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CRITICAL REVIEW

Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum

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Abstract

Two specific reversal agents for direct oral anticoagulants (DOACs) have been approved in the United States: idarucizumab for dabigatran reversal and andexanet alfa for apixaban and rivaroxaban reversal. Non-specific prohemostatic agents such as prothrombin complex concentrate (PCC) and activated PCC have also been used for DOAC reversal. The goal of this document is to provide comprehensive guidance from the Anticoagulation Forum, a North American organization of anticoagulation providers, regarding use of DOAC reversal agents. We discuss indications for reversal, provide guidance on how the individual reversal agents should be administered, and offer suggestions for stewardship at the health system level.

1 | INTRODUCTION

The direct oral anticoagulants (DOACs) comprise the direct thrombin inhibitor, dabigatran, and the direct factor Xa inhibitors, apixaban, betrixaban, edoxaban, and rivaroxaban. Collectively, these agents have been approved by the United States Food and Drug Administration (US FDA) for prevention of stroke and systemic embolism in non-valvular atrial fibrillation, prevention and treatment of venous thromboembolism (VTE), and secondary prevention of arterial ischemic events in patients with chronic coronary or peripheral artery disease.[1–5] As a class, DOACs have now eclipsed vitamin K antagonists (VKAs) as the most widely prescribed oral anticoagulants in the Unites States and elsewhere.[6–8]

Adam Cuker and Allison Burnett are co-first authors.

Two key advantages of the DOACs compared with VKAs are a reduced incidence of major bleeding and simplified perioperative management.[9,10] Nevertheless, patients taking DOACs may present with serious bleeding or need for an urgent unplanned procedure. Major bleeding was reported in 2.1% to 3.6% of patients randomized to treatment with a DOAC in phase III clinical trials. Two DOACs, along with warfarin, are among the top ten drugs contributing to emergency department visits in the US.[9,11,12]

Two specific DOAC reversal agents have been approved by the US FDA: idarucizumab (Praxbind, Boehringer Ingelheim) for reversal of dabigatran and andexanet alfa [coagulation factor Xa (recombinant) inactivated-zhzo; Andexxa, Portola Pharmaceuticals] for reversal of apixaban and rivaroxaban.[13,14] Non-specific prohemostatic agents have also been used off-label for DOAC reversal including prothrombin complex concentrate (PCC) (multiple brands) and activated prothrombin complex concentrate (APCC) [FEIBA (Anti-Inhibitor Coagulant Complex), Takeda Pharmaceutical Company].[15,16] Various factors complicate the use of these agents in clinical practice including availability, potential risk of thrombosis, cost, preparation, and a lack of data on the comparative effectiveness of different reversal strategies. Moreover, US FDA-approved reversal agents are not indicated for use with all DOACs or in all clinical scenarios where reversal may be considered.[13,14]

The purpose of this document is to provide clinical guidance from the Anticoagulation Forum, a North American organization of anticoagulation providers, regarding the use of DOAC reversal agents based upon the best available information, including situations in which high-quality evidence is absent. We discuss indications for DOAC reversal, provide detailed guidance on how the individual reversal agents should be administered, and offer suggestions for management strategies and stewardship at the health system level.

2 | METHODS

As with previous Anticoagulation Forum guidance documents,[17] we prioritized a set of key questions regarding DOAC reversal through discussion and consensus among the authors (Table 1). We searched PubMed to identify evidence related to these questions. This search was supplemented by articles from the authors' files and manual review of references. We prioritized studies of patients that reported patient-important outcomes (ie, bleeding, thromboembolism, mortality) over in vitro, animal, and healthy volunteer studies. We also reviewed relevant information in US FDA product package inserts and on www.clinicaltrials.gov. For each question, a summary of the evidence is provided, followed by guidance representing unanimous consensus of the authors.

3 | GUIDANCE

3.1 | (1) When should reversal agents be used to manage DOAC-associated bleeding?

3.1.1 | Evidence summary

Even before specific reversal agents for the DOACs became available, outcomes of DOAC-associated bleeding compared favorably with VKAs. In a 2015 meta-analysis of 13 randomized trials involving more than 100 000 patients, DOACs were associated with a 47% reduction in the risk of fatal bleeding (RR 0.53, 95% CI 0.43-0.64) compared with VKAs.[18] Similar observations have been made in the post-marketing setting. In a real-world study of 2002 patients with anticoagulant-associated bleeding, the case-fatality rate was lower with DOACs than warfarin (10% vs 15%; RR 0.66, 95% CI 0.49-0.89).[19]

The largely favorable outcomes of DOAC-associated bleeding in the pre-antidote era suggest that many patients with DOAC-associated bleeding do not require reversal agents and may be managed with supportive measures alone. Such measures include discontinuation of DOAC and other medications known to interfere with hemostasis (eg, antiplatelet agents), compression of or procedural management directed at the bleeding site, volume resuscitation, and transfusion support. Patients with mucosal bleeding (eg, epistaxis, uterine bleeding) may benefit from antifibrinolytic therapy. Oral activated charcoal may be used to remove unabsorbed DOAC from the gastrointestinal tract, particularly if it was taken in the last several hours.[20] Reversal agents should be reserved for life-threatening bleeding, critical site bleeding, or major bleeding that does not respond to the aforementioned supportive measures.

When considering a reversal agent, it is also important to assess the degree of anticoagulation and the likelihood that the anticoagulant is contributing to bleeding. Assays for measurement of plasma DOAC concentration are not available at all centers, particularly on a stat basis. If such assays are not available, degree of anticoagulation can be estimated based on the specific agent, dose, interval since last dose, and renal and hepatic function.[20] A reversal agent should only be considered when there is demonstration or expectation of clinically relevant DOAC levels.

3.1.2 | Guidance statement 1

In all patients with DOAC-associated major bleeding, we suggest treatment with supportive measures. We suggest administration of a reversal agent only if bleeding 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.

3.2 | (2) How should reversal agents be used to manage dabigatran-associated bleeding?

3.2.1 | Evidence summary

Idarucizumab, a humanized, monoclonal, anti-dabigatran antibody fragment, was evaluated in 301 patients with dabigatran-associated major bleeding in the REVERSE-AD study.[21] The most common sites of bleeding were gastrointestinal and intracranial. Of 203 evaluable patients, 134 (68%) had cessation of bleeding within 24 h. The median time to achievement of hemostasis was 2.5 h. The relationship between reduction in plasma dabigatran levels and hemostatic efficacy was not reported. Approximately one quarter of patients

TABLE 1 Prioritized questions and guidance statements on DOAC reversal

Question	Guidance statement
(1) When should reversal agents be used to manage DOAC-associated bleeding?	In all patients with DOAC-associated major bleeding, we suggest treatment with supportive measures. We suggest administration of a reversal agent only if bleeding 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.
(2) How should reversal agents be used to manage dabigatran-associated bleeding?	In patients with dabigatran-associated major bleeding in whom a reversal agent is warranted, we suggest treatment with idarucizumab 5 g IV. If idarucizumab is not available, we suggest treatment with APCC 50 units/kg IV.
(3) How should reversal agents be used to manage factor Xa inhibitor-associated bleeding?	In patients with rivaroxaban-associated or apixaban-associated major bleeding in whom a reversal agent is warranted, we suggest treatment with andexanet alfa dosed according to the US FDA label (Table 2). If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units. In patients with edoxaban-associated or betrixaban-associated major bleeding in whom a reversal agent is warranted, we suggest off-label treatment with either high dose andexanet alfa (800 mg bolus given at 30 mg/min followed by a continuous infusion of 8 mg/min for up to 120 min) or four-factor PCC 2000 units.
(4) When should reversal agents be used before an invasive procedure?	In DOAC-treated patients who require an invasive procedure, we suggest that a reversal agent be administered only if the procedure cannot be safely performed while the patient is anticoagulated, cannot be delayed, and there is demonstration or reasonable expectation that the patient has clinically relevant plasma DOAC levels.
(5) How should reversal agents be used to manage a dabigatran-treated patient before an invasive procedure?	In dabigatran-treated patients who require an urgent procedure and in whom a reversal agent is warranted, we suggest treatment with idarucizumab 5 g IV. If idarucizumab is not available, we suggest treatment with APCC 50 units/kg IV.
(6) How should reversal agents be used to manage a factor Xa inhibitor-treated patient before an invasive procedure?	In factor Xa inhibitor-treated patients who require an urgent procedure and in whom a reversal agent is warranted, we suggest treatment with andexanet alfa at the same dosing used for major bleeding. If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units.
(7) Are reversal agents indicated for patients who present with DOAC overdose without bleeding?	In patients with DOAC overdose without bleeding, we suggest against the routine use of reversal agents.
(8) Are reversal agents indicated for DOAC-treated patients who present with trauma without bleeding?	In DOAC-treated patients who present with trauma without bleeding, we suggest against the routine use of reversal agents.
(9) What strategies can be employed by health systems to promote optimal utilization of DOAC reversal agents?	To promote optimal use of DOAC reversal, we suggest that health systems develop and implement overarching strategies that promote multidisciplinary, shared stewardship of these agents. We suggest utilization of evidence-based clinical tools and processes that facilitate adherence with agreed-upon restrictions for judicious prescribing and use. We suggest system-level approaches be streamlined to the fullest extent possible via leveraging of the electronic health record, as well as maximized efficiency of pharmacy order processing, admixture, and delivery strategies. We further suggest that health systems develop contingency plans to be prepared for a variety of acquisition challenges, as well as close collaboration with vendors and billing departments to capitalize on cost mitigation opportunities. We suggest periodic formal evaluation of DOAC reversal practices to assess for appropriateness and identify opportunities for further optimization. Lastly, we suggest that dedicated stewardship programs be established, whenever possible, to drive development, implementation, consistent application, and evaluation of anticoagulation-related optimization strategies including, but not limited to, appropriate and judicious use of DOAC reversal agents.

Abbreviations: APCC, activated prothrombin complex concentrate; DOAC, direct oral anticoagulant; PCC, prothrombin complex concentrate; US FDA, United States Food and Drug Administration.

experienced a re-elevation in plasma dabigatran levels 24 h after idarucizumab infusion. Treatment was generally well-tolerated. The thrombotic rate in the overall study cohort was 4.8% at 1 month. Events included VTE (n = 10), ischemic stroke (n = 7), myocardial infarction (n = 6), and systemic embolism (n = 2). Half of thrombotic events occurred within 5 days of infusion and one-third occurred after resumption of anticoagulation. Anti-idarucizumab antibodies were present in 3.8% of subjects at study entry; an additional 1.9% developed antibodies after infusion. Titers were low and did not appear to interfere with idarucizumab activity.[21] Idarucizumab was approved by the US FDA in 2015 for dabigatran reversal.[13] The dose is 5 g (two 2.5 g vials). The label allows for re-dosing if coagulation parameters become re-elevated and clinically relevant bleeding occurs.

APCC is a plasma-derived concentrate of the vitamin K-dependent clotting factors in which a fraction of the clotting factors has been activated by proteolytic cleavage. APCC was evaluated in 14 patients with dabigatran-associated major bleeding. The median initial dose was 44 units/kg (range 24-98). Four patients received a second dose

1 to 14 h after the first dose. Hemostasis was adjudicated as good in 9 (64%), moderate in 5 (36%), and poor in none. There were no thromboembolic events.[22] PCC and recombinant factor VIIa for dabigatran reversal have been investigated in in vitro, animal, and healthy volunteer studies (reviewed in[23]), but not in prospective studies of patients with dabigatran-associated bleeding.

Hemodialysis may be used to remove dabigatran from the circulation.[24] In patients with renal impairment, a single session typically reduces plasma drug levels by about 50%.[25] In practice, it is often impractical to place a dialysis catheter and initiate hemodialysis in a coagulopathic patient with serious bleeding due to the bleeding risk and time-consuming nature of the procedure.

3.2.2 | Guidance statement 2

In patients with dabigatran-associated major bleeding in whom a reversal agent is warranted (see guidance statement 1), we suggest treatment with idarucizumab 5 g IV. If idarucizumab is not available, we suggest treatment with APCC 50 units/kg IV.

3.3 | (3) How should reversal agents be used to manage factor Xa inhibitor-associated bleeding?

3.3.1 | Evidence summary

Andexanet alfa is a modified recombinant factor Xa. It is catalytically inactive and cannot participate in coagulation, but it retains the ability to bind to and sequester factor Xa inhibitors. It was approved by the US FDA in May 2018 for management of life-threatening or uncontrollable bleeding in patients taking apixaban or rivaroxaban based on the "Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors" (ANNEXA-4) study.[26]

The ANNEXA-4 study enrolled 352 patients (128 on rivaroxaban, 194 on apixaban, 10 on edoxaban, and 20 on enoxaparin). The two most common primary sites of bleeding were intracranial (64%) and gastrointestinal (26%). A low dose of andexanet alfa (400 mg bolus given over 15 to 30 min followed by a continuous infusion of 4 mg/min for 120 min) was administered to patients on apixaban and those who had last taken rivaroxaban >7 h ago. A high dose (800 mg bolus given over 30 min followed by a continuous infusion of 8 mg/min for 120 min) was administered to patients who had taken rivaroxaban within the last 7 h, or at an unknown time, as well as those who had received edoxaban or enoxaparin.[26]

An efficacy analysis was conducted in 134 patients on apixaban and 100 patients on rivaroxaban, who met criteria for major bleeding and had a plasma DOAC level ≥75 ng/mL at study entry. The mean reduction in anti-Xa activity at the completion of the andexanet alfa bolus was 92%. Hemostasis was judged to be good or excellent in 83% and 80% of apixaban-treated and rivaroxaban-treated patients, respectively. There was no significant relationship between reduction in anti-Xa activity and hemostatic efficacy.[26]

A safety analysis was undertaken in the overall study population. Forty thrombotic events (7 myocardial infarctions, 15 transient ischemic attacks or ischemic strokes, 18 VTEs) occurred in 34 (10%) patients at 30 days. Eleven patients had a thromboembolic event within 5 days of receiving andexanet alfa and 8 patients had an event after restarting anticoagulation.[26] The US FDA prescribing information for andexanet alfa includes a black box warning regarding the risk of venous and arterial thromboembolic events.[14] Dosing instructions from the prescribing information[14] are summarized in Table 2, and differ slightly from the dosing used in ANNEXA-4.[26]

Considering the prothrombotic potential of andexanet alfa, and the absence of a relationship between reduction in anti-Xa activity and hemostatic efficacy in ANNEXA-4,[26] more data are needed on its efficacy and safety relative to usual care. Such information is expected from a recently initiated phase 4 randomized controlled trial comparing andexanet alfa with usual care in patients with acute intracranial hemorrhage receiving an oral factor Xa inhibitor (ClinicalTrials.gov number, NCT03661528).

Andexanet alfa has been shown to reverse edoxaban in a rabbit bleeding model and in healthy volunteers.[27,28] Only 10 edoxaban-treated patients were enrolled in ANNEXA-4, though there is a plan to enroll more in an extension of the study in Germany and Japan.[26] Andexanet alfa also reversed betrixaban in a healthy control study.[29,30] There are no published outcomes of andexanet alfa in betrixaban-treated patients.

PCCs are plasma-derived concentrates of the vitamin K-dependent clotting factors in their inactive form. Four-factor PCC contains factors II, VII, IX, and X, whereas three-factor PCC contains predominantly factors II, IX, and X, and no or trivial concentrations of factor VII. PCC for reversal of bleeding in patients taking factor Xa inhibitors has been evaluated in two prospective cohort studies. In a Swedish study, 84 patients with factor Xa inhibitor-associated major bleeding were treated with four-factor PCC. Patients weighing <65 kg received 1500 units; patients weighing >65 kg received 2000 units. Hemostasis was judged to be effective in 58 (69%) patients. Two subjects were diagnosed with ischemic stroke 5 and 10 days after PCC administration.[31] In a Canadian study, 66 patients on rivaroxaban or apixaban with major bleeding were treated with four-factor PCC at a fixed dose of 2000 units. Hemostatic efficacy was assessed as good, moderate, and poor in 65%, 20%, and 15% of patients, respectively.

TABLE 2 Dosing and administration of andexanet alfa according to the United States Food and Drug Administration package insert

		Time from last dose	
Drug	Last Dose	<8 h or unknown	≥8 h
Rivaroxaban	≤10 mg	Low dose[a]	Low dose[a]
	>10 mg or unknown	High dose[b]	
Apixaban	≤5 mg	Low dose[a]	
	>5 mg or unknown	High dose[b]	

[a]Initial 400 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 4 mg/min for up to 120 min.
[b]Initial 800 mg IV bolus at target rate of 30 mg/min followed by continuous infusion at 8 mg/min for up to 120 min.

Five (8%) patients experienced thromboembolic events at 30 days.[32] In settings where four-factor PCC is not available, some experts have advocated supplementing three-factor PCC with fresh frozen plasma to provide factor VII. APCC and recombinant factor VIIa for reversal of oral factor Xa inhibitors have been investigated in in vitro, animal, and healthy volunteer studies (reviewed in[23]), but not in prospective studies of patients with factor Xa inhibitor-associated bleeding.

Although others have recommended weight-based dosing of four-factor PCC (50 units/kg) for factor Xa inhibitor reversal,[20] we prefer a fixed dose of 2000 units because it has been studied in patients with factor Xa inhibitor-associated bleeding.[31,32] Additional advantages of fixed dosing include greater simplicity for the ordering provider and pharmacy and reduced cost.

3.3.2 | Guidance statement 3

*In patients with rivaroxaban-associated or apixaban-associated major bleeding in whom a reversal agent is warranted (see guidance statement 1), we suggest treatment with andexanet alfa dosed according to the US FDA label (*Table 2*). If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units.*

In patients with edoxaban-associated or betrixaban-associated major bleeding in whom a reversal agent is warranted (see Guidance statement 1), we suggest off-label treatment with either high dose andexanet alfa (800 mg bolus followed by a continuous infusion of 8 mg/min for up to 120 min) or four-factor PCC 2000 units.

3.4 | (4) When should reversal agents be used before an invasive procedure?

3.4.1 | Evidence summary

In light of the cost and prothrombotic potential of DOAC reversal agents, their use should only be considered before an invasive procedure if (a) the bleeding risk associated with the procedure is sufficiently high that it cannot be safely performed while the patient is anticoagulated and (b) the procedure is emergent (ie, cannot be delayed).

Procedures with minimal bleeding risk (eg, minor dermatological procedures, cataract surgery, minor dental procedures) do not warrant interruption of anticoagulants and may proceed without DOAC interruption or reversal.[33,34] In addition, emerging evidence for certain cardiac electrophysiology procedures has demonstrated equivalent or superior safety with continuation of anticoagulation.[35–37] The use of reversal agents in advance of such procedures is likely not necessary, irrespective of the urgency of the procedure.

Other procedures require temporary interruption of anticoagulation. In the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study,[10] 3007 patients taking rivaroxaban, apixaban, or dabigatran for atrial fibrillation who were scheduled for an elective procedure requiring interruption of anticoagulation were managed using a standardized protocol. For patients undergoing a low bleeding risk procedure, anticoagulation was held one day before surgery. For those undergoing a high bleeding risk procedure, anticoagulation was held two days before surgery. Anticoagulation was held for longer in patients taking dabigatran with a creatinine clearance <50 mL/min (2 days before minor and 4 days before major surgery). Outcomes were favorable; the incidence of major bleeding and arterial thromboembolism at 30 days was <2% and <1%, respectively. Although laboratory measurement of DOAC levels was not used to guide management, a post hoc analysis demonstrated that plasma DOAC levels were low (<50 ng/mL) or undetectable at the time of surgery in more than 90% of patients.[38]

If the patient requires an emergent procedure that cannot be safely delayed in accordance with the PAUSE protocol,[10] it may be useful to measure or estimate the plasma DOAC concentration to determine the need for reversal. Assays for measurement of plasma DOAC concentration are not available at all centers, particularly on a stat basis. If an assay suitable for quantitation is not available, a normal thrombin time can be used to exclude clinically relevant dabigatran concentrations and an unfractionated or low molecular weight heparin anti-Xa assay below the lower limit of quantitation can be used to exclude clinically relevant concentrations of factor Xa inhibitor. Unfortunately, neither the prothrombin time nor the activated partial thromboplastin time are generally sufficiently sensitive to exclude such concentrations, though reagents vary in their sensitivity.[39,40]

3.4.2 | Guidance statement 4

In DOAC-treated patients who require an invasive procedure, we suggest that a reversal agent be administered only if the procedure cannot be safely performed while the patient is anticoagulated, cannot be delayed, and there is demonstration or reasonable expectation that the patient has clinically relevant plasma DOAC levels.

3.5 | (5) How should reversal agents be used to manage a dabigatran-treated patient before an invasive procedure?

3.5.1 | Evidence summary

Idarucizumab was evaluated in 202 dabigatran-treated patients requiring an urgent invasive procedure in the REVERSE-AD study. The median time from idarucizumab infusion to initiation of the procedure was 1.6 h. Of 197 evaluable patients, periprocedural hemostasis was judged to be normal, mildly abnormal, or moderately abnormal in 93.4%, 5.1%, and 1.5% of patients, respectively. None had severely abnormal hemostasis.[21] On the basis of these findings, the US FDA approved idarucizumab for reversal of dabigatran prior to urgent procedures.[13] As with reversal of dabigatran-associated major bleeding, the dose is 5 g (two 2.5 g vials).

There are no published data on use of APCC for reversal prior to surgery in dabigatran-treated patients. Justification for treatment in this context is extrapolated from indirect evidence from studies of bleeding patients[22] as well as in vitro, animal, and healthy volunteer

studies (reviewed in[23]) (see "(2) How should reversal agents be used to manage dabigatran-associated bleeding?" above).[22]

3.5.2 | Guidance statement 5

In dabigatran-treated patients who require an urgent procedure and in whom a reversal agent is warranted (see guidance statement 4), we suggest treatment with idarucizumab 5 g IV. If idarucizumab is not available, we suggest treatment with APCC 50 units/kg IV.

3.6 | (6) How should reversal agents be used to manage a factor Xa inhibitor-treated patient before an invasive procedure?

3.6.1 | Evidence summary

There are no published data on use of andexanet alfa, APCC, or PCC for reversal prior to surgery in factor Xa inhibitor-treated patients. Justification for treatment with these agents for this indication is extrapolated from indirect evidence from studies of bleeding patients[26,31,32] as well as in vitro, animal, and healthy volunteer studies (reviewed in[23]) (see "(3) How should reversal agents be used to manage factor Xa inhibitor-associated bleeding?").

3.6.2 | Guidance statement 6

In factor Xa inhibitor-treated patients who require an urgent procedure and in whom a reversal agent is warranted (see guidance statement 4), we suggest treatment with andexanet alfa at the same dosing used for major bleeding. If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units.

3.7 | (7) Are reversal agents indicated for patients who present with DOAC overdose without bleeding?

3.7.1 | Evidence summary

Patients presenting with intentional or inadvertent DOAC overdose should receive standard drug poisoning management including supportive care and stabilization procedures in consultation with a clinical toxicologist and/or regional poison control center. Patients should also be thoroughly evaluated for the presence of bleeding and, if present, receive appropriate management including oral activated charcoal and/or reversal agents, if warranted (see "(3.1) When should reversal agents be used to manage DOAC-associated bleeding?").

Most patients with acute DOAC overdose, however, do not present with bleeding. In one study of 52 patients with acute dabigatran, rivaroxaban, or apixaban over-dosage, 7 (13%) presented with major bleeding, 2 presented with minor bleeding, and 43 were asymptomatic.[41] Management of such patients in published case reports is highly variable. Several cases of massive rivaroxaban overdose have been managed successfully without bleeding and without administration of blood products or reversal agents, attributed in part to the saturation of gastrointestinal absorption at dosages above 50 mg.[42–45] Cases involving apixaban and dabigatran have likewise been conservatively managed with success.[46–49] While blood products and idarucizumab have also been administered safely in some overdose cases, their impact on clinical outcomes is unclear.[41,42,50–53]

Considering the uncertain risk of bleeding due to overdose, the relatively short half-life of the DOACs, the cost and prothrombotic potential of reversal agents, and the lack of evidence supporting their use in this context, the authors suggest that DOAC reversal agents not be routinely administered in cases of DOAC overdose without bleeding. DOAC reversal may be considered in special cases in which the patient is judged to be at high risk for catastrophic bleeding (eg, recent neurosurgery).

3.7.2 | Guidance statement 7

In patients with DOAC overdose without bleeding, we suggest against the routine use of reversal agents.

3.8 | (8) Are reversal agents indicated for DOAC-treated patients who present with trauma without bleeding?

3.8.1 | Evidence summary

DOAC-treated patients presenting with trauma should undergo standard trauma evaluation and management appropriate for the mechanism of injury including a deliberate investigation for hemorrhage. If the patient is found to have traumatic bleeding or requires an invasive procedure, administration of a reversal agent may be warranted depending on the severity of the bleed or the urgency and bleeding risk of the procedure (see "(3.1) When should reversal agents be used to manage DOAC-associated bleeding?" and "(3.4) When should reversal agents be used before an invasive procedure?").

Most trauma patients on a DOAC do not present with bleeding. Thirty-one patients taking dabigatran, rivaroxaban, or apixaban presented to a level I trauma center after a ground level fall with head injury. None had intracranial hemorrhage.[54] In another center, of 33 dabigatran-treated patients who presented after blunt head trauma, only one was found to have intracranial hemorrhage. Among the other 32 patients, one received a reversal agent (for cervical spine fracture). The remaining 31 patients did not receive a reversal agent and had generally favorable outcomes.[55]

Considering the variable and relatively low incidence of bleeding with trauma, the cost and prothrombotic potential of reversal agents, and the lack of evidence supporting their use for this indication, the authors suggest that reversal agents not be routinely administered to DOAC-treated patients presenting with trauma without bleeding.

3.8.2 | Guidance statement 8

In DOAC-treated patients who present with trauma without bleeding, we suggest against the routine use of reversal agents.

3.9 | (9) What strategies can be employed by health systems to promote optimal utilization of DOAC reversal agents?

3.9.1 | Evidence summary

There are several real and potential challenges associated with DOAC reversal strategies that may be broadly grouped into acquisition and cost, operational logistics, and appropriate utilization. Upstream recognition of and familiarity with these challenges will allow health systems and individual clinicians to develop and implement strategies for optimal use of DOAC reversal agents.

As health systems vary significantly in their available resources, structure, and function, a "one-size-fits-all" approach for optimizing DOAC reversal is not possible. However, there are core tenets related to DOAC reversal that should be applied across all hospitals, including utilization of standardized, system-level, multidisciplinary efforts that promote shared stewardship of these therapies. If resources permit, a dedicated antithrombosis stewardship team may be particularly beneficial for spearheading development, implementation, and maintenance of necessary tools and systematic processes pertaining to DOAC reversal.[56] Regardless of chosen structure or involved parties, efforts should be focused on multipronged strategies that effectively address challenges associated with DOAC reversal.

3.9.2 | Acquisition and cost

Drug acquisition may be impacted by availability and/or cost of a given reversal agent. For example, periodic drug shortages or recalls may render a reversal agent temporarily unavailable,[57] and alternative approaches should be delineated *a priori* to avoid critical delays in therapy. In the case of andexanet alfa, manufacturing complexity limited its initial availability, with only hospitals serving as ANNEXA-4 study sites having access to the Generation 1 (100 mg/vial) product immediately following US FDA approval in May 2018. To gain a better understanding of how health systems are addressing andexanet alfa, the Anticoagulation Forum recently conducted an online survey of its members. Responses were collected via Google survey from September to December 2018. Of the 53 responding hospitals, 41 (77%) had not yet added andexanet alfa to their formulary, with 37% citing lack of availability as a reason. These hospitals reported using weight-based 4-Factor PCC (71%), fixed-dose 4-Factor PCC (22%), APCC (5%) and 3-Factor PCC (2%) for FXa inhibitor reversal (unpublished data). On December 31, 2018, the US FDA approved manufacture of a Generation 2 (200 mg/vial) product), which is anticipated to significantly increase availability of andexanet alfa.

Health systems should have alternative strategies delineated *a priori* within their evidence-based reversal protocols to prevent critical delays in care in the event of drug recalls or shortages. If supply of a given reversal agent is not sufficient to stock all hospitals, it may be prudent for hospitals within a geographic region to discuss some type of medication sharing strategy. Alternatively, it may be preferable for critical access hospitals to have the drug on hand so they can "drip and ship" the patient to a larger medical center with more resources and advanced therapies.[58]

All DOAC reversal agents are associated with significant financial cost, with specific antidotes generally being more expensive than non-specific factor concentrates (Table 3). Andexanet alfa poses a notable financial challenge for hospitals. In our online survey, 66% of hospitals who had not yet added andexanet alfa to formulary cited cost as a reason. Cost will remain constant with availability of the Generation 2 product ($5500/200 mg vial; $27 500 for low dose; $49 500 for high dose). Hospitals can alleviate cost burden by obtaining DOAC reversal agents on consignment through their respective vendor or, if not available on consignment, keeping a limited number of doses on hand based on anticipated need. For PCC and APCC, expedient delivery of non-reconstituted drug to the bedside allows for the product to be returned to the pharmacy if reversal is ultimately not pursued. A similar approach may be used for idarucizumab (sending the unopened box kit to the bedside) as long as the kit is returned to pharmacy unopened so that the product remains protected from light. Health systems should be aware of New Technology Add-On (NTAP) payments available for andexanet alfa through the Centers for Medicare and Medicaid Services (CMS).[62] Health systems may be reimbursed up to $14 062.50 (~50% of the acquisition cost of low-dose andexanet alfa) for qualifying Medicare inpatient cases. The NTAP for andexanet alfa is set to expire 3 years from the CMS effective approval date of October 1, 2018. Additionally, hospitals that "drip and ship" andexanet alfa may be able to apply for reimbursement of outpatient administration using specific C codes or J codes (personal communication with Evan Howland, Portola, January 11, 2019).[63] Close collaboration between clinicians and the health system billing department will ensure optimal use of these cost mitigation strategies.

3.9.3 | Operational logistics

Given the high cost and prothrombotic potential of DOAC reversal agents, judicious use is essential. Centralized, controlled access is prudent to optimize appropriate use (eg, indication, dosing) and storage (eg, refrigeration, light protection). In the Anticoagulation Forum's online survey, 100% of responding hospitals with andexanet alfa on formulary reported storage within the main pharmacy. Because DOAC reversal agents are usually given in urgent or emergent situations, controlled access must be carefully and effectively balanced with infrastructure that promotes rapid delivery to the bedside. Standardized tools and processes should be implemented to facilitate stat routing of orders to the pharmacy department for rapid pharmacist review and order processing. Dosing should be simplified whenever possible and when supported by evidence, such as fixed dose vs weight-based dosing of PCCs,[31,32] to avoid dosing errors and delays in care. Dose preparation may also contribute to prolonged turnaround. For example, a low dose of andexanet alfa is 880 mg and requires five 200 mg vials (with 120 mg waste). Each vial requires approximately 3 to 5 min for dissolution and then must be transferred to a syringe or IV bag. In our survey, hospitals with andexanet alfa on formulary that have administered doses reported turnaround times ranging from 20 to 60 min. Strategies that minimize admixture time,

TABLE 3 Characteristics of DOAC reversal agents

	Andexanet Alpha	Idarucizumab	4F-PCC	APCC
Trade name (Manufacturer)	Andexxa® (Portola Pharmaceuticals)	Praxbind® (Boehringer Ingelheim)	Kcentra® (CSL Behring)	FEIBA® (Takeda)
Classification	Specific antidote	Specific antidote	Non-specific prohemostatic agent	Non-specific prohemostatic agent
Onset of action	2 to 5 min[59]	<5 min[60]	Unknown in DOAC patients	Unknown in DOAC patients
Half-life	• Pharmacodynamic: 30 to 60 min[59] • Terminal: 5 to 7 h[14]	• Pharmacodynamic: 45 min[60] • Terminal: 4 to 8 h[60]	Dependent on half-lives of individual clotting factors Elevated levels of clotting factors likely persist for at least 24 h	Dependent on half-lives of individual clotting factors Elevated levels of clotting factors likely persist for at least 24 h
Route of elimination	Unknown	Renal[60]	Hepatic	Hepatic
Dosage forms	Generation 1: 100 mg vials of lyophilized powder for reconstitution (To be phased out per US FDA)[14] Generation 2 (2019): 200 mg vials of lyophilized powder for reconstitution	5 g boxed kit, provided as two separate ready-to-use vials each containing 2.5 g/50 mL idarucizumab[13]	Potency based on FIX content Single use boxed kits containing: • A suitable volume (20 or 40 mL) of sterile water for injection • Filter transfer set • One vial lyophilized powder for reconstitution in nominal dosage strengths: • 500 unit vial (range 400-620) • 1000 unit vial (range 800-1240) • Alcohol swab	Potency based on amount of factor VIII inhibitor bypassing activity in units Single use boxed kits containing: • A suitable volume (10 mL, 20 mL or 50 mL) of sterile water for injection • One needleless transfer device • One vial lyophilized powder for reconstitution in nominal dosage strengths: • 500 units (range 350-650) • 1000 units (range 700-1300) • 2500 units (range 1750-3250)
Acquisition cost	100 mg vial: $2750 (To be phased out per US FDA) 200 mg vial: $5500	5 g kit: ~ $3500 to 4200[a]	~ $1.60 to 2.77 per unit	$1.64/unit[a]
New technology add on payment (NTAP) available from CMS	Up to $14 062.50 or 50% of low dose acquisition cost by the CMS when andexanet exceeds the Medicare Severity Diagnosis-Related Groups payment amount using pre-specified codes	None	None	None
Storage	• Intact vials require refrigeration (2°C-8°C) • Consider clearly emphasizing andexanet alfa is only used for reversal of factor Xa inhibitors via use of bold lettering and/or brightly colored labels on storage areas/bins	• Intact vials require refrigeration (2°C-8°C) and storage in the original carton to protect from light • Consider clearly emphasizing idarucizumab is only to be used for dabigatran reversal via use of bold lettering and/or brightly colored labels on storage areas/bins	• Does not require refrigeration • Store in the original carton to protect from light[15]	• Does not require refrigeration • Store in the original carton to protect from light[16]

(Continues)

TABLE 3 (Continued)

	Andexanet Alpha	Idarucizumab	4F-PCC	APCC
Stability	• Shelf life is 24 months • Reconstituted vials • 8 h at room temperature (25°C) • 24 h refrigerated (2°C-8°C) • Reconstituted product in IV bag • 8 h at room temperature (25°C)	• Shelf life is 24 months • Unopened vials may be maintained at room temperature (25°C) up to 48 h if stored in original package and protected from light • At room temperature and not protected from light, it must be used within 6 h[61]	• Shelf life is 36 months • Reconstituted Kcentra must be used within 4 h[15]	• Shelf life is 24 months • Must be used within 3 h after reconstitution • Do not refrigerate after reconstitution[16]
Preparation	• Reconstitute each 200 mg vial with 20 mL sterile water for injection • Swirl and do not shake to avoiding foaming • Dissolution time is 3 to 5 min per vial • Final concentration 10 mg/ ml • Withdraw reconstituted solution using a 60 mL syringe and transfer to an empty polyolefin or polyvinyl chloride IV bag with a volume of ≤250 ml[14]	• May be delivered to bedside as intact kit. Allows return of unused product to pharmacy • No preparation required if giving as 2 consecutive 2.5 g infusions • If giving as 2 consecutive 2.5 mg boluses, withdraw reconstituted contents from each vial with a sterile syringe[13]	• May be reconstituted at the bedside using provided diluent and transfer kit. Allows return of unused product to pharmacy • Multiple vials of reconstituted Kcentra may be pooled in a syringe or empty IV bag for administration	• May be reconstituted at the bedside using provided diluent and transfer kit. Allows return of unused product to pharmacy • Multiple vials of reconstituted FEIBA may be pooled in a syringe or empty IV bag for administration
Administration	• Administer via a separate infusion line until further data available • Prime the infusion line with the appropriate volume • Bolus given IV at 30 mg/min (3 mL/min) using a 0.2 to 0.22 μm in-line low protein binding filter • Infusion given IV at 4 mg/min (0.4 mL/min) using a 0.2 to 0.22 μm in-line low protein binding filter[14] • Flush the IV line with normal saline to ensure delivery of full dose	• If a pre-existing intravenous line is used for administration of idarucizumab, it must be flushed with normal saline prior to infusion • New IV lines should be primed • No other infusion should be administered simultaneously via the same intravenous access • Administer the 2 vials as two consecutive infusions or as two boluses using a syringe within 15 min • Flush the IV line with normal saline to ensure delivery of full dose[15]	• Administer through a separate infusion line and do not mix with other medicinal products • The total dose of Kcentra should be infused within 15 to 30 min • More rapid administration may be done depending on clinical situation, but monitoring for signs and symptoms of thrombosis is essential	• Flush venous access lines with isotonic saline prior to and after infusion of FEIBA • Do not administer in the same tubing or container with other medicinal products • The total dose of FEIBA should be infused within infused within 15 to 30 min • More rapid administration may be done depending on clinical situation, but monitoring for signs and symptoms of thrombosis is essential

Abbreviations: CMS, Centers for Medicare and Medicaid Services; DOAC, direct oral anticoagulant; US FDA, United States Food and Drug Administration.
[a]May vary by vendor. These numbers are from Cardinal Health as of January 7, 2019.

such as rapid, concurrent reconstitution of all needed vials, should be sought. Although it may add to turnaround time, expedient hand-delivery rather than pneumatic tube delivery of these critical, high-cost agents is suggested to avoid product degradation and/or physical loss. Realistic expectations of turnaround times for DOAC reversal agents should be communicated within protocols and to individual providers as this may mitigate discontent and frustration.

3.9.4 | Appropriate utilization

It is important for health systems to conduct regular formulary and protocol reviews to identify needed modifications based on availability and evolving evidence pertaining to DOAC reversal strategies. For example, the specific antidotes have relatively short half-lives (Table 3). Whether repeat dosing in some clinical situations is warranted has not been adequately studied.[64] Comparative effectiveness studies of DOAC reversal strategies are lacking, making it challenging to draw definitive conclusions as to their overall risk vs benefit and impact on patient important outcomes such as mortality.[21,26] Health systems should remain well-informed as to emerging evidence related to DOAC reversal and adjust practices accordingly. Additionally, it is essential to clearly delineate restrictions on prescribing and use of DOAC reversal agents based on input from key stakeholders, including but not limited to emergency medicine, trauma, neurosurgery, critical care, and pharmacy. In our online survey, all responding hospitals with andexanet alfa on formulary reported strict criteria for use, such as intracranial hemorrhage or major gastrointestinal bleeding, apixaban or rivaroxaban use within the prior 18 h, no recent administration of PCC or APCC, and repeat dosing not permitted. Many also reported that prescribing is limited to specific providers, such as attending physicians of particular specialties. These types of restrictions, once agreed upon, should be embedded within institutional reversal guidelines, protocols, and order sets to facilitate adherence. Importantly, a mechanism for reporting inappropriate prescribing to hospital administration will provide valuable support to frontline clinicians charged with promoting adherence to the restrictions.

We support the Joint Commission's National Patient Safety Goal (NPSG) 03.05.01 pertaining to reducing harm from anticoagulant therapy. Element of performance (EP) 2 of this NPSG states that all healthcare entities that dispense anticoagulant medications should "use approved protocols and evidence-based guidelines for reversal of anticoagulation and management of bleeding events related to each anticoagulant medication".[65] We further suggest that health systems utilize standardized, evidence-based practices to manage patients requiring anticoagulant reversal for urgent invasive procedures. Additionally, health systems should fully leverage their electronic health record whenever possible to support clinicians in appropriate use of DOAC reversal strategies. Lack of familiarity with the DOACs among clinicians has been repeatedly reported in the literature,[61,66,67] and is likely to be true of DOAC reversal strategies as well. Idarucizumab is specific for dabigatran reversal, and will have no effect on factor Xa inhibitors. Similarly, andexanet alfa will not reverse dabigatran. Utilization of the incorrect specific antidote may lead to patient harm and unnecessary drug costs. Use of standardized electronic order sets that contain evidence-based clinical decision support will facilitate efficient selection of the appropriate reversal strategy for a given clinical situation.[68] Healthcare staff and patients should receive education related to DOACs and their reversal at regular intervals. Provider education content should encompass not just clinical aspects, such as when to use reversal agents, but also operational aspects, such as electronic order sets for rapid ordering of DOAC reversal agents. All patients prescribed an oral anticoagulant should be counseled to obtain and wear a medical alert bracelet or necklace, or carry a wallet card, that states which specific oral anticoagulant they are taking, and if possible, the time(s) they typically take their medication. This will aid in implementation of prompt, appropriate reversal interventions when needed.

Lastly, health systems should identify means to consistently track and evaluate DOAC reversal cases. Granular details should include reversal agent utilized, appropriateness of use, procedural adherence, process measures (eg, turnaround times), and outcome measures such as achievement of hemostasis, thrombotic events, and mortality. Hospitals should use internal benchmark data for continuous quality improvement regarding management of DOAC-associated bleeding events, with regular feedback to staff and administration. Such efforts clearly require a resource commitment, and this should be regarded as an important investment towards improved patient care and patient safety.

3.9.5 | Guidance statement 9

To promote optimal use of DOAC reversal practices, we suggest that health systems develop and implement overarching strategies that promote multidisciplinary, shared stewardship of these agents. We suggest utilization of evidence-based clinical tools and processes that facilitate adherence with agreed-upon restrictions for judicious prescribing and use. We suggest system-level approaches be streamlined to the fullest extent possible via leveraging of the electronic health record, as well as maximized efficiency of pharmacy order processing, admixture, and delivery strategies. We further suggest that health systems develop contingency plans to be prepared for acquisition challenges, as well as close collaboration with vendors and billing departments to capitalize on cost mitigation opportunities. We suggest periodic formal evaluation of DOAC reversal practices to assess for appropriateness and identify opportunities for further optimization. Lastly, we suggest that dedicated stewardship programs be established. Whenever possible, they should be used to drive development, implementation, consistent application, and evaluation of anticoagulation-related optimization strategies including, but not limited to, appropriate and judicious use of DOAC reversal agents.

4 | CONCLUSION

With the recent advent of potentially life-saving, but also costly and potentially prothrombotic DOAC reversal agents, it is imperative that clinicians and institutions be prepared to use these agents in a manner that is both cost-effective and optimizes patient outcomes. Prudent use of DOAC reversal agents requires consideration of indications and appropriate use; knowledge of how the agents are stored,

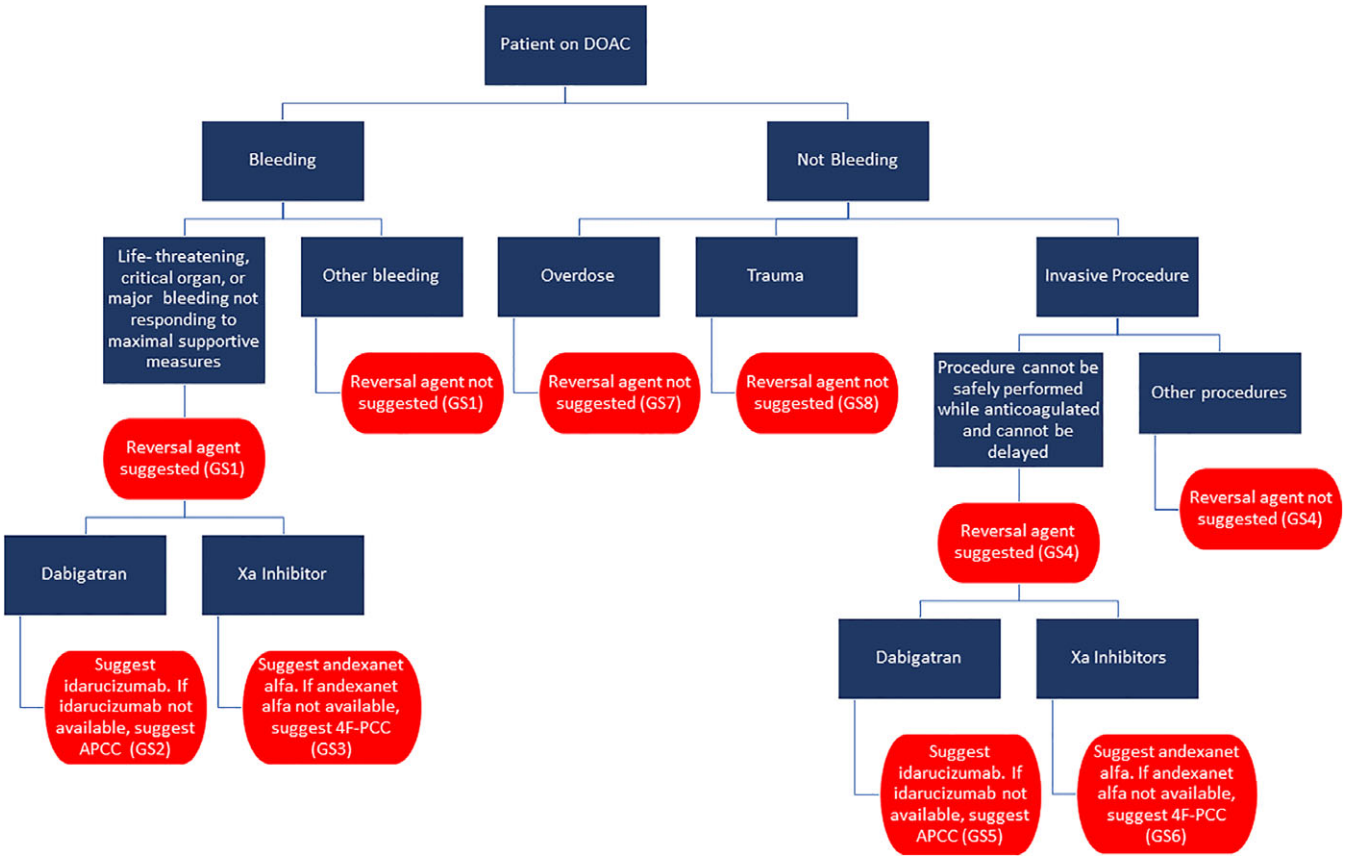

FIGURE 1 Summary of guidance on DOAC reversal. Please refer to the text and Table 1 for detailed guidance statements. APCC, activated prothrombin complex concentrate; DOAC, direct oral anticoagulant; GS, guidance statement; 4F-PCC, four-factor prothrombin complex concentrate

prepared, and administered; and management strategies and stewardship at the health system level. Table 1 and Figure 1 summarize our guidance statements for DOAC reversal.

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CONFLICT OF INTEREST

Adam Cuker reports that his institution has received research funding on his behalf from Alexion, Bayer, Bioverativ, Novo Nordisk, Pfizer, Shire, Spark, and Syntimmune and that he has served as a consultant for Genzyme, Kedrion, and Synergy. Allison Burnett reports that she has received honoraria from Wolters Kluwer. Mark Crowther reports that his institution has received research funding on his behalf from Bayer, Pfizer, Heart and Stroke Foundation, and Leo pharma; that he has received personal fees from Shionogi, Alexion, Octapharma, BMS Canada, CSL Behring, Servier Canada, Diagnostica Stago and Asahi Kasei; that he has sat on data safety monitoring boards for Daiichi; and that he holds stocks in Alnylam. Jack Ansell reports that that he has served as a consultant for Alere, Instrumentation Laboratories, Perosphere, and Roche Diagnostics and that he holds stock in Perosphere. Diane Wirth reports that she has served on speaker bureaus for Janssen and Portola and that she has served as a consultant for EMMI Solutions. Scott Kaatz reports that his institution has received research funding on his behalf from Janssen and that he has served as a consultant or advisory board member for BMS, Janssen, Pfizer, Portola, and Roche. Darren Triller and Elizabeth M. Van Cott report that they have nothing to disclose.

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