

PRACTICE



THERAPEUTICS

Specific antidotes for bleeding associated with direct oral anticoagulants

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An 83 year old woman is brought to the emergency department by her care giver who noticed her altered mental status following two episodes of passing black faeces. The woman has a history of ischaemic stroke associated with atrial fibrillation and hypertension and is on dabigatran for stroke prevention. She took her last dose a few hours ago. Computed tomography of the head shows no acute intracranial abnormalities. Abdominal and rectal exams are normal. Her blood pressure is 82/56 mm Hg. The multidisciplinary team in charge of her care arrives to talk with her and her family about antidotes for reversing her anticoagulation.

Direct oral anticoagulants (DOACs) are a relatively new class of oral anticoagulants developed as alternatives to vitamin K antagonists such as warfarin, and are indicated in non-valvular atrial fibrillation and venous thromboembolism (Box 1).

Patients on DOACs might require rapid reversal of anticoagulant activity in situations such as a life threatening bleed, major trauma, or urgent surgery. The average half-life of DOACs is around 12 hours in healthy adults. All DOACs are eliminated renally to some degree (table 1⇓). Expert opinion suggests that in many instances, bleeding can be managed by withholding the DOAC and providing supportive care such as fluid resuscitation and transfusion of blood products,²¹ particularly in patients with normal renal function or if the last dose was taken several hours beforehand. An antidote might be indicated in patients with major or life threatening bleeding such as intracranial haemorrhage or massive gastrointestinal bleed who are clinically unstable (hypotension, mental status changes), who have diminished renal function or recent DOAC ingestion, or who are not responding to general supportive measures.

In this article, we discuss strategies to reverse anticoagulant activity of DOACs, focusing on newer specific antidotes.

What drugs are available to reverse bleeding caused by direct oral anticoagulants?

Non-specific reversal agents

Non-specific pharmacologic strategies to manage bleeding associated with DOACs include administration of coagulation factor concentrates, such as inactive prothrombin complex concentrates (Octaplex, Beriplex/KCentra), activated prothrombin complex concentrates (FEIBA), and recombinant activated factor VII (rFVIIa, Novoseven).²² These agents, which comprise either active or inactive clotting factors, have been investigated in patients on vitamin K antagonists such as warfarin or acenocoumarol. Patients being treated with vitamin K antagonists experience diminished levels of circulating clotting factors in plasma over time. Thus, replenishment with factor concentrates is logical and has been shown to be beneficial in reversing vitamin K antagonist anticoagulant activity.²³⁻²⁶

Conversely, patients on DOACs have normal levels of clotting factors in plasma, but enzymatic activity towards thrombus formation is directly blocked, making administration of factor concentrates less logical and beneficial.

Specific antidotes

More recent research focuses on antidotes specifically engineered to bind and neutralise the anticoagulant activity of both direct thrombin inhibitors and direct factor Xa (FXa) inhibitors. The agents currently being investigated include idarucizumab, a drug-specific antidote; andexanet alfa, a class-specific antidote; and ciraparantag, a universal antidote. Of these, only idarucizumab has been licensed for this indication. Table 2⇓ lists characteristics of these drugs.

What you need to know

Direct oral anticoagulants (DOACs) are shown to be safe and effective alternatives to vitamin K antagonists in appropriately selected patients, despite a lack of specific antidotes.

For most bleeding events, expert opinion suggests that cessation of the DOAC and supportive care will likely be sufficient.

Currently, only one specific antidote, idarucizumab, is licensed for use and is indicated to reverse dabigatran in patients with life threatening haemorrhage or need for urgent surgery.

Box 1: Direct oral anticoagulants (DOACs)*Commercially available DOACs include*

the direct thrombin inhibitor dabigatran etexilate (Pradaxa)

the direct factor Xa inhibitors apixaban (Eliquis), edoxaban (Lixiana, Savaysa), and rivaroxaban (Xarelto).

DOACs have advantages over vitamin K antagonists (eg, warfarin), including

rapid onset and offset of action

fewer drug, disease state, and dietary interactions

fixed dosing

no need for routine monitoring of anticoagulant activity.^{1,2}

Randomised controlled trials and meta-analyses among patients with non-valvular atrial fibrillation or acute venous thromboembolism have shown DOACs to be at least as effective as vitamin K antagonists in preventing or treating thromboembolic events.³⁻¹³

Candidates for DOAC treatment meet the following criteria:

Good renal and hepatic function

Lack of major drug interactions with concomitant P-glycoprotein or CYP3A4 inhibitors or inducers (eg, amiodarone, carbamazepine, clarithromycin, dronaderone, ketoconazole, itraconazole, phenytoin, ritonavir, or rifampin)

High likelihood of adherence (because of the short half-life of DOACs)

Confirmed ability to access the drug for the duration of treatment, as DOACs are expensive.^{1,2}

DOACs are shown to be associated with less major bleeding and total bleeding compared with warfarin.¹⁴ Despite an improved safety profile, many clinicians and patients are hesitant to use DOACs because of a lack of antidotes.

Patients treated with DOACs and experiencing a major bleed require fewer interventions and have better outcomes, including less fatal bleeding, than patients treated with vitamin K antagonists,¹⁵⁻¹⁹ despite no available specific DOAC antidotes at the time of those analyses.

How well do they work?

The evidence on effectiveness and safety of these drugs is still preliminary. Most trials have not had a comparator arm or have been conducted in healthy volunteers, thereby making an assessment of effectiveness difficult.

Idarucizumab

A phase III, industry-sponsored trial, RE-VERSE AD, examined the efficacy and safety of idarucizumab in patients treated with dabigatran who had serious bleeding or required urgent surgery. Publication of interim data on 90 patients³¹ led to expedited licensure of this agent in 2015. The study has now been completed and data for 494 patients were presented at the American Heart Association meeting in November 2016.³² All patients received 5 g idarucizumab and were followed for 90 days, without a comparator group. The single cohort design was chosen as there is no standard of care in this setting and it would be unethical to compare an antidote to placebo alone.

Anticoagulant activity was measured using dilute thrombin time and ecarin clotting time, which have shown good correlation with dabigatran plasma concentrations. Reversal effects occurred within minutes, and values remained below the upper limit of normal for both assays through 24 hours. Time taken to stop bleeding in both groups ranged from 3 to 5 hours. Results are summarised in table 3↓.

There were no reports of hypersensitivity. At 90 days follow-up, 6.3% of patients (31/494) had experienced a thrombotic event, including 8 ischaemic strokes, 7 myocardial infarctions, 15 venous thromboembolisms, and 1 systemic arterial embolism. Of patients at risk at 90 days, nearly 20% (47/254) died in both groups combined. Without a comparator group, it is difficult to state with certainty whether or not idarucizumab contributed to these events. Thrombotic events might also be due to

anticoagulant reversal in patients with increased underlying thrombotic risk, increased coagulation activation in the setting of bleeding, and acute medical illness, or delayed resumption of anticoagulation in patients with ongoing risk factors for thrombosis, such as diminished mobility while hospitalised.

Recent analyses indicate that resumption of anticoagulation after major haemorrhage is associated with better outcomes, including mortality, compared with not resuming.³³

Idarucizumab appears effective for dabigatran reversal, however additional data are needed and the lack of a comparator group makes it challenging to draw definitive conclusions. Haemostasis was not rigorously defined, so these outcomes must be interpreted with caution. Importantly, an appreciable number of patients had no clinically relevant dabigatran activity at baseline. For example, 113/494 patients had a normal dilute thrombin time at study enrolment. This highlights the potential utility of readily available screening assays to identify patients who are not likely to benefit from high cost antidotes.³⁴

Andexanet alfa

Two phase III trials have reported good safety and efficacy with andexanet alfa for reversal of apixaban and rivaroxaban in healthy adult volunteers (age 50-75) compared with placebo.³⁵ ANNEXA-4 is an ongoing phase III multicenter, prospective, open-label, single group study of adult anticoagulation patients with acute major bleeding within 18 hours of administration of a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin). There is planned enrolment of 250 patients, with encouraging interim results for 67 patients recently published.³⁶ The manufacturer, Portola Pharmaceuticals, is currently seeking licensure in North America and Europe.

Ciraparantag

In a double-blind Phase II, placebo-controlled trial among 80 healthy adult men, ciraparantag resulted in immediate and sustained full reversal of edoxaban.³⁷ Similar results have been reported for enoxaparin.³⁸ While these results are encouraging, data from later phase trials is needed regarding clinical outcomes in patients receiving repeat doses and with active bleeding complications. A potential advantage of ciraparantag over idarucizumab and andexanet alfa is its universal application to reverse all DOACs (and many other anticoagulants), which might expedite antidote selection and administration.

How cost effective are these antidotes?

Given their infancy and lack of comparator groups in phase III studies to date, data on cost effectiveness for these specific antidotes is not yet available.

The cost of idarucizumab in the United States is approximately \$3500 for a 5 g 2-vial kit. At our institution, prothrombin complex concentrate (KCentra) costs \$1.60/unit and is dosed at 50 units/kg for DOAC associated major haemorrhage. For an average 70-80 kg patient, this equates to \$5600-\$6400, making idarucizumab potentially less expensive. Cost data for andexanet alfa and ciraparantag are not available.

How do they compare with other reversal agents?

Evidence for use of factor concentrates for DOAC reversal is limited to in vitro studies, animal models, and healthy human volunteers, and shows conflicting results.²² No human studies of specific DOAC antidotes have included an active comparator arm. Thus, it remains unknown if non-specific pharmacological approaches to DOAC reversal such as prothrombin complex concentrates might be as safe and effective as these medications.³⁹

Further comparative effectiveness studies are needed to understand the risks and benefits of prothrombin complex concentrates and specific antidotes in the setting of DOAC related bleeding.

Mark Crowther is on the advisory board of Portola pharmaceuticals and has advised on development of Andexanet alfa. He has done consultancies with Boehringer Ingelheim which produces dabigatran and idarucizumab, Bayer and Janssen and BMS/Pfizer, which produce direct oral anticoagulants.

Deborah Siegal is on the advisory board of Boehringer Ingelheim which produces dabigatran and idarucizumab; and of Daiichi Sankyo which produces edoxaban. She has given a lecture on this topic for Portola Pharmaceuticals.

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Tips for safe prescribing and use of DOAC antidotes

- Only consider DOAC antidotes when there is a life-threatening bleed or need for urgent invasive procedures.
- Confirm which DOAC the patient is taking, as the only currently licensed available antidote, idarucizumab, will only reverse dabigatran.
- Determine the time of last ingestion, if possible, and evaluate current renal function.
- Develop easy to access guidelines within your institution to promote rapid distribution and accurate administration of needed antidotes.
- Discuss with your patient resuming anticoagulants in a timely manner to avoid thrombotic complications and death.

Tips for patients

- Be familiar with the brand and generic names of your specific blood thinner, as well as the name of its antidote.
- Be aware of why you take a blood thinner and for what period of time you are to take it.
- Always take your blood thinner as directed (eg, never miss or take extra doses).
- Pick a set time to take your blood thinner and stick to that schedule.
- Know the signs and symptoms of clotting and bleeding, what to do if you have problems and when to call for help.
 - Clotting
 - pain, redness, warmth or swelling in your extremities
 - shortness of breath, dizziness, sweating/fever, racing heart, chest pain, bloody cough
 - extreme headache, weakness on one side of your body, slurred speech, trouble with speaking, drooping or numbness of the face
 - Bleeding
 - weakness, fatigue, dizziness, light headedness
 - drowsiness, confusion, nausea
 - sudden severe back pain
 - excessive bruising
 - blood in the urine or stool
 - nosebleed that does not stop within 10 minutes with compression
 - vomiting or coughing up blood
 - excessive bleeding during menstrual period
- Call for help if you
 - experience any of the above signs and symptoms
 - are involved in a major accident
 - experience a blow to the head
 - are unable to stop any bleeding
- Obtain and wear a medical alert bracelet that states the name of your specific blood thinner.
- Carry a wallet card that has details about what blood thinner you are on, what time of day you take it, and contact information for the doctor who manages your blood thinner.
- Follow up with your doctor regularly (at least annually, and possibly as frequently as every three to six months) so they can check your kidney and liver function, make sure you do not have any concerning drug interactions with your blood thinner, to let them know about any upcoming surgeries you might need, and to reassess your need for ongoing blood thinner therapy.
- Communicate openly with your doctor about any problems you are having with your blood thinner (eg, difficulty obtaining medication, side effects, bleeding or clotting problems).

How patients were involved in the creation of this article

We based the patient tips on questions commonly asked by our patients. We solicited input on the wording and content of the patient tips from laypersons unfamiliar with this topic. They provided helpful feedback such as using less medical terminology, to make it easier for patients to understand.

Education into practice

- Does your hospital have an anticoagulant reversal protocol, guideline, or clinical pathway and does it include DOACs and their antidotes?

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Tables

Table 1 | Select pharmacokinetics of DOACs20

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target(s)	Ila	Xa	Xa	Xa
Peak effect	1.5-3 h	2-4 h	1-3 h	1-2 h
Half-life*	12-17 h	5-9 h	9-14 h	10-14 h
Renal elimination	80%	33%	25%	35-50%

Table 2 | Specific antidotes for DOAC reversal²¹²⁷²⁸²⁹

	Idarucizumab	Andexanet alfa	Ciraparantag
DOAC(s) reversed	Dabigatran	Apixaban Edoxaban Rivaroxaban	Dabigatran Apixaban Edoxaban Rivaroxaban
Mechanism of action (↓)	Monoclonal antibody fragment that binds dabigatran with affinity 350-fold greater than between dabigatran and thrombin	Decoy Xa molecule that binds FXa inhibitor anticoagulants, restoring function of endogenous FXa	Anticoagulant binding via non-covalent hydrogen bonds and charge-charge interactions
Studied doses	5 g IV given as two 2.5 g boluses over 5-10 minutes within 15 minutes of each other	Apixaban: 400 mg bolus+480 mg infusion over 2 hours Rivaroxaban, edoxaban, enoxaparin: 800 mg bolus+960 mg infusion over 2 hrs If >7 hrs since last rivaroxaban dose, decrease bolus and dose by 50%	100-300 mg IV single dose
Onset of action	<5 minutes	<2 minutes	5-10 minutes
Half-life	Biphasic Initial: ~45 minutes Terminal: ~10 hours	1 hour	Duration of action: 24 hours
Elimination	Renal	Not reported	Renal
Storage	Refrigerated	Refrigerated	Room temperature
Status	Licensed by US, Canadian and European regulators	Application for license submitted to regulators	Phase II trials
Approved indications	Reversal of dabigatran in patients with: - Need for urgent/emergent surgery - Life-threatening or uncontrolled bleeding	N/A	N/A
Comments	Will not reverse FXa inhibitors	Will not reverse dabigatran Also binds and alters activity of the indirect FXa inhibitors UFH, LMWH, and fondaparinux ³⁰	Reported to bind to all DOACs, UFH, LMWH, and fondaparinux ³⁰

DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; UFH: unfractionated heparin; Xa: factor Xa

Table 3| Summary of clinical trial results for REVERSE-AD32

Agent	DOAC reversed	Study design	Study population	Comparator	Primary efficacy outcome	Secondary outcomes
Idarucizumab	Dabigatran	Phase III multicenter prospective cohort	n=494 [†] Adult patients on dabigatran requiring reversal for: • life threatening bleed (Group A); n=298 • need for urgent surgery (Group B); n=196	None	Maximum % reversal of anticoagulant effect (dTT) within 4 hours of infusion [‡] Group A 235/238 (>98%) Group B 141/143 (>98%) <i>Similar results for ECT</i>	<u>Time to haemostasis</u> Group A: 3.5 hours Group B: 4-5 hours <u>Peri-procedural hemostasis (Group B)</u> 178/191 (93%) <u>Thrombotic events</u> <u>30 days</u> Group A 13/298 (4.4%) Group B 9/196 (4.6%) <u>90 days</u> Groups A and B 31/494 (6.3%) <u>Re-initiation of anti-thrombotic therapy</u> Group A 216/298 (72%) Median time=5.3 days Group B 177/196 (90%) Median time: 1.2 days <u>Mortality</u> <u>30 days</u> Group A 31/250 (12.3%) Group B 20/164 (12.4%) <u>90 days</u> Group A 27/149 (18.7%) Group B 20/105 (18.5%)

[†]Planned enrolment: 503. Data presented is for interim analysis of 494 patients presented at American Heart Association meeting

[‡]Only calculated for patients with elevated dTT at baseline

dTT: dilute thrombin time, an assay that measures thrombin mediated conversion of fibrinogen to fibrin

ECT: ecarin clotting time, an assay that measures the intermediary protease meizothrombin which is generated during conversion of prothrombin to thrombin

dTT and ECT show good correlation with dabigatran plasma concentrations

Figure

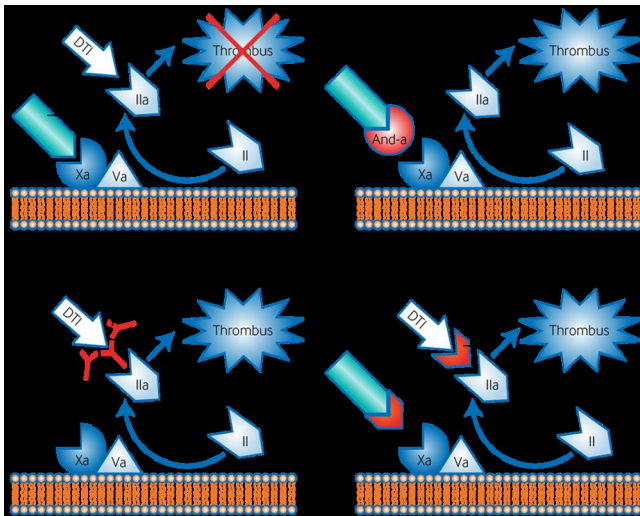


Fig 1 Mechanism of action of specific direct oral anticoagulant antidotes. A: Under normal hemostatic conditions, the prothrombinase complex (comprising factor Xa and Va) converts prothrombin (factor II) to thrombin (factor IIa) as needed. Presence of a direct factor Xa inhibitor prevents this conversion and thus thrombus formation. Similarly, the presence of a direct thrombin inhibitor (DTI, dabigatran) prevents thrombus formation. B: Idarucizumab, an antibody fragment, binds dabigatran, preventing thrombin inhibition and enabling thrombus formation. C: Andexanet alfa (And-a) acts as a decoy Xa molecule, binding Xa inhibitors and allowing thrombus formation. D: Ciraparantag binds factor Xa inhibitors and dabigatran via hydrogen bonds and charge-charge interactions to prevent thrombin inhibition and allow thrombus formation