Reversal agents for non-vitamin K antagonist oral anticoagulants

Jerrold H. Levy[1], James Douketis[2,3] and Jeffrey I. Weitz[2,3]

Abstract | The non-vitamin K antagonist oral anticoagulants (NOACs) include dabigatran, which inhibits thrombin, and apixaban, betrixaban, edoxaban, and rivaroxaban, which inhibit coagulation factor Xa. Although clinical studies of NOACs were conducted without antidotes, patient outcomes with major bleeding when receiving NOACs were no worse than those in patients treated with a vitamin K antagonist. Nonetheless, in patients with life-threatening bleeding or requiring urgent surgery, the capacity for rapid NOAC reversal is likely to increase patient safety. Three NOAC reversal agents are in various stages of development: idarucizumab, a specific reversal agent for dabigatran; andexanet alfa, which reverses factor Xa inhibitors; and ciraparantag, which is purported to reverse all NOACs. Idarucizumab is licensed in many countries, andexanet is under consideration by regulatory agencies, and ciraparantag is undergoing phase III evaluation. In the absence of licensed reversal agents for the oral factor Xa inhibitors, prothrombin complex concentrates are often used in patients taking these agents who present with life-threatening bleeding. In this Review, we summarize the approved indications for the NOACs, outline how to measure their anticoagulant effects, describe the mechanism of action of the reversal strategies, assess the preclinical and clinical data supporting their use, provide guidance on potential indications for reversal, and offer a management approach for patients treated with NOACs who present with serious bleeding or require urgent surgery.

Non-vitamin K antagonist oral anticoagulants (NOACs) were developed to overcome the limitations of vitamin K antagonists (VKAs), such as warfarin. Designed to be given in fixed doses without routine coagulation monitoring, the NOACs are at least as effective as VKAs for the prevention of stroke and systemic embolism in patients with atrial fibrillation, or for treatment of venous thromboembolism, and are associated with less intracranial bleeding[1–4]. Five NOACs are currently available: dabigatran, which inhibits thrombin; and apixaban, betrixaban, edoxaban, and rivaroxaban, which inhibit coagulation factor Xa[1–4].

Anticoagulants of all types can contribute to bleeding, and the NOACs are no exception. When compared with VKAs for stroke prevention in atrial fibrillation and for treatment of venous thromboembolism in phase III trials that included >100,000 patients, rates of major bleeding with the NOACs were similar to or lower than those with VKAs[2]. A consistent finding was that NOACs were associated with a lower risk of intracranial bleeding than VKAs and with a risk of nonintracranial major bleeding that was similar to or lower than that with VKAs[2]. However, compared with VKAs, NOACs seem to confer an increased risk of gastrointestinal bleeding (dabigatran, edoxaban, and rivaroxaban) and have the potential to be associated with heavier menstrual bleeding (apixaban and rivaroxaban)[2,5,6]. VKAs can be reversed with vitamin K and prothrombin complex concentrates (PCCs). By contrast, no reversal agents were available for the NOACs when the phase III trials were conducted. Despite the lack of antidotes, the case–fatality rates in patients with major bleeding who were taking NOACs were similar to or lower than those in patients taking VKAs[7]. Nonetheless, the availability of reversal agents has the potential to increase the safety of NOACs in patients with life-threatening bleeding or in those requiring urgent surgery[7,8].

In this Review, we describe the licensed indications for the NOACs, outline how to measure the anticoagulant effects of the NOACs to help to identify patients in need of reversal and to monitor the extent of reversal, describe the mechanisms of action of the reversal strategies, review the preclinical and clinical data supporting their use, provide guidance on potential indications for reversal, and outline an approach to managing patients taking NOACs who present with serious bleeding or require urgent surgery.

[1]*Department of Anesthesiology, Critical Care, and Surgery, Duke University Medical Center, 2301 Erwin Road, 5691H HAFS, Box 3094, Durham, North Carolina 27710, USA.*
[2]*Department of Medicine, McMaster University, 1280 Main Street West, Hamilton, Ontario L8S 4L8, Canada.*
[3]*Thrombosis and Atherosclerosis Research Institute, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada.*

Correspondence to J.H.L.
jerrold.levy@duke.edu

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Key points

- The non-vitamin K antagonist oral anticoagulants (NOACs) include dabigatran, which inhibits thrombin, and apixaban, betrixaban, edoxaban, and rivaroxaban, which inhibit factor Xa
- Three NOAC reversal agents are in various stages of development: idarucizumab is licensed in many countries, andexanet is under consideration by regulatory agencies, and ciraparantag is undergoing phase III evaluation
- Idarucizumab is approved for dabigatran reversal in patients requiring emergency surgery or urgent procedures and in those with life-threatening or uncontrolled bleeding
- In the absence of licensed reversal agents for the oral factor Xa inhibitors, prothrombin complex concentrates are increasingly used in patients taking these agents who present with life-threatening bleeding

Indications and properties of NOACs

The NOACs that are currently available for clinical use include the direct thrombin inhibitor dabigatran etexilate (Pradaxa; Boehringer Ingelheim)[7], and the direct factor Xa inhibitors apixaban (Eliquis; Bristol-Myers Squibb/Pfizer)[7], betrixaban (Bevyxxa; Portola Pharmaceuticals)[9], edoxaban (Savaysa or Lixiana; Daiichi Sankyo), and rivaroxaban (Xarelto; Johnson and Johnson/Bayer HealthCare)[7]. To date, NOACs are indicated in four clinical settings: stroke prevention in patients with nonvalvular atrial fibrillation or flutter (apixaban, dabigatran, edoxaban, and rivaroxaban), treatment of venous thromboembolism (apixaban, dabigatran, edoxaban, and rivaroxaban), prevention of venous thromboembolism after hip or knee replacement surgery (apixaban, dabigatran, and rivaroxaban; edoxaban is also licensed for this indication but only in Japan), and prevention of venous thromboembolism in medically ill patients (betrixaban, but only in the USA).

Three pharmacological properties of the NOACs are pertinent in patients with serious bleeding or requiring urgent surgery. First, the NOACs have a rapid onset of action, with a peak anticoagulant effect 1–3 h after intake. Therefore, timing since the last dose is an important consideration in someone who presents with bleeding or requires urgent surgery. Second, NOACs have shorter half-lives than warfarin (10–14 h and 36–42 h, respectively). Therefore, without reversal, the period of supportive therapy for bleeding is shorter with the NOACs than with warfarin, and a delay of 8–12 h is likely to be sufficient to enable major surgery. Third, all the NOACs are cleared to some extent by the kidneys: 25% for apixaban, 6–13% for betrixaban, 80% for dabigatran, 50% for edoxaban, and 33% for rivaroxaban[7] (TABLE 1). This clearance is pertinent because patients with major bleeding or requiring urgent surgery might have acute kidney injury, in which case the NOAC can accumulate in the blood, and its clearance might be delayed. Therefore, with these points in mind, with a patient taking a NOAC who presents with serious bleeding or requires urgent surgery, it is important to identify which drug was prescribed for which indication, determine the dose that was taken and the time since the last dose, assess the severity of the bleed or the urgency of surgery, and measure the serum creatinine level and calculate the creatinine clearance to assess renal function.

Measuring anticoagulant effects of NOACs

Although the NOACs do not require routine anticoagulation monitoring, measurement of their anticoagulant effect can be helpful to determine their contribution to serious bleeding, identify the optimal timing of surgery, and detect accumulation in patients with acute

Table 1 | **NOAC targets, licensed indications, and considerations**[4,7,64]

Parameter	Apixaban	Betrixaban	Dabigatran	Edoxaban	Rivaroxaban
Target	Factor Xa	Factor Xa	Thrombin	Factor Xa	Factor Xa
FDA-approved indications	Nonvalvular AF, VTE (treatment*, secondary prevention, prophylaxis‡)	VTE (prophylaxis§)	Nonvalvular AF, VTE (treatment‖, secondary prevention, prophylaxis)	Nonvalvular AF, VTE (treatment§)	Nonvalvular AF, VTE (treatment*, secondary prevention, prophylaxis‡)
Safety in nonvalvular AF	Lower risk of major bleeding than with warfarin	Lower risk of major bleeding than with warfarin	Higher risk of GI bleeding than with warfarin	Lower risk of major bleeding than with warfarin; higher risk of GI bleeding (60 mg dose) than with warfarin	Higher risk of GI bleeding than with warfarin
Specific reversal agent	Andexanet alfa	Andexanet alfa	Idarucizumab	Andexanet alfa	Andexanet alfa
Half-life (h)	12	20	8–15	10–14	7–11
Renal clearance (%)	25	6–13	80	50	33
Dialysable	No	No	Yes	No	No
Prodrug	No	No	Yes	No	No
Bioavailability (%)	60	34	6	62	60–80
Time to peak effect (h)	1–2	3–4	1–3	1–2	2–4

AF, atrial fibrillation; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; VTE, venous thromboembolism. *Twice daily for the first 21 days of VTE treatment; once daily for other indications for rivaroxaban or twice daily for apixaban. ‡Approved for VTE prophylaxis after knee or hip surgery only. §Prophylaxis of VTE in adult patients hospitalized for an acute medical illness and for extended use. ‖After 5–10 days of parental anticoagulant treatment only.

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Table 2 | **Laboratory testing for non-vitamin K antagonist oral anticoagulants**[13,15,20,57,65–67]

Drug	Quantitative assays	Qualitative assays	Not recommended
Direct factor Xa inhibitors (apixaban, betrixaban, edoxaban, rivaroxaban)	Specific, calibrated anti-factor Xa assays	None currently available; viscoelastic assays (ROTEM) are not predictive	Prothrombin time (except rivaroxaban where there can be a dose-related prolongation), activated partial thromboplastin time, dilute thrombin time or thrombin time assays, or heparin-specific assays such as the activated clotting time assay
Dabigatran	Diluted thrombin time (available in some specialized centres in the USA), ecarin clotting time (not available in the USA)	Activated partial thromboplastin time, thrombin time; viscoelastic assays (ROTEM) might correlate with plasma levels	Chromogenic anti-factor Xa assays, heparin-specific assays such as the activated clotting time assay

ROTEM, rotational thromboelastometry.

kidney injury[10–13]. The coagulation tests that are available to measure the anticoagulant effects of NOACs are outlined[14–16] (TABLE 2).

Dabigatran. The activated partial thromboplastin time (aPTT) and, if available, the thrombin time are useful screening tests. Dabigatran prolongs the aPTT in a concentration-dependent manner, but the results plateau with higher drug levels. The responsiveness of the aPTT to dabigatran is reagent-dependent, and some reagents are more sensitive than others. Nonetheless, a prolonged aPTT in a patient treated with dabigatran who presents with serious bleeding or requires urgent surgery would be an indication for reversal. Although a normal aPTT does not exclude the presence of dabigatran, a normal aPTT probably excludes a clinically important dabigatran anticoagulant effect, particularly if a highly sensitive aPTT is used[17]. The thrombin time is very responsive to the anticoagulant effect of dabigatran, and even low levels of dabigatran prolong the test results. Therefore, a normal thrombin time excludes the presence of dabigatran[18].

The diluted thrombin time and ecarin clotting or chromogenic assays have been introduced to quantify plasma dabigatran concentrations. A comparison of the ecarin chromogenic assay with the diluted thrombin times in blood from patients treated with dabigatran reported accurate drug level measurements over a wide range of dabigatran concentrations, and both tests could detect levels <50 ng/ml[19]. Although these assays are not approved by the FDA, they are licensed in other countries. However, the tests are not available in all hospitals. Viscoelastic testing using rotational thromboelastometry (ROTEM) has been shown to correlate with dabigatran levels and is another potential method for measuring its effects (TABLE 2).

Oral factor Xa inhibitors. The oral factor Xa inhibitors have a greater effect on the prothrombin time (PT) than on the aPTT. However, their effects on the PT vary depending on the reagent used for the test and on the drug. Rivaroxaban has the greatest effect on the PT, whereas apixaban has the least. Therefore, if a responsive thromboplastin reagent is used, the PT can be a helpful indicator for rivaroxaban but not for the other oral factor Xa inhibitors[15,20].

Plasma levels of the oral factor Xa inhibitors can be quantified using an anti-factor Xa assay with drug-specific calibrators. Alternatively, low-molecular-weight heparin can be used as the calibrator, and NOAC drug levels can then be determined by referencing drug-specific calibration curves constructed by determining the effect of known concentrations of the oral factor Xa inhibitor on anti-factor Xa activity determined using the low-molecular-weight heparin standard[21]. Although all modern coagulometers can perform anti-factor Xa assays with rapid turnaround times, the tests are not widely available. Viscoelastic testing (ROTEM) is not sensitive on the basis of current testing to determine anti-factor Xa activity (TABLE 2).

Specific reversal agents

Three specific NOAC reversal agents have been developed: idarucizumab, which reverses dabigatran; andexanet, which reverses apixaban, betrixaban, edoxaban, and rivaroxaban as well as heparins; and ciraparantag, which is purported to reverse all NOACs and heparins. Each of these agents has a distinct mechanism of action (FIG. 1) and pharmacological properties (TABLE 3).

Idarucizumab. Idarucizumab is a humanized monoclonal Fab antibody fragment that binds dabigatran with 350-fold higher affinity than thrombin and is licensed for clinical use in most countries[22,23]. After intravenous administration, idarucizumab has a half-life of approximately 45 min in patients with normal renal function, and a longer half-life in those with renal impairment[22,23]. In phase II studies that included younger volunteers (aged 18–45 years) and older volunteers (aged 45–80 years) with normal or moderately impaired renal function who were given dabigatran, idarucizumab produced rapid reversal as evidenced by normalization of the diluted thrombin time and reduction in the level of free dabigatran[22–24].

The RE-VERSE AD trial[17,25], a phase III, prospective cohort study, enrolled 503 patients treated with dabigatran who presented with serious bleeding (group A) or required urgent intervention or surgery that could not be delayed for at least 8 h (group B)[17,25]. Idarucizumab was administered as two intravenous boluses of 2.5 g (total of 5.0 g), each given over 5–10 min. This dose

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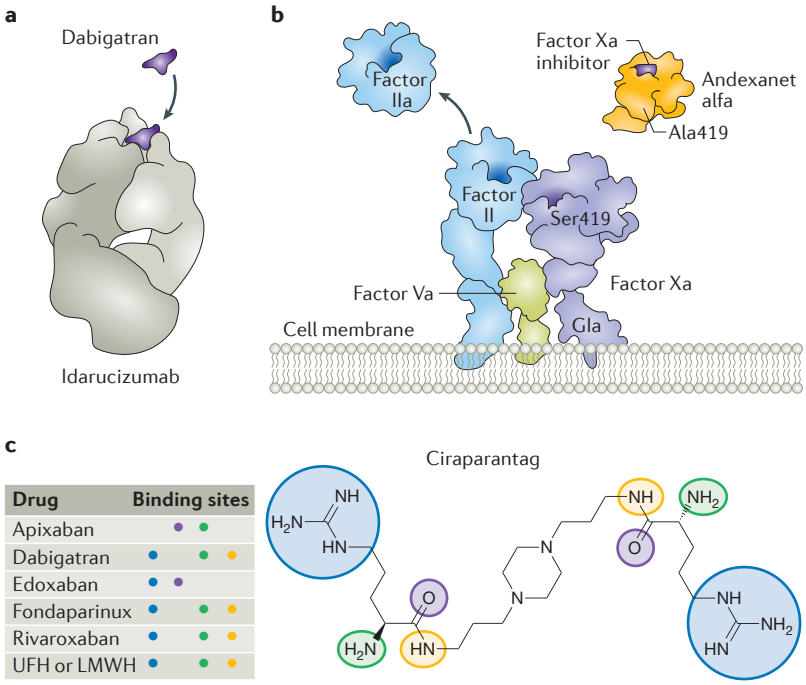

Drug	Binding sites
Apixaban	● ●
Dabigatran	● ● ●
Edoxaban	● ●
Fondaparinux	● ● ●
Rivaroxaban	● ● ●
UFH or LMWH	● ● ●

Figure 1 | **Reversal agents for non-vitamin K antagonist oral anticoagulants.** **a** | Idarucizumab is an antibody antigen-binding fragment (Fab) that binds to dabigatran with an affinity >350 times that of thrombin and effectively and immediately reverses its anticoagulant effect. **b** | Andexanet alfa is a modified recombinant coagulation factor Xa molecule that competitively binds factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban) and is catalytically inactive. Andexanet has been modified to include amino acid substitutions and deletion of the γ-carboxyglutamic acid (Gla)-rich membrane-binding domain to prevent assembly of factor Xa and factor Va and creation of the prothrombinase complex. **c** | Ciraparantag is a synthetic inorganic molecule that binds multiple anticoagulation agents through noncovalent hydrogen bonding and charge–charge interactions. LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

was chosen on the basis of its ability to reverse 99% of the calculated body load of dabigatran as measured in the RE-LY trial[26]. A total of 301 patients were enrolled in group A and 202 patients in group B at 173 sites in 39 countries[17]. Over 95% of the patients were receiving dabigatran for atrial fibrillation, and the median age was 78 years. The median patient-reported times from the last dabigatran dose to idarucizumab administration were 14.6 h in group A and 18.0 h in group B. Patients had multiple comorbidities, including a creatinine clearance <50 ml/min in 43.3% of patients. Of the 301 patients in group A, 137 (45.5%) presented with gastrointestinal bleeding, 98 (32.6%) with intracranial haemorrhage, and 78 (25.9%) with trauma-associated bleeding. Bleeding was adjudicated as life-threatening or major in 265 (88%) of the patients in group A and required surgical intervention in 61 (20.3%) patients; 114 patients (37.9%) had haemodynamic instability at presentation. Of the 202 patients in group B, 197 (98%) underwent surgery, including 49 (24.3%) abdominal, 41 (20.3%) orthopaedic, 37 (18.3%) cardiovascular, 14 (6.9%) hepatobiliary, and 14 (6.9%) chest trauma procedures, as well as 17 (8.4%) craniotomies.

The primary end point of the RE-VERSE AD study was the maximum reversal of dabigatran anticoagulation within 4 h of idarucizumab administration as determined by the diluted thrombin time or ecarin clot time. Secondary end points included safety and restoration of haemostasis. Median maximal reversal of dabigatran within 4 h was 100% as determined with either the diluted thrombin time or ecarin clot time. Among patients in group A, the median time to cessation of bleeding in evaluable patients without intracranial bleeding was 2.5 h. The median time to surgery or procedure in group B patients was 1.6 h, and haemostasis was assessed by the surgeon as normal in 93.4%, mildly abnormal in 5.1%, and moderately abnormal in 1.5% of patients. The 30-day mortality was 13.5% in group A and 12.6% in group B. Thromboembolic events occurred in 5.0% of group A and 4.6% of group B patients at 30 days, and only 8 of 34 patients with adjudicated thrombotic events had anticoagulation restarted. Within 72 h of administration of idarucizumab, antithrombotic therapy was restarted in 69 of the 301 patients in group A (22.9%) and in 135 of the 202 patients in group B (66.8%). No major adverse immunological or hypersensitivity safety signals were reported[17]. Overall, idarucizumab was effective in emergency settings for dabigatran reversal in patients with uncontrolled bleeding or undergoing urgent surgery. Haemostasis was assessed by the surgeon as being normal in 93.4% of the patients undergoing surgery or other procedures, including those undergoing major cardiovascular surgery.

Andexanet. Andexanet is a recombinant variant of human factor Xa that has its active-site serine residue replaced with alanine to eliminate catalytic activity and the membrane-binding γ-carboxyglutamic acid (Gla) domain deleted to prevent its incorporation into the prothrombinase complex[27,28]. Andexanet binds oral factor Xa inhibitors with an affinity similar to that of native factor Xa, but also reverses the actions of low-molecular-weight heparin and unfractionated heparin. Andexanet also competes with factor Xa for binding to tissue factor pathway inhibitor (TFPI), thereby forming a nonproductive complex and lowering circulating TFPI activity. Without regulation of the coagulation factor VIIa–tissue factor complex by TFPI, levels of prothrombin fragment 1.2, thrombin–antithrombin complexes, and D-dimers transiently increase. This effect is attenuated in the presence of oral factor Xa inhibitors because they compete with TFPI for binding to andexanet[28].

In phase II studies in healthy volunteers, intravenous andexanet transiently reversed the anti-factor Xa activity of apixaban, edoxaban, and rivaroxaban in a dose-dependent manner[29,30]. Andexanet is also reported to reverse betrixaban[31]. In volunteers aged 50–75 years, an andexanet intravenous bolus of 400 mg in patients who had been given apixaban or 800 mg in patients who had been given rivaroxaban rapidly but transiently reversed >90% of the anti-factor Xa activity[29]. Higher doses of andexanet are needed to reverse rivaroxaban or edoxaban than apixaban because plasma concentrations are higher with once-daily dosing than with twice-daily dosing, and because rivaroxaban and edoxaban have

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larger volumes of distribution than apixaban. To achieve more sustained reversal for apixaban, andexanet was given as a 400-mg intravenous bolus followed by an infusion of 4 mg/min for 120 min (880 mg total)[29]. For rivaroxaban, andexanet was administered as an 800-mg intravenous bolus followed by a continuous infusion of 8 mg/min for 120 min (1,760 mg in total). After stopping the infusion, there was a rebound increase in anti-factor Xa activity, but normalization of thrombin generation, as measured by endogenous thrombin potential, was sustained starting at 8 h and continuing for 3 days during the measurement period, a finding that might be important for sustained efficacy[29]. The prolonged effect on thrombin generation might reflect, at least in part, andexanet binding to TFPI[32].

The ongoing, phase III ANNEXA-4 trial[33] is a multicentre, prospective study that is enrolling patients with major bleeding within 18 h of apixaban, edoxaban, enoxaparin, or rivaroxaban administration. Patients who were taking apixaban and those whose last dose of rivaroxaban was >7 h before starting andexanet receive a bolus of 400 mg followed by a 2-h infusion at a dose of 480 mg. Patients who were taking edoxaban or enoxaparin and those whose last dose of rivaroxaban was ≤7 h before starting andexanet receive a bolus of 800 mg followed by a 2-h infusion at a dose of 960 mg. The two co-primary outcomes are the percentage change in anti-factor Xa activity and the rate of excellent or good haemostatic efficacy 12 h after stopping the andexanet infusion, as assessed by an independent adjudication committee using prespecified criteria. Haemostatic efficacy in patients with intracerebral haemorrhage was evaluated by measuring changes in haematoma volume as assessed by brain imaging. Excellent haemostasis was defined as an increase in haematoma size of ≤20% over baseline at both 1 h and 12 h after andexanet infusion, and volume increases of ≤35% over baseline at 12 h were considered to be good, with similar scoring used for subarachnoid and subdural bleeding[33]. For gastrointestinal bleeding, efficacy was evaluated on the basis of the haemoglobin and haematocrit levels at 12 h, as compared with baseline, with a decrease of <10% considered to be excellent, and a decrease of 10–20% with the administration of ≤2 units of blood products considered to be good[33]. For overt bleeding, haemostatic efficacy was considered to be excellent if it occurred within 1 h of andexanet administration, and good if it occurred within 4 h with no additional coagulation intervention. Patients were followed up for up to 30 days.

Data for the first 67 patients enrolled in the study have been published[33]. The mean age was 77 years, and 32 were receiving rivaroxaban 20 mg daily, 31 were receiving apixaban 5 mg twice daily, and four were receiving enoxaparin. The gastrointestinal tract was the primary site of bleeding in 33 (49%) patients, intracranial bleeding occurred in 28 (42%) patients, and bleeding occurred at other sites in six (9%) patients. Only the 47 patients with mean baseline anti-factor Xa activity ≥75 ng/ml were included in the efficacy analysis[33]. The mean time from presentation to andexanet administration was 4.8 h. In the 26 patients taking

Table 3 | **Reversal strategies for NOACs**

Parameter	Idarucizumab[17,23]	Andexanet alfa[29,33]	Ciraparantag[35,68]	Prothrombin complex concentrates[40,42]
Structure	Antibody fragment	Recombinant factor Xa variant	Synthetic cationic molecule	Factors II, VII, IX, and X, and proteins C and S
Agents reversed	Dabigatran	Apixaban, betrixaban, edoxaban, rivaroxaban, and heparins	All NOACs and heparins	Vitamin K antagonists
Mechanism of action	Binds dabigatran with high affinity	Competes with factor Xa for binding apixaban, betrixaban, edoxaban, and rivaroxaban	Nonspecific binding	Increase critical haemostatic factor levels
Phase I–II clinical studies (*n*)	Young and older volunteers (283)	Elderly volunteers (83)	Healthy volunteers (80)	Unknown
Phase III clinical studies (*n*)	Uncontrolled bleeding or urgent procedures or surgery (503)	Acute major bleeding (67); currently >100 enrolled	Unknown	Acute major bleeding (202), urgent surgery or invasive interventions (181)
Regulatory approval	Approved in most countries	Under evaluation by FDA and European Medicines Agency	Not submitted	Approved for warfarin reversal and factor repletion
Mode of delivery	Bolus or infusion of 2.0 or 2.5 g vials (given ≤15 min apart in RE-VERSE AD trial[17])	Apixaban: 400 mg intravenously, then 4 mg/kg for 2 h (total dose 880 mg); rivaroxaban: 800 mg loading dose, then 8 mg/kg for 2 h (total dose 1,760 mg)	Infusion	Infusion at 0.12 ml/kg/min (~3 units per kg/min) up to a maximum rate of 8.4 ml/min
Storage conditions	2–8 °C; before use, the unopened vial can be kept at room temperature (25 °C) for up to 48 h	2–8 °C	Room temperature	2–25 °C; before use, the unopened vial can be kept at room temperature for up to 4 h
Shelf life (months)	36	12 (expected)	Unknown	36
Estimated costs	US$3,482.50	Unknown	Unknown	US$1.27 per unit; for 70 kg: 25 IU/kg = ~$2,250 and 50 IU/kg = ~$4,500

IU, international units; NOAC, non-vitamin K antagonist oral anticoagulant.

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rivaroxaban, median values of anti-factor Xa activity decreased from 277 ng/ml at baseline to 16.8 ng/ml at the end of the bolus, and increased to 30.6 ng/ml at the end of the 2-h infusion. However, 4 h after the infusion, the median anti-factor Xa activity increased to 177.7 ng/ml. In the 20 patients taking apixaban, the median anti-factor Xa activity decreased from 150 ng/ml at baseline to 10.3 ng/ml at the end of the bolus, and increased to 12.5 ng/ml at the end of the 2-h infusion and to 103 ng/ml 4 h later. Despite differences in anti-factor Xa levels, clinical haemostasis was adjudicated as excellent or good in 37 of the 47 (79%) patients who had taken rivaroxaban or apixaban. At 30 days, thrombotic events had occurred in 12 (18%) patients and death had occurred in 10 (15%) patients. Anticoagulation therapy was restarted in 18 patients (27%) by 30 days, but only one of the 12 patients with thrombotic events had been restarted on a therapeutic dose of an anticoagulant before the event[33].

Although andexanet seems to improve haemostasis in patients taking apixaban or rivaroxaban, confirmation is required in a larger number of patients taking these drugs and in those taking edoxaban. Also, the utility of andexanet for reversal in patients requiring urgent surgery or intervention needs to be determined. Currently, andexanet is under review by the FDA and European Medicines Agency.

Ciraparantag. Ciraparantag (PER977; Perosphere) is a small, cationic molecule that has been reported to bind all the NOACs and to heparins via hydrogen bonding and charge–charge interactions[34]. Ciraparantag also binds calcium chelators, such as sodium citrate. Consequently, reversal can be measured only using the whole blood clotting time. In an attempt to facilitate such measurements, Perosphere has developed a point-of-care microfluidic device, but this device is yet to be licensed by regulatory agencies. In volunteers given a single 60 mg oral dose of edoxaban or a single 1.5 mg/kg subcutaneous dose of enoxaparin, an intravenous bolus of ciraparantag restored the whole blood clotting time to background levels and seemed to normalize clot structure as evaluated using scanning electron microscopic imaging[35]. A study investigating the utility of ciraparantag for rivaroxaban reversal is ongoing[36].

Box 1 | **Indications for administration of NOAC reversal agents**

- Life-threatening bleeding in a closed space or critical organ: intracranial haemorrhage, pulmonary haemorrhage, retroperitoneal bleeding, compartment syndrome
- Emergency surgery in patients at high risk of bleeding: cardiovascular or thoracic surgery, hepatic or other major organ surgery, neurosurgery, orthopaedic surgery
- Emergency procedural intervention in patients at high risk of bleeding: placement of an intracranial pressure-monitoring device, lumbar puncture, placement of vascular access for dialysis
- Uncontrollable haemorrhage despite standard transfusional and clinical management

Reversal agents should not be used for elective surgery or procedural interventions that can be delayed long enough to allow drug clearance, gastrointestinal bleeds that respond to supportive measures, or high drug levels or excessive anticoagulation without associated bleeding. NOAC, non-vitamin K antagonist oral anticoagulant.

Other reversal strategies

Although andexanet is under regulatory review, and ciraparantag is in development, neither agent has been approved. Consequently, an unmet need for a reversal strategy for the oral factor Xa inhibitors remains. To fill this gap, PCC is the prohaemostatic agent that is most commonly used. The rationale for its use stems from studies using surrogate biomarkers in healthy volunteers, from case reports, and from *ex vivo* and *in vivo* studies suggesting that PCC reverses the anticoagulant effects of NOACs[37–40]. Multiple studies in healthy volunteers given apixaban, edoxaban, or rivaroxaban have shown that administration of three-factor or four-factor PCC partially restores the PT and thrombin generation to normal or near-normal levels[37–40]. In addition, a study in healthy volunteers given a single 60 mg dose of edoxaban showed that at a dose of 50 international units (IU)/kg, four-factor PCC restored punch biopsy skin bleeding to baseline values[40]. By contrast, when intravenous tranexamic acid or the same dose of PCC was given to volunteers who had taken rivaroxaban at a dose of 20 mg twice daily for 3 days to achieve steady-state drug levels, neither intervention affected punch biopsy bleeding[41]. In both studies, PCC normalized thrombin generation and partially restored the PT to baseline values.

In a prospective cohort study, Majeed and colleagues evaluated the efficacy of PCC (median dose 2,000 IU; range 1,500–2,000 IU) for management of major bleeding in 84 patients receiving apixaban or rivaroxaban, including intracranial bleeding in 59 patients (70.2%) and gastrointestinal bleeding in 13 patients (15.5%)[42]. PCC was effective in 58 (69.1%) patients, including 16 of the 59 (27%) patients with intracranial bleeding, but was ineffective in the remainder. Two patients suffered an ischaemic stroke at 5 and 10 days after PCC administration, respectively, and 27 patients died within 30 days of treatment. Despite the limited clinical data, guidelines recommend four-factor PCC in doses ranging from 25 IU/kg to 50 IU/kg for reversal of oral factor Xa inhibitors in patients with serious bleeding.

If PCC is ineffective at stopping the bleeding, factor eight inhibitor bypassing activity (FEIBA; Shire) and recombinant coagulation factor VIIa (rFVIIa) have been suggested. FEIBA is a PCC that contains coagulation factors II, IX, and X, and activated factor VII, as well as protein C, protein S, TFPI, and trace amounts of coagulation factors V and VIII[43], whereas rFVIIa is a recombinant activated factor VII that binds to tissue factor at sites of vascular injury and induces thrombin generation[44]. Both therapies are approved for use in patients with haemophilia and antibody inhibitors to factor VIII or IX; they have also been used in an off-label manner to treat life-threatening bleeding associated with NOACs mainly on the basis of *in vitro* data[45–48]. One prospective evaluation of FEIBA for intracranial haemorrhage used 50 units per kg together with brain imaging performed 6 h after dosing and compared with the baseline[49]. Of the 127 patients evaluated, five (three receiving rivaroxaban and one each receiving apixaban or dabigatran) presented within 48 h and received FEIBA within a median of 13 h from their last NOAC dose. None of the patients had

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Box 2 | **Managing bleeding or emergency surgery in patients taking NOACs**

Mild bleeding
- Identify and manage bleeding site
- Stop anticoagulant if necessary
- Restart anticoagulant as soon as possible

Moderate-to-severe bleeding

Resuscitation:
- Haemodynamic and haemostatic resuscitation
- Obtain coagulation test results and calculate creatinine clearance

Control source of bleeding:
- Identify source of bleeding and treat if possible

Reversal:
- Consider reversal if there is ongoing bleeding (see below)

Life-threatening bleeding

Reversal of anticoagulant:
- Dabigatran: idarucizumab (5 g by intravenous bolus)
- Apixaban, edoxaban, or rivaroxaban: four-factor prothrombin complex concentrate (PCC; 25–50 units/kg). If there is ongoing bleeding despite PCC, consider activated PCC (50 units/kg) or recombinant coagulation factor VIIa (90 μg/kg)

With massive or uncontrollable haemorrhage:
- Initiate massive transfusion protocol
- Consider tranexamic acid (1 g intravenously)

Emergency surgery
- Measure non-vitamin K antagonist oral anticoagulant drug levels if possible, but do not wait for test results if surgery is urgent
- Reverse dabigatran with idarucizumab
- Consider four-factor PCC for reversal of apixaban, edoxaban, or rivaroxaban either before surgery or during or after surgery if there is excessive bleeding

haematoma expansion or other thrombotic complications[49]. Another retrospective report of FEIBA (20 units per kg) administered for intracranial haemorrhage included 11 patients, 55% of whom showed stable changes on CT scan after FEIBA administration, whereas 36% had worsening scans, and two patients developed thrombotic events[50]. Although rFVIIa was studied in patients with intracranial haemorrhage, including patients treated with warfarin, its efficacy has not been demonstrated[44,51,52]. Of note, factor VIIa normalizes the PT in patients treated with warfarin but does not correct thrombin generation[53]. Evaluation of its use in nonhaemophilia bleeding and coagulopathy showed a small but significant increase in arterial thrombotic complications in elderly patients[54]. The potential application of factor VIIa in early guidance documents has been replaced with specific reversal strategies and increasing efficacy data for the use of PCCs as a therapy for life-threatening haemorrhage.

Management approaches

Most patients with anticoagulant-associated bleeding can be managed with supportive measures that include fluid administration and, when appropriate, packed red blood cells and temporary interruption of anticoagulation. Laboratory investigations should include baseline blood counts, determination of the PT and aPTT, creatinine and creatinine clearance, and measurement of the NOAC drug concentration if the appropriate assay is available. In the absence of quantitative assays, the aPTT was found to correlate with the diluted thrombin time in the RE-VERSE AD trial[17] and can be used as a useful screening assay for dabigatran. For patients treated with apixaban or rivaroxaban, if the PT is normal and bleeding is life-threatening, then a reversal strategy should be considered if the last dose of drug was taken within the past 24 h.

A summary of indications for reversal agents is listed in BOX 1. Urgent reversal of anticoagulation is warranted in patients with bleeding associated with haemodynamic collapse and with bleeding in a critical site (for example, intracranial, intraocular, or pericardial). Reversal is also warranted in patients requiring urgent surgery that cannot be delayed. Reversal can be initiated before laboratory results are available in these patients to avoid delay. In addition to administering a reversal agent, haemostatic and haemodynamic resuscitation should be considered with life-threatening haemorrhage along with the use of massive transfusion protocols.

The timing of the last dose of a NOAC is important (BOX 2) because reversal is rarely needed if the last dose was taken >24 h ago, unless severe renal impairment delays drug clearance. In patients who have taken an overdose, activated charcoal can reduce absorption and plasma drug levels if the drug was taken in the past 2–4 h (REFS 55,56). Concomitant medications can also influence treatment. For example, platelet transfusion can be considered in patients taking long-acting antiplatelet drugs, such as clopidogrel or prasugrel[57].

Dabigatran reversal entails administration of idarucizumab. Surgery can start as soon as it is administered. The adequacy of reversal can be determined by following the aPTT or, if available, the diluted thrombin time or ecarin clot time. In patients with recurrent bleeding after idarucizumab administration or in those requiring another procedure, a second dose of idarucizumab can be considered if the aPTT or another test result suggests that the dabigatran concentration remains elevated.

For reversal of oral factor Xa inhibitors, four-factor PCC is warranted in patients with life-threatening bleeding. It can be given before urgent surgery for bleeding management. If the patient requires urgent surgery but is not bleeding, PCC can be given during or after surgery if there is excessive bleeding that cannot be controlled with other measures.

In terms of other specific interventions, haemodialysis can be considered for dabigatran reversal. However, with the widespread availability of idarucizumab for dabigatran reversal, haemodialysis is rarely needed even in patients with acute kidney injury. Haemodialysis is not a consideration for reversal of apixaban, edoxaban, or rivaroxaban because these drugs are highly protein-bound and cannot be dialysed.

Tranexamic acid can also be considered. This antifibrinolytic agent inhibits clot degradation and is increasingly used to manage bleeding in patients with trauma or in those undergoing major cardiac or orthopaedic surgery[58,59]. Although no evidence exists for its utility in NOAC-associated bleeds, tranexamic acid has few adverse effects when given intravenously at a dose of 1 g (REF. 41).

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After an anticoagulant-related major bleed, whether intracranial, gastrointestinal, or elsewhere, clinicians should consider resuming anticoagulant therapy because evidence consistently shows that this strategy confers a reduction in stroke and overall mortality that offsets any increase in recurrent bleeding[60–62]. The timing of anticoagulant resumption should be individualized on the basis of the potential for bleeding recurrence; however, many patients can resume anticoagulation within 1–2 weeks after a gastrointestinal bleed and 3–4 weeks after an intracranial bleed[61–63].

Conclusions

The NOACs are replacing VKAs for many indications. Although less intracranial bleeding occurs with the NOACs than with VKAs, serious bleeding still occurs, and patients taking NOACs might require urgent surgery. Idarucizumab enables rapid and sustained reversal of dabigatran, and andexanet is poised to do the same for oral factor Xa inhibitors. Until andexanet is available, however, PCC might be of use. Cohort studies suggest that PCC improves haemostasis, but evaluation of its effectiveness will require direct comparisons with andexanet. Specific reversal agents are expensive, and anticoagulant reversal places patients at risk of thrombosis. Therefore, reversal should be reserved for patients in need, and anticoagulation therapy should be restarted promptly after patients have stabilized. Additional reversal agents and procoagulants are in the early stages of development. How these agents will compare with andexanet and ciraparantag remains to be determined.

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Author contributions

J.H.L. researched data for the article, and all the authors discussed its content. J.H.L. and J.I.W. wrote the manuscript, and all the authors reviewed and edited the article before submission.

Competing interests statement

J.H.L. is on the scientific advisory or steering committees of Boehringer Ingelheim, CSL Behring, Grifols, Instrumentation Laboratories, Janssen, Leading Biosciences, Merck, Octapharma, Pfizer, and Portola. J.D. is on the scientific advisory board of AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Leo Pharma, Pfizer, and Sanofi; and is a consultant for Janssen. J.I.W. served as a consultant and received honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Janssen, Novartis, and Pfizer.

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