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Huisman, M.V.; Fanikos, J.

REVIEW

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Idarucizumab and Factor Xa Reversal Agents: Role in Hospital Guidelines and Protocols

Menno V. Huisman, MD, PhD,[a] John Fanikos, RPh, MBA[b]

[a]Department of Medicine—Thrombosis and Hemostasis, Leiden University Medical Center, Netherlands; [b]Department of Pharmacy Services, Brigham and Women's Hospital, Boston, Mass.

ABSTRACT

As expected with all antithrombotic agents, there is a risk of bleeding complications in patients receiving direct oral anticoagulants (DOACs) because of the DOAC itself, acute trauma, invasive procedures, or underlying comorbidities. For many bleeding events, a prudent course of action will be to withdraw the DOAC, then "wait and support" the patient, with the expectation that the bleeding event should resolve with time. Likewise, DOAC therapy may be interrupted ahead of a planned procedure, the stopping time being dependent on the agent involved and the patient's renal function. However, urgent reversal of anticoagulation is required in patients with serious or life-threatening bleeding or in those requiring urgent surgery or procedures. Novel specific reversal agents, either under development or recently approved, will need to be incorporated into local anticoagulation reversal protocols. For dabigatran-treated patients, idarucizumab recently has been approved for clinical use in cases of life-threatening or uncontrolled bleeding or when patients require emergency surgery or urgent procedures, both associated with a high risk of bleeding. As clinical experience with individual specific reversal agents grows, their roles in managing major bleeding events in DOAC−treated patients will become better defined. Future research, as well as ongoing use of idarucizumab, should help establish when it is appropriate to re-dose with idarucizumab, co-administer with prothrombin complex concentrates, or re-initiate DOAC after idarucizumab use. Ongoing trials should help identify the appropriate doses and expected durations of effect for andexanet alfa and ciraparantag, which are likely to vary depending on the individual oral anticoagulants.

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Oral anticoagulants are widely used to reduce the risk of thromboembolic events in patients with nonvalvular atrial fibrillation. Historically, the vitamin K antagonist, warfarin, was the oral anticoagulant of choice, generating decades of experience and corresponding data.[1] More recently, the direct oral anticoagulants (DOACs) have gained widespread acceptance in the management of patients with nonvalvular atrial fibrillation and venous thromboembolism due in part to their favorable safety, efficacy, and ease of use when compared with warfarin.[2,3]

As expected with antithrombotic drugs, bleeding is the most common adverse event associated with the use of

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Requests for reprints should be addressed to Menno V. Huisman, MD, PhD, Department of Medicine—Thrombosis and Hemostasis, Leiden University Medical Center, Room C7-68g, Albinusdreef 2, 2333 ZA Leiden, Netherlands.

E-mail address: m.v.huisman@lumc.nl

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DOACs, whether precipitated by the DOAC directly, by factors such as acute trauma or invasive procedures, or by underlying comorbidities. Although bleeding-related outcomes in clinical trials of DOACs in patients with atrial fibrillation have been favorable,[4-7] the lack of a reversal agent often has been considered as a disadvantage for DOACs.[3,8] This has prompted the development of the specific reversal agents (reviewed in articles by Reilly et al, Pollack, and Milling and Kaatz in this special issue).[9-11] Idarucizumab (Boehringer Ingelheim International GmbH, Ingelheim, Germany) is a humanized monoclonal antibody fragment that specifically binds to dabigatran and is approved by the U.S. Food and Drug Administration and the European Medicines Agency for use in dabigatran-treated patients who require reversal of the anticoagulant effects of dabigatran (ie, if there is life-threatening or uncontrolled bleeding, or for emergency surgery/urgent procedures).[12] There are a further 2 specific reversal agents in development: andexanet alfa (r-Antidote, Portola Pharmaceuticals, Inc, South San Francisco, Calif), a factor Xa decoy that binds to direct and indirect factor Xa inhibitors; and ciraparantag (Perosphere Inc, Danbury, Conn), a potential reversal agent for both direct and indirect factor Xa inhibitors, as well as factor IIa inhibitors.[13,14]

The objective of this review is to provide practical guidance that can be used when incorporating these DOAC–specific reversal agents into existing guidelines and protocols for the management of serious bleeding events or in patients undergoing urgent surgery while receiving DOACs. The review also discusses how the individual reversal agents may be used, as well as any unresolved issues that might be addressed by ongoing and future trials.

CURRENT GUIDELINES AND STRATEGIES FOR DOAC REVERSAL

The European Heart Rhythm Association (EHRA) has provided guidance for clinicians managing bleeding events (**Table 1**) and surgical procedures in DOAC-treated patients with nonvalvular atrial fibrillation, as have other

Table 1 European Heart Rhythm Association Guidelines for Practical Measures to Help Control Bleeding in Patients Who Are Anticoagulated with a DOAC

	Direct Thrombin Inhibitors (Dabigatran)	Factor Xa Inhibitors (Apixaban, Edoxaban, and Rivaroxaban)
Non-life-threatening bleeding	Inquire last intake and dosing regimen Estimate normalization of hemostasis: Normal renal function: 12-24 h CrCl 50-80 mL/min: 24-36 h CrCl 30-50 mL/min: 36-48 h CrCl <30 mL/min: ≥48 h	Inquire last intake and dosing regimen Normalization of hemostasis: 12-24 h
	Maintain diuresis	
	Local hemostatic measures: Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh-frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as an adjuvant.	Local hemostatic measures: Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy) Fresh-frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as an adjuvant. Desmopressin can be considered in special cases (coagulopathy or thrombopathy).
	Consider dialysis (preliminary evidence: ~65% of dabigatran can be removed after 4 h).	
	Charcoal hemoperfusion can be considered (based on preclinical data).	
Life-threatening bleeding	All of the above Idarucizumab 5 g IV PCC 50 U/kg (with additional 25 U/kg if clinically needed) (but no clinical data) Activated PCC (50 U/kg; max 200 U/kg/d), no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated FVII (rFVIIa; 90 μg/kg), no data about additional benefit and expensive (only animal evidence)	All of the above PCC 50 U/kg (with additional 25 U/kg if clinically needed) (healthy volunteer data) Activated PCC (50 U/kg; max 200 U/kg/d), no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated FVII (rFVIIa; 90 μg/kg), no data about additional benefit and expensive (only animal evidence)

CrCl = creatinine clearance; FVII = factor VII; IV = intravenously; PCC = prothrombin complex concentrate; RBC = red blood cells; rFVIIa = recombinant factor VIIa.

Adapted from Heidbuchel et al.[15]

authors.[15-18] Likewise, the Neurocritical Care Society and Society of Critical Care Medicine have devised guidelines for DOAC reversal in patients with intracranial hemorrhage.[19]

Bleeding Events and Hemostasis

As a consequence of the short half-life and predictable pharmacokinetics of the DOACs, most bleeding events can be resolved simply by waiting long enough (12-24 hours) for the DOAC plasma levels to decline to subtherapeutic concentrations while providing supportive measures to the patient.[15,20] Key parameters that will guide the selection of this "wait and support" approach are the timing of the last dose and qualitative estimates from routine laboratory coagulation assays to establish the general range of the DOAC-induced anticoagulation effect. In addition, factors influencing plasma concentrations should be taken into consideration, such as drug−drug interactions and the patient's renal function. In patients receiving dabigatran, the time to drug elimination is strongly influenced by renal function. Dialysis may be considered to increase dabigatran clearance, although there is limited clinical experience to support the use of dialysis in this setting.[15,21]

Patients with life-threatening or uncontrolled bleeding, however, require more immediate reversal of the anticoagulant effects of DOACs. Prothrombin complex concentrates and activated prothrombin complex concentrates have been used for reversal of DOAC anticoagulation, although their efficacy has not been firmly established in prospective, randomized trials[15,22] (see review by Eikelboom and Merli[23] in this special issue). The potential anticoagulant reversal benefits of prothrombin complex concentrates and activated prothrombin complex concentrates also need to be balanced against their potential prothrombotic effects.[15,24,25] Both the updated EHRA practical guide and the Neurocritical Care Society/Society of Critical Care Medicine intracranial hemorrhage guidelines recommend administering the recently approved reversal agent, idarucizumab, in patients receiving dabigatran.[15,19] A proposed algorithm for deciding

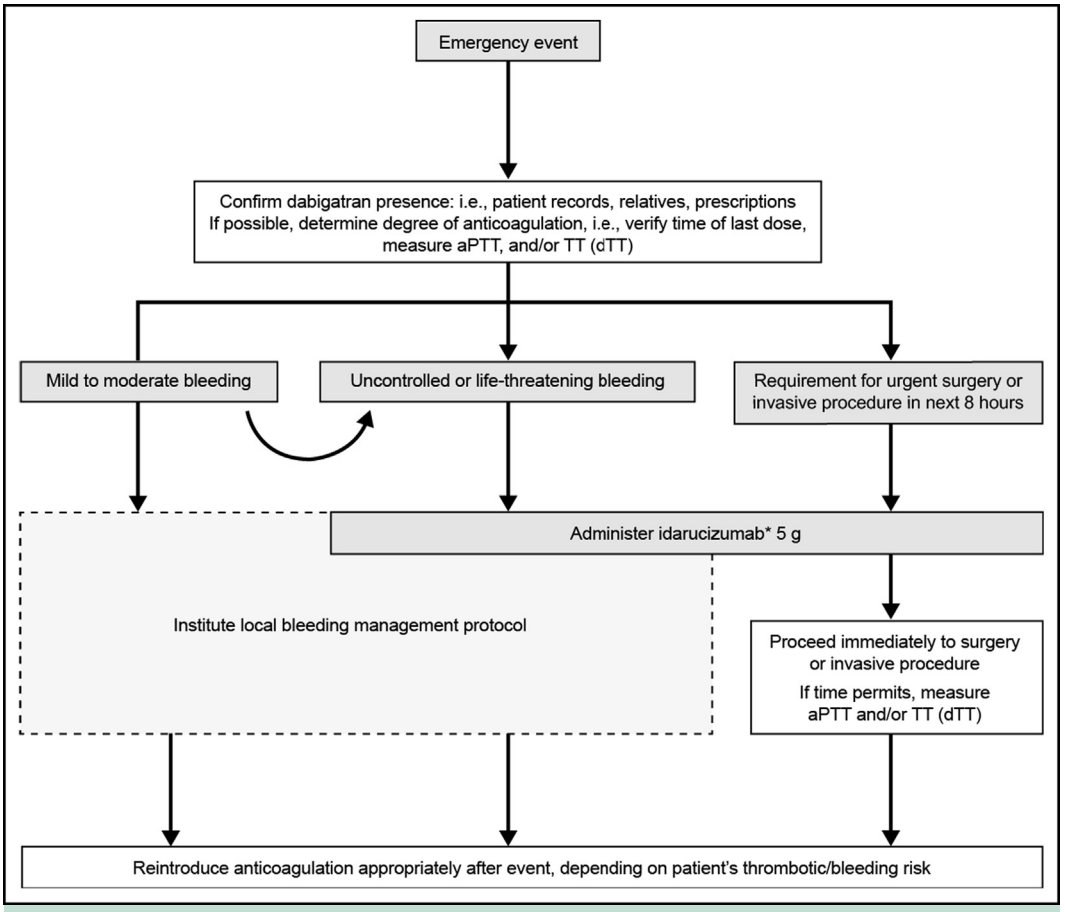

Figure Suggested algorithm for the management of dabigatran-treated patients who experience a bleeding episode or who require urgent surgery/invasive procedures. *Administer two 50-mL vials of idarucizumab (each containing 2.5 g) intravenously. In rare cases when dabigatran-related anticoagulation persists after a course of idarucizumab, and bleeding continues in the patient, a second 5 g dose of idarucizumab may be considered. aPTT = activated partial thromboplastin time; dTT = diluted thrombin time; TT = thrombin time. Reproduced with permission from: Eikelboom JW, Quinlan DJ, van Ryn J, Weitz JI. Idarucizumab: the antidote for reversal of dabigatran. *Circulation*. 2015;132:2412-2422.[26]

if and when to treat with idarucizumab is provided in Figure. In the absence of a currently approved specific reversal agent for factor Xa inhibitors, these guidelines recommend prothrombin complex concentrates or activated prothrombin complex concentrates in patients receiving apixaban, edoxaban, or rivaroxaban.

Patients Undergoing Planned or Urgent Surgery

The EHRA practical guide also contains guidance on when to stop DOAC therapy in patients undergoing a planned surgical procedure that carries a bleeding risk. The timing of the withdrawal of the DOAC is dependent on the particular agent, patient factors (eg, kidney function, age, history of bleeding, and concomitant medication), and the degree of bleeding risk associated with individual procedures. Dabigatran therapy should be stopped at least 24 to 48 hours ahead of low-risk procedures, depending on renal function, and at least 48 to 96 hours ahead of high-risk procedures. The factor Xa inhibitors should be stopped at least 24 to 36 hours before low-risk procedures and at least 48 hours before high-risk procedures.[12] Common coagulation tests (eg, activated partial thromboplastin time for dabigatran) may be helpful in providing a qualitative evaluation of the waning anticoagulant effects, as may specific coagulation tests (diluted thrombin time for dabigatran or chromogenic anti-factor Xa assays for factor Xa inhibitors) that are not yet approved in the United States.[15]

These stopping times may not always be feasible for more urgent procedures, and in these cases, reversal of anticoagulation is required. As is the case in patients with life-threatening bleeding, prospective data on the use of prothrombin complex concentrates in the preoperative setting are lacking.[15] Patients receiving dabigatran who require emergency surgery or urgent procedures may receive idarucizumab (administered as 2 consecutive intravenous infusions of 2.5 g in 50 mL apiece) for the reversal of dabigatran (Figure).[12] A published interim analysis of the phase 3, cohort study Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) included 39 patients receiving dabigatran who required a surgery or procedure that could not be delayed for at least 8 hours and required normal hemostasis.[27,28] In these patients, idarucizumab reversed the anticoagulant effects of dabigatran (as assessed by diluted thrombin time or ecarin clotting time) in 93% and 88% of patients, respectively. Of note, idarucizumab obviated the need for surgery in 1 patient, and 2 patients were too unstable for surgery. In the 36 patients who subsequently had a procedure, 33 were considered to have normal intraoperative hemostasis by the investigator.[27]

KEY CONSIDERATIONS FOR SPECIFIC REVERSAL AGENTS

With the increasing availability of the specific reversal inhibitors, clinicians will be required to incorporate these agents into their institutional guidelines/protocols for the urgent reversal of DOACs. This will raise a number of considerations, which are discussed in the following sections. Because conditions can vary between institutions, each organization may need to adapt existing guidelines to their particular situation as they consider the key factors that influence patient outcomes. An example of a template local guidance document can be found in Table 2, which is provided as a starting point for the development of more individualized local protocols.

Appropriate Patient Selection

As discussed earlier, the use of specific reversal agents should be reserved for life-threatening bleeding or in patients in whom an urgent invasive procedure is required. The approved uses for these agents are likely to differ on the basis of the patient populations studied in phase 3 trials. The idarucizumab phase 3 trial (Reversal Effects of Idarucizumab on Active Dabigatran [RE-VERSE AD]) included adult patients with overt, uncontrollable, or life-threatening bleeding (group A) or who required surgery or other invasive procedures that could not be delayed for at least 8 hours (group B).[27,28] Patients were selected on the basis of clinical judgment that immediate reversal was required and included those with acute trauma, as well as those who were expected to die within 3 days or require surgery within 24 hours.[27] The approved indication for idarucizumab reflects this trial population.[12]

In contrast, the ongoing phase 3 andexanet alfa trial (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXa Inhibitors [ANNEXA]-4; NCT02329327) includes patients with an acute major bleeding episode requiring urgent reversal of apixaban, rivaroxaban, edoxaban, or enoxaparin (administered in the past 18 hours).[29] Patients expected to undergo surgery (excluding minimally invasive procedures) in <12 hours are excluded, as are patients with an expected survival of <1 month. The selection of patients also is based on a set of predefined criteria: acute bleeding that is potentially life-threatening, in a critical area or organ, or associated or expected to be associated with decreases in hemoglobin levels of ≥ 2 g/dL or current or expected hemoglobin levels of ≤ 8 g/dL. Thus, these criteria are similar to the current International Society for Thrombosis and Haemostasis guidelines for nonsurgical patients, although patients who have received blood products (including whole blood and prothrombin complex concentrates) in the past 7 days are excluded.[30] When considering the magnitude of bleeding that may require urgent reversal, the variability in major bleeding definitions used in DOAC trials should be taken into account, as should the variability in definitions of effective periprocedural hemostasis, which are used to determine the effectiveness of management strategies.[4-7,31]

The differing mode of actions or drug targets of the individual agents (Table 3) will need to be taken into consideration when selecting the appropriate agent. Idarucizumab is specific to and only effective against

Table 2 Considerations Regarding Potential Use of Idarucizumab: Prototypical Table to Guide Decision-making

Indications	Life-Threatening or Uncontrolled Bleeding	Emergency Surgery or Invasive Procedures	Moderate to Mild Bleeding
Criteria	Life-threatening bleeding leading to hemodynamic compromise or threatening a vital organ (eg, CNS or spinal cord, intraocular, intrapulmonary, retroperitoneal, or intramuscular with compartment syndrome) Unresponsive to conventional measures Potentially leading to disability	Emergency surgery or urgent procedures that cannot be delayed for at least 8 h and that require immediate hemostasis	Non—life-threatening bleeding that does not involve a vital organ or in patients in whom surgery or invasive procedures can be delayed* *Idarucizumab is NOT indicated for cases of mild or moderate bleeding.
Baseline laboratory tests to assess anticoagulation	Need to order aPTT, ECT, or dTT in all patients when possible (depending on local availability of individual assays): Coagulation assay times that may indicate significant elevation of coagulation parameters (results need to be considered in light of local assay standards): aPTT (median baseline PTT ~50 sec)†[21] ECT (median baseline ECT ~75 sec)†[27] dTT (median baseline dTT ~45 sec)†[27]		
Dabigatran ingestion confirmed?	Known timing/ingestion of dabigatran (prescribed anticoagulant, standard dosage, known last dose?) Potential dabigatran overdose (accidental, deliberate?)		Expected minimum timing for elimination of clinically relevant dabigatran concentrations: CrCl ≥50 mL/min: ≥24 h CrCl <50 mL/min: ≥48 h
Idarucizumab	Consider administering idarucizumab immediately		Idarucizumab is not recommended for cases of moderate to mild bleeding.
Dosing	Intravenous administration of idarucizumab; 5 g total dose administered as 2 consecutive infusions or bolus injections of 2.5 g/50 mL each		Not applicable
Monitoring	Signs and symptoms of bleeding or thrombotic events Repeat aPTT, ECT, or dTT at 4 h and at 12-24 h postadministration (as per local protocols)		
Local resources	Names and contact information of local experts, offices, and laboratories that are available to guide patient selection and treatment choices		

aPTT = activated partial thromboplastin time; CNS = central nervous system; CrCl = creatinine clearance; dTT = dilute thrombin time; ECT = ecarin clotting time; PTT = partial thromboplastin time.

†Rounded median baseline values for each assay for patients taking dabigatran, as per listed citation. Values are provided for general guidance only; need to consider performance of each assay under local or central laboratory conditions.

dabigatran,[27,28,38] whereas andexanet alfa has been developed to target the currently approved factor Xa inhibitors[8,13] (and not dabigatran), and ciraparantag has been designed as a "universal" inhibitor for DOACs and heparins.[33-35,37] Therefore, the decision regarding which agent to use will depend on which particular DOAC is prescribed. Patients receiving specific reversal agents will need to receive additional supportive care to control bleeding because the reversal agents have been designed to reverse the anticoagulant effect of DOACs rather than to control bleeding.

Dosing and Administration

The 3 specific reversal agents are all administered intravenously, with andexanet alfa requiring an infusion pump. The recommended dose of idarucizumab is 5 g, which is supplied in 2 separate vials (2.5 g/50 mL idarucizumab per vial) that are ready for administration by sequential bolus injections or continuous intravenous infusion.[12] The vials need to be stored at a temperature range of 36°F to 46°F, without freezing. Likewise, andexanet alfa is a recombinant protein product that may need to be refrigerated and is expected to be administered at different doses according to the particular factor Xa inhibitor in question. In light of these recommendations, each institution will need to define its "best option" storage location on the basis of internal inventory control procedures and the relative ease-of-access in emergency situations. Ciraparantag is stable at room temperature, and thus, has the potential for out-of-hospital use.

In the RE-VERSE AD trial, idarucizumab demonstrated immediate neutralization of dabigatran's anticoagulant activity.[27] However, increases in unbound dabigatran concentration, which were accompanied by prolonged diluted thrombin time and ecarin clotting time values, occurred in

Table 3 Reversal Agent Characteristics

Specific Reversal Agent	Molecular Entity	Mechanism of Action	Target(s)	Route of Administration	Time to/Duration of Response	Clinical Trial Patient Populations
Andexanet alfa	Recombinant protein derived from human FXa[8,13]	Designed to competitively bind FXa inhibitors with high affinity, but lacks catalytic activity of native FXa[8,13]	Direct FXa inhibitors LMWH Fondaparinux[8,13]	By IV bolus or direct infusion[8,32]	Effect noted by 5 min, peak effect will last ~2 h after bolus injection or for 1-2 h after 2-h infusion[8,32]	Healthy older volunteers[32]
Ciraparantag	Engineered small molecule[33-35]	Binds heparins, oral FXa and FIIa inhibitors via extensive hydrogen bonds[33-35]	Direct FXa inhibitor DTI LMWH Heparin Fondaparinux[33-35]	By single IV bolus[33,36]	Effect begins within 30 min, lasts up to 24 h[33-35]	Healthy volunteers[36,37]
Idarucizumab	Fully humanized monoclonal antibody fragment (Fab)[38]	High affinity binding to dabigatran[38]	Dabigatran[38]	Via short IV infusion or bolus injection[12]	Immediate onset, effect will last up to 24 h[27,39]	Healthy volunteers[39,40] Patients with serious bleeding or in need of emergent invasive procedures

DTI = direct thrombin inhibitor; FIIa = factor IIa; FXa = factor Xa; IV = intravenous; LMWH = low-molecular-weight heparin.

some patients at 12 or 24 hours. This may be attributed to the redistribution of dabigatran from the tissues back into the plasma[27] and highlights the need for an approved and accessible assay for dabigatran, such as diluted thrombin time or activated partial thromboplastin time. Administration of an additional 5-g dose of idarucizumab may be considered in patients who have reappearance of clinically relevant bleeding together with an elevated coagulation parameter after administration of idarucizumab.[12,41] Likewise, readministration of idarucizumab may be considered in patients who require a second emergency procedure and have elevated coagulation parameters. However, the safety and effectiveness of repeat treatment with idarucizumab have yet to be established.

Findings from phase 2 trials suggest that the dose of andexanet alfa will vary depending on the anticoagulant agent (see review by Milling and Kaatz in this special issue).[11] Doses of andexanet alfa used in the ANNEXA-A and ANNEXA-R trials resulted in reversal of the anticoagulant activity of apixaban or rivaroxaban in older healthy participants within minutes after administration and for the duration of the infusion.[32] However, the appropriate dose of andexanet alfa for apixaban or rivaroxaban in patients with bleeding complications has yet to be defined and may vary depending on the time since the last anticoagulant dose, the total body load of the anticoagulant agent, and the underlying renal function. Guidance will be required regarding the optimal duration of the infusion, especially because a readily available laboratory test to quantify levels of factor Xa anticoagulation is currently lacking in the United States. In addition, andexanet alfa doses and durations of therapy to reverse the effects of low-molecular-weight heparins or fondaparinux will need to be defined, as will the appropriate doses of ciraparantag to reverse the effects of the different anticoagulants in clinical use.

Coadministration with Nonspecific Hemostatic Agents

As specific reversal agents continue to be approved for the reversal of DOACs (factor II or factor Xa inhibitors), the role, if any, that the currently available coagulation factors or concentrates play in the management of pathologic bleeding events can be expected to evolve.[15,20,42] However, there is limited clinical experience with the use of coagulation concentrates and DOAC-specific reversal agents. Patients with bleeding in the RE-VERSE AD trial were permitted to receive supportive care, including prothrombin complex concentrates and other blood products, during the trial.[28] Consequently, of the first 90 patients, 4 received activated prothrombin complex concentrates and 23 received fresh-frozen plasma.[27] However, outcomes data for these patients have not been reported. Furthermore, blood products, including prothrombin complex concentrates, are not permitted in the ongoing major bleeding andexanet alfa ANNEXA-4 trial within 7 days of screening.[29]

Re-Initiation of Anticoagulant Therapy

Clinicians also will need to decide when anticoagulation should be reestablished after use of a specific reversal agent. This will be dependent on the patient's individual risk of bleeding versus thromboembolism, but will also need to take into account the reversal agent used. In healthy volunteers, dabigatran anticoagulation could be reestablished within 24 hours of idarucizumab use.[41] In the RE-VERSE AD trial, most patients re-initiated anticoagulant therapy after reversal, with the restart time varying: a median time of 4.1 days in patients with life-threatening bleeding versus 1.4 days in patients requiring urgent surgery.[43] Although the half-lives of dabigatran and idarucizumab are prolonged in patients with renal impairment, the adjustment of timing of re-initiation of dabigatran is not necessary.[12,21] Data are required to identify when anticoagulation may be re-established after andexanet alfa or ciraparantag use, particularly if patients require an emergent procedure with extracorporeal life support and immediate heparinization.

Safety

No safety concerns for idarucizumab were highlighted in the RE-VERSE AD trial; the 18 deaths that were reported were due to the index event or underlying condition, and the 5 thrombotic events (including 1 occurring within 72 hours of idarucizumab administration) were in patients who had not re-initiated anticoagulant therapy.[27] This is in line with preclinical and phase 1 trials in which idarucizumab showed no prothrombotic effects (see the review by Reilly, et al in this special issue).[9] In addition, it should be noted that there is a risk of serious adverse events with idarucizumab use in patients with hereditary fructose intolerance resulting from the sorbitol excipient.[12]

The safety of andexanet alfa and ciraparantag has yet to be established in patients with bleeding complications. Although andexanet alfa has demonstrated no procoagulant activity in ex vivo clotting assays,[13] transient increases in the levels of D-dimer and prothrombin 1 and 2 were reported in the ANNEXA-A and ANNEXA-R trials.[32] However, this did not result in increases in thrombin generation or thrombotic events in these healthy volunteers. Even so, safety data from patients with major bleeding will be required to exclude a potential prothrombotic effect with andexanet alfa use.

As with all proteins, there is a potential for immunogenicity with both idarucizumab and andexanet alfa. However, preliminary data from trials in healthy volunteers suggest that this may not be a concern for idarucizumab because it has not been associated with the formation of new persistent antibodies, and there were no adverse events suggestive of immunogenic reactions.[39] Likewise, in the ANNEXA-A and ANNEXA-R trials, antibodies to factor X or factor Xa, as well as neutralizing antibodies against andexanet alfa, were not detected.[32] However, further research will be required to assess the immunogenicity of idarucizumab or andexanet alfa in treated patients.

CONCLUSIONS

Considerations of specific anticoagulation reversal agents are expected to include questions regarding the appropriate clinical setting for these agents. It is not anticipated that these agents will be used to manage mild or moderate bleeding events, which are usually well controlled by general supportive measures. Most likely, the role of specific reversal agents will be to help treat serious bleeding events in DOAC-treated patients. At the present time, the approved indications for idarucizumab are for cases of life-threatening or uncontrolled bleeding, or when patients require emergency surgery or urgent procedures, each associated with a high risk of bleeding.[12] Ongoing clinical research should address unresolved issues, such as the optimal dose and duration for andexanet alfa and ciraparantag in patients with bleeding complications, as well as DOAC re-initiation strategies after treatment with these reversal agents, particularly in patients in whom emergent reversal of anticoagulation is required.

As clinical experience continues to evolve, the potential role of prothrombin complex concentrates and other nonspecific agents as supportive therapy in combination with specific reversal agents will be better understood.[20] In addition, the identification of potential "go-to" local experts (eg, hematologists, cardiologists, or pharmacists) at each institution, who should be consulted in cases of severe and uncontrolled bleeding, will be expected to improve patient care and outcomes.

Finally, the relevant clinical societies may be asked to support the widespread availability of these specific reversal agents in all major and regional hospitals so that critical cases may be treated as urgently as possible. For the smaller, regional hospitals and rural healthcare facilities, ultimate decisions to maintain stocks of these agents may depend on local conditions. They will have to assess the cost—benefit of relying on rapid transportation options or onsite availability of each agent as they become available.

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