When analyzing healthcare utilization of major factor Xa inhibitor–related bleeds by site, ICH bleeds (including intracerebral, subdural, and subarachnoid) were associated with the longest average length of hospital stay, as shown in **Table 2**.[45]

US 2018 projections anticipated that 169,099 patients would be admitted to a hospital for an apixaban- or rivaroxaban-related bleeding event.[21] This translates into 408 patients each day in 2018. Projected mortality was 70 patients dying each day from bleeding related to apixaban or rivaroxaban.[21] On a per-hospital basis, it is estimated that approximately 3 factor Xa inhibitor–related bleeds are reported per US hospital each month.[23]

Another concern is that approximately half of all patients who experience a bleed while on factor Xa inhibitor therapy

Table 2. Hospital Length of Stay for Bleeds Associated with the Use of Factor Xa Inhibitors[45]

Major Bleeding Site	Top Quintile Average Length of Stay[a]
Intracranial hemorrhage	17 days
Other critical site bleeding	13 days
Major trauma	10 days
GI bleed with hemodynamic instability	10 days

[a]Top 20% average length of stay.
GI indicates gastrointestinal.

are reinitiated on treatment within 90 days of the bleeding event.[46] In a 2017 study by Milling and colleagues, 41% of patients were restarted on anticoagulation within 30 days of experiencing an acute major bleeding episode.[15]

Lack of Truly Suitable Alternatives for DOAC Anticoagulation Reversal

Prior to FDA approval of andexanet alfa, options for reversing factor Xa inhibitors were limited to the use of nonspecific therapies. Nonspecific therapies were utilized because no specific treatment was available. In addition to general measures for the management of bleeding (ie, cessation of anticoagulant and antiplatelet therapies, bleeding control, transfusions if needed, and volume and hemodynamic support), nonspecific reversal strategies include hemodialysis, activated charcoal, 4F-PCCs, tranexamic acid, and desmopressin.[47] None of these options, however, specifically reverse the effects of DOAC medications. Activated charcoal inhibits oral absorption of the drug, whereas hemodialysis is intended to remove the medication circulating in the bloodstream. One review article indicates that hemodialysis is not effective for the removal of rivaroxaban or apixaban because both of these agents are highly protein-bound (ie, 95% and 87%, respectively).[48] Tranexamic acid is an antifibrinolytic agent that inhibits the breakdown of blood clots[49]; desmopressin (a synthetic analog of vasopressin) increases levels of von Willebrand factor and coagulation factor VIII.[50]

In the absence of a specific reversal agent, some clinicians have advocated the off-label use of PCC and activated PCC (aPCC). In particular, 4F-PCC is mentioned in several protocols on the management of life-threatening or uncontrolled bleeding related to DOAC therapy.[51] Use of 4F-PCC has been recommended when the specific reversal agent was not available or when the identity of the anticoagulant was unknown.[52] The use of 4F-PCC and other PCCs, however, has not been proven effective for DOAC reversal.[51] The existing literature regarding these agents includes retrospective case reviews with inconsistent data and results. The approved indication for 4F-PCC is for reversal of the effects of the VKA warfarin, with 4F-PCC lacking FDA approval for reversing the effects of DOACs. Available evidence suggests that the use of 4F-PCC for factor Xa reversal may be no more effective than withholding anticoagulation.[53]

A 2015 review by Dzik reported that the 4F-PCC product available in the United States did not differ from placebo with respect to anti-Xa activity.[51] In vitro studies conducted by Lu and colleagues in 2019 indicated that PCCs showed no apparent reversal activity with therapeutic levels of factor Xa inhibitors.[54] Use of a PCC produced only a marginal indirect effect on thrombin generation through supplementation of coagulation factors when the inhibitor concentrations were sufficiently low. Further, PCC did not appear to have an effect on the inhibition of thrombin generation by apixaban or rivaroxaban unless the factor Xa inhibitor concentration was <75 ng/mL.[54]

Another disadvantage associated with the use of 4F-PCC is that the treatment itself may be prothrombotic. Use of 4F-PCC has been associated with arterial and venous thromboembolic events.[55]

The Importance of Hematoma Expansion in Intracerebral Hemorrhage

In 2014 Yaghi and colleagues reported that hematoma expansion is an independent determinant of outcome in intracerebral hemorrhage. The investigators also noted that predictors of poor outcome in patients with intracerebral hemorrhage include early hematoma expansion, larger hematoma volume, and the presence of intraventricular hemorrhage, in addition to advanced age and low Glasgow coma scale.[56] Furthermore, the researchers state that "the only potentially modifiable predictor is hematoma expansion, which may occur in 16% to 38% of patients and its prevention may possibly alter the course and outcome of the disease."[56]

Yaghi and colleagues defined hematoma expansion as at least a 33% increase in hematoma volume over 24 hours.[56] In their study of predictors of hematoma expansion in patients with spontaneous intracerebral hemorrhage, the researchers found that anticoagulation therapy (with warfarin) was one of

the few predictors of hematoma expansion, despite the use of vitamin K and fresh frozen plasma to reverse warfarin-induced coagulopathy. Their study included 200 patients with intracerebral hemorrhage. ICU length of stay (8 ± 8 days with hematoma expansion vs 4 ± 6 days without; $P = .004$), intubation rate (82% vs 32%, respectively; $P = .034$), and hospital mortality (68% vs 20%, respectively; $P < .001$) were all significantly associated with hematoma expansion.[56]

4-Factor Prothrombin Complex Concentrate Had No Effect Whatsoever on Prevention of Hematoma Expansion in Patients with Intracerebral Hemorrhage

A 2018 study by Gerner and colleagues evaluated 146 patients with intracerebral hemorrhage related to DOAC administration.[35] Of the 146 patients, 94 were treated with 4F-PCC prior to follow-up imaging; 37 did not receive treatment with 4F-PCC but did undergo follow-up imaging. The primary study outcome was the occurrence of hematoma enlargement, which was defined as a relative parenchymal volume increase of >33% from initial imaging to follow-up imaging.[35] Hematoma enlargement occurred in 35.1% (33 of 94) of patients who had been treated with 4F-PCC and in 35.1% (13 of 37) of those who did not receive 4F-PCC therapy.[35] In other words, 4F-PCC had no clinical benefit in reducing hematoma enlargement in patients with intracerebral hemorrhage.

Secondary outcomes of the Gerner study were in-hospital mortality, 3-month mortality, and 3-month functional outcomes.[35] In-hospital mortality rates and 3-month mortality rates did not differ among patients with and without 4F-PCC treatment. Overall in-hospital mortality was 19.9% (29 of 146 patients) and overall 3-month mortality was 29.5% (43 of 146 patients).[35] Functional outcome was categorized as favorable (modified Rankin score [mRS] of 0-3) or unfavorable (mRS of 4-6).[35] In those treated with 4F-PCC, a favorable outcome at 3 months was achieved in 31.1% (32 of 103) of patients versus 39.5% (17 of 43) in those not treated with 4F-PCC therapy—a finding that did not achieve statistical significance ($P = .32$).[35]

Treatment Guidelines

With the recent FDA approval of specific DOAC reversal agents, several key professional societies and organizations have updated their bleed reversal management guidelines regarding oral anticoagulants. Evidence from clinical trials has contributed to an improved understanding regarding the most appropriate management of factor Xa–associated bleeding. The following section provides a summary of these updates.

2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

Published in December 2017, this report was designed to address the clinical problem of management of bleeding in patients treated with anticoagulants, including DOACs and VKAs, for any indication.[14] The decision pathway produced by the writing committee was comprehensive and considered multiple factors, including bleeding severity, acute medical and surgical management, the need for reversal, the appropriateness and time of restarting anticoagulation, and the effects of relevant comorbidities and concomitant pharmacotherapy. Ultimately, the recommendations contained within the decision pathway included guidance for the temporary or permanent interruption of therapy, approaches to the management of bleeding, treatment with reversal agents, and indications for and timing of the reinstitution of anticoagulant therapy.[14]

With regard to major bleeds, reversal is recommended with a specific reversal agent if the agent is available.[14] The report also states that in situations involving life-threatening bleeds, critical site bleeds, or other scenarios in which bleeding cannot be controlled, reversal of the anticoagulant agent is required.[14] At the time the 2017 ACC article was published, no specific antidote was clinically available for the reversal of factor Xa inhibitors.[14] A section on andexanet alfa was included, however, which described the 90% reduction in anti–factor Xa activity and active drug levels accomplished in the clinical trial.[14]

The potential utility of PCC, aPCC, and 4F-PCC was also addressed. The task force explained that neither PCC nor aPCC demonstrated efficacy or safety in factor Xa inhibitor–treated patients experiencing bleeding or requiring urgent surgery.[14] Additionally, the task force determined that the results observed with 4F-PCC were not consistent across all parameters and studies.[14]

An online and mobile application (ManageAnticoag) derived from this 2017 guideline was released by the ACC in June 2018. The tool recommends andexanet alfa as first-line therapy when reversal of apixaban or rivaroxaban is needed because of a life-threatening or critical site bleed, or in situations in which bleeding cannot be controlled by other measures.[57,58]

CHEST Guideline and Expert Panel Report

In November 2018, the American College of Chest Physicians published "Antithrombotic Therapy for Atrial Fibrillation"—a guideline and expert panel report. The guideline endorses apixaban, edoxaban, or dabigatran 110 mg for patients with prior unprovoked bleeding, warfarin-related

bleed, or at high risk for bleeding.[41] There is also a recommendation for either VKAs or NOACs to be utilized for at least 3 weeks prior to and 4 weeks following electrical or pharmacologic cardioversion.[41]

The document mentions that many physicians and patients have been reluctant to use NOACs because of the perception that they cannot manage bleeding associated with NOACs, particularly without a specific antidote or reversal agent.[41] By the time the document was published, however, the FDA had approved andexanet alfa. The panel provided recommendations for the management of bleeding for patients receiving NOACs. These included specific reversal agents for NOACs, including idarucizumab and andexanet alfa. The guideline does recommend administering an NOAC-specific reversal agent or PCC if a reversal agent is not available for severe or life-threatening bleeding.[41] Multiple specific reversal agents are discussed, including idarucizumab, andexanet alfa, and ciraparantag.[41]

Professional societies and other key stakeholders are increasingly recognizing the need for specific anticoagulation reversal agents.

Additional direction on the management of NOAC-associated bleeding describes the situations in which reversal agents are most appropriate. The document also points out that nonspecific reversal agents are not only less effective than specific reversal agents, but they may also have prothrombotic effects. Furthermore, these agents have not been shown to improve outcomes.[41] The report also indicates that although coagulation testing can identify patients likely to benefit from specific reversal agents, it is still reasonable to administer the reversal agent immediately in patients with life-threatening bleeding that is presumed to be due to NOAC therapy without waiting for the results of a laboratory test.[41]

American Society of Hematology (ASH)

In November 2018, the "American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy" were published.[59] Its recommendations 18a and 18b indicate that for patients with life-threatening bleeding during oral factor Xa inhibitor treatment of venous thromboembolism, the ASH guideline panel suggested the use of 1 of 2 options in addition to the cessation of oral direct factor Xa inhibitor therapy. One option was the administration of 4F-PCC. The other option was the administration of coagulation factor Xa (recombinant), inactivated-zhzo—that is, andexanet alfa. The guideline endorsed proceeding with the administration of andexanet alfa as opposed to not proceeding. The recommendation levels for both of these (18a and 18b) were conditional based on low certainty of the evidence available at the time.[59]

2019 ACC/AHA/HRS Focused Update of the 2014 Atrial Fibrillation Guideline

The 2019 ACC/American Heart Association (AHA)/Heart Rhythm Society (HRS) guideline update on atrial fibrillation issued a Class IA recommendation (their strongest) endorsing NOACs preferentially over warfarin in NOAC-eligible patients with atrial fibrillation (except in those with moderate to severe mitral stenosis or a mechanical heart valve).[3] The guideline recommends idarucizumab as a reversal agent for dabigatran (class IB recommendation)[3] and andexanet alfa (class IIa recommendation) for reversal of rivaroxaban and apixaban[3]; the indications are those approved by the FDA.

Anticoagulation Forum

In March 2019, the Anticoagulation Forum, a North American organization of anticoagulation providers, published comprehensive guidance pertaining specifically to the use of DOAC reversal agents. They recommend the administration of reversal agents for DOACs when patients are experiencing bleeding that is "life-threatening, into a critical organ, or is not controlled with maximal supportive measures and there is demonstration or reasonable expectation that the patient has clinically relevant plasma DOAC levels."[5] Guidance statement 2 endorses idarucizumab for the reversal of dabigatran-associated major bleeding.[5] Guidance statement 3 endorses andexanet alfa for the reversal of rivaroxaban-associated or apixaban-associated major bleeding.[5] Guidance statement 6 suggests andexanet alfa therapy in factor Xa inhibitor–treated patients who need to undergo an urgent procedure in which reversal is warranted.[5] The full recommendations are summarized in a flow chart.[5]

American College of Emergency Physicians (ACEP)

In November 2019, ACEP published new consensus recommendations regarding anticoagulation reversal strategies

in the emergency department setting.[60] The ACEP statement highlights the importance of emergency treatment and supportive interventions, including source control, diagnostic testing, and risk stratification for anticoagulant-associated bleeding.[60] The recommendations include an algorithm for anticoagulation reversal or replacement. Within the algorithm decision tree, ACEP recommends andexanet alfa as the tier 1 reversal agent for patients receiving apixaban, betrixaban, edoxaban, and rivaroxaban. PCC (4F-PCC preferred over 3F-PCC) is suggested for DOAC treatment only if the first-line reversal agent (ie, andexanet alfa) is not available.[60]

Conclusion

Overwhelming evidence demonstrates the significant clinical and economic burden associated with DOAC major bleeding. DOACs have gained rapid adoption based on their ease of use and superior safety compared with warfarin and other VKAs. The use of DOACs is expected to increase with expanding indications and endorsements by multiple professional societies. The ACC now endorses DOAC therapy preferentially over warfarin in patients who are DOAC-eligible for stroke prophylaxis or in those with atrial fibrillation, in the absence of a mechanical heart valve or moderate to severe mitral stenosis.[3]

Professional societies and other key stakeholders are increasingly recognizing the need for specific anticoagulation reversal agents, particularly given the paucity of clinical support for the use of 4F-PCC to reverse non–VKA-associated bleeds. In emergent situations, the facility would have these agents on hand to quickly and effectively reverse the effects of anticoagulation-related major bleeds. To that end, in July 2019, The Joint Commission issued Sentinel Event Alert 61 on managing the risks of DOACs.[34] Among the key messages of that Alert are the following: (1) Evidence-based protocols and practice guidelines should be used for the reversal of anticoagulation and the management of bleeding events, and (2) Hospitals and critical access hospitals should stock the specific reversal agents for use with each type of DOAC.[34]

Andexanet alfa is a biologic agent that specifically targets and binds to factor Xa inhibitors, rapidly reversing and inactivating the drug following completion of an IV bolus and sustained throughout IV infusion up to 120 minutes.[61] Hospital pharmacies should consider stocking andexanet alfa so that rivaroxaban- or apixaban-treated patients who present with life-threatening or uncontrolled bleeding have access, without delay, to the most effective therapy. ■

Intracranial Hemorrhage and Factor Xa Inhibitors

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Sarasota Memorial Hospital (SMH), located in Sarasota, Florida, is a large community hospital with a Comprehensive Stroke Center. Approximately 120 patients present with intracranial hemorrhage (ICH) to SMH each year. Mortality and disability rates are high in patients with ICH, with those who survive often having a poor quality of life. In patients with ICH related to anticoagulation, the outcomes are even worse.

Of all ICHs, approximately 25% are related to anticoagulation. Mortality rates and poor outcomes are more than double in patients with ICH associated with anticoagulation compared with those who are not receiving anticoagulation. For patients with ICH associated with the use of factor Xa (FXa) inhibitors, inpatient mortality is approximately 25% and 30-day mortality is approximately 50%. Overall, only 20% of patients are independent 6 months following ICH; 60% are independent 6 months following ischemic stroke.

Hematoma expansion is one of the most significant predictors of poor outcome in patients with ICH.[62,63] In fact, only 5 milliliters (1 teaspoon) of hematoma expansion is associated with a 25% increased risk for mortality.[63] In the first 3 hours following the onset of ICH stroke symptoms, about 38% of hematomas expand >33%.[64,65] In the next 3 to 6 hours, 10% to 15% of hematomas continue to expand if left untreated.[66] Anticoagulation nearly triples the likelihood of hematoma expansion.[67] Within this context, rapid reversal of anticoagulation is critical to mitigate mortality and disability from ICH.[68-70]

Over the past several years, SMH has observed a trend regarding anticoagulant use in patients presenting with ICH. In 2015 at SMH, 14% of patients with anticoagulant-associated

ICH had been on an FXa inhibitor and 86% had been on warfarin.[66] By 2018, 67% of patients with anticoagulant-associated ICH had been on an FXa inhibitor and 33% had been on warfarin. The majority of anticoagulant-associated ICHs at SMH are now related to anticoagulation with FXa inhibitors, primarily rivaroxaban and apixaban.

An important advancement in the reversal of anticoagulation with warfarin was the development of prothrombin complex concentrates (PCCs).[71] The use of PCCs was a significant improvement over the use of fresh frozen plasma (FFP). Although FFP was effective, 4-factor PCC (Kcentra®, Kankakee, IL: CSL Behring LLC; 2018) was even more effective in achieving a speedy reduction in international normalized ratio. It was also quicker to administer and required less volume.[71]

When direct thrombin inhibitors and FXa inhibitors were introduced, no specific reversal antidote was available for either type of direct oral anticoagulant.[4] That changed in 2015, when idarucizumab was approved by the US Food and Drug Administration (FDA).[11] The use of idarucizumab, however, was very specific for reversing the effects of the direct thrombin inhibitor dabigatran.[72]

However, a specific reversal agent for FXa inhibitors was lacking.[73] Although physicians may administer PCCs in patients requiring urgent FXa inhibitor reversal, there remains a lack of controlled clinical trial evidence supporting their use in this patient population. No clearly elucidated mechanistic rationale describes how PCCs can be effective in specifically reversing the FXa inhibitor–induced anticoagulation effect. Most of the published studies on PCCs are anecdotal in nature or based on retrospective data.[60] Since these studies have many inherent biases and design issues, the quality of evidence is very weak.[53] Furthermore, PCCs are not FDA-approved for the reversal of FXa inhibitors. In May 2018, andexanet alfa was the first agent specifically approved for the reversal of anticoagulation in patients treated with rivaroxaban or apixaban who experience life-threatening or uncontrolled bleeding.[74] This development provided SMH with a new option in treating patients who require timely, effective rivaroxaban or apixaban reversal.

Many patients who experience bleeding can be managed with conservative measures. Some patients do require specific reversal of anticoagulation, however, due either to life-threatening bleeding or to the need for an urgent surgery or procedure. From 2015 to 2017, the medical staff at SMH saw about 2 patients per month with critical or life-threatening FXa inhibitor–related bleeds. As FXa inhibitor use has increased, the hospital now sees an average of 3 to 4 patients per month who present with life-threatening bleeding related to FXa inhibitor use. These patients include those with ICH, gastrointestinal bleeding, or major trauma, all of whom often have unstable hemodynamics. Some of these patients require emergent or urgent surgery or procedures.

The Anticoagulation Committee is responsible for the oversight and utilization of all anticoagulation reversal agents at SMH. The committee is represented by at least 6 specialties, including pharmacy, neurology, hematology, and trauma. The committee has developed institutional, evidence-based guidelines for use with all anticoagulation reversal agents. These guidelines have been distributed to all staff and are used throughout the institution. Every 2 months the committee meets and reviews all cases.

In 2018, SMH made a decision to stock each FDA-approved specific reversal agent. This decision demonstrates the hospital's commitment to providing state-of-the-art treatment and quality patient care. ■

Anticoagulant-Related Bleeding from DOACs

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Anticoagulant use is a leading cause of drug-related adverse events among patients presenting to hospital emergency departments in the United States.[17] When a patient presents to the emergency department with anticoagulant-related bleeding, specific reversal of anticoagulation may be required.[14] In the past, patients on warfarin were treated with vitamin K to restart the synthesis of clotting factors. After the development of prothrombin complex concentrates (PCCs), however, patients with warfarin-related bleeding were treated with products such as 4-factor (II, VII, IX, X)

PCC (4F-PCC); 3-factor (II, IX, X) PCC (3F-PCC); or the factor VIII inhibitor bypassing agent FEIBA© (Westlake Village, CA: Baxter Healthcare Corporation; 2013).[14,75] Historically, patients who experienced anticoagulant-related bleeding associated with the use of direct oral anticoagulants (DOACs) were also treated with PCCs, as no specific reversal agents were available for DOACs until more recently.[14]

Today, specific reversal agents are available for some of the DOACs.[60] These newer agents are tailored and designed specifically to reverse the effects of these anticoagulants.[1,76,77] They do not bind to other receptor sites or targets, and demonstrate minimal intrinsic anticoagulant or procoagulant properties.[72,78]

At Brigham and Women's Hospital (BWH) in Boston, Massachusetts, the medical staff treats many patients who present with anticoagulant-related bleeding. On average, 1 patient per week requires treatment because of critical or life-threatening bleeding related to the use of apixaban or rivaroxaban. In addition, several patients have been treated for critical or life-threatening bleeding associated with dabigatran use.

At BWH, prescriptions for DOACs have been on the rise, whereas those for warfarin have been on the decline. As a result, the number of warfarin-treated patients enrolled in their Anticoagulation Management Service has decreased by approximately 60% to 70% since its peak. Given these changes in utilization, hospitals and healthcare systems need to be prepared to manage patients who present with major DOAC-related bleeding events.

Approximately 10 years ago, BWH founded an anticoagulant stewardship program that was modeled after antimicrobial stewardship. The anticoagulant stewardship comprises a group of practitioners who are readily available and can act immediately when anticoagulation-related events occur or are suspected. The group includes a hematologist, a cardiologist, and a pharmacist. Every day, a highly skilled pharmacist follows all patients with complex anticoagulation or bleeding issues. These may include patients with hemophilia, those with heparin-induced thrombocytopenia, or critically ill individuals on mechanical circulatory support. The pharmacist has become the first line of contact for patients with difficult-to-treat anticoagulation or bleeding problems, and hematologists and cardiologists are available for consultation if their expertise and advice are needed. This approach capitalizes on the intellectual capacity within the organization and the resources that can be brought to bear. The anticoagulation stewardship has been successful and has become part of the multidisciplinary infrastructure at BWH.

When developing protocols and guidelines for the hospital-wide use of particular agents, BWH garners opinions from leaders across the hospital system. For the anticoagulation and reversal protocols, the key opinion leaders include hematologists, cardiologists, and pharmacists. In addition, a nurse assesses proposals from a logistical standpoint. The leaders scrutinize the literature (including national guidelines and consensus statements), evaluate the pharmacokinetics, assess the drugs, offer recommendations, and determine the types of patients who will benefit from each treatment. Recommendations are developed, refined, and typically revised through multiple iterations until consensus is reached. The leadership also develops nursing protocols related to drug administration. The entire process is robust and entails evaluating routine practice for any need to change patient selection or interpret the value. Commentary from key opinion leaders is incorporated into the BWH guidelines.

Once the institutional protocols have been established, guidelines are converted into action steps for use by all staff members. Educational materials are developed and distributed to clinicians, nurses, and all relevant personnel. Information is readily accessible through the hospital's intranet site.

BWH is part of Partners Healthcare (now Mass General Brigham), which includes several smaller community and rehabilitation hospitals. Formulary decisions and institutional protocols are often centrally developed and then passed across the system, thus impacting the smaller community hospitals. Educational materials, including global monographs, more focused guideline sets, and protocols for preparing and administering specific drugs, are then distributed to these sites. A standard system-wide order set is incorporated into the electronic health record system for each anticoagulant reversal agent. The intent is to disseminate information across the system to any healthcare providers who may need it.

Currently, all hospitals in the Partners Healthcare system stock andexanet alfa—the specific reversal agent for apixaban and rivaroxaban. BWH also stocks idarucizumab—the reversal agent for dabigatran. Patients with anticoagulant-related major bleeding are often now treated in the community hospital, with some critical cases transferred to BWH. BWH was one of the first hospitals to have commercial access to andexanet alfa. Nonetheless, the institution's decision to stock specific anticoagulation reversal agents throughout every hospital in the system demonstrates its dedication to excellence for all patients. ■

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Using an electrochemiluminescence (ECL)-based assay, 145 ANDEXXA-treated healthy subjects were tested for antibodies to ANDEXXA as well as antibodies cross-reacting with factor X (FX) and FXa. Low titers of anti-ANDEXXA antibodies were observed in 26/145 healthy subjects (17%); 6% (9/145) were first observed at Day 30 with 20 subjects (14%) still having titers at the last time point (Days 44 to 48).

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ADVERSE REACTIONS

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