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Review Article

Emergency care of patients receiving non-vitamin K antagonist oral anticoagulants

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Abstract

Non-vitamin K antagonist oral anticoagulants (NOACs), which inhibit thrombin (dabigatran) and factor Xa (rivaroxaban, apixaban, edoxaban) have been introduced in several clinical indications. Although NOACs have a favourable benefit-risk profile and can be used without routine laboratory monitoring, they are associated—as any anticoagulant—with a risk of bleeding. In addition, treatment may need to be interrupted in patients who need surgery or other procedures. The objective of this article, developed by a multidisciplinary panel of experts in thrombosis and haemostasis, is to provide an

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update on the management of NOAC-treated patients who experience a bleeding episode or require an urgent procedure. Recent advances in the development of targeted reversal agents are expected to help streamline the management of NOAC-treated patients in whom rapid reversal of anticoagulation is required.

Keywords: anticoagulants; coagulation monitoring; emergencies; haemorrhage; reversal

Editor's key points

- Current recommendations for the management of bleeding and emergency procedures in patients treated with NOACs are based on expert opinion and limited clinical experience.
- When a patient on NOAC treatment presents for emergency care, co-morbidities (including renal impairment) and concomitant treatments associated with increased bleeding should be identified; measuring the anticoagulant effect of NOACs may be helpful.
- Currently available therapeutic options include non-specific pro-haemostatic agents, therapies aimed at reducing drug exposure, and the specific reversal agent idarucizumab, targeted at dabigatran.

Non-vitamin K antagonist oral anticoagulants (NOACs), also referred to as direct oral anticoagulants, have been developed as direct and specific inhibitors of single activated coagulation factors.[1,2] Two classes of agents that inhibit thrombin (dabigatran) and factor Xa (rivaroxaban, apixaban, edoxaban) have been introduced in several clinical indications. Although NOACs have a favourable benefit-risk profile, they are associated—as any anticoagulant—with a risk of bleeding. In addition, treatment may need to be interrupted in patients who need surgery or other procedures.

The objective of this article, developed by a multidisciplinary panel of experts in thrombosis and haemostasis, is to provide an update on the management of NOAC-treated patients who experience a bleeding episode or require an urgent procedure.

Pharmacological characteristics and current indications of NOACs

NOACs carry several advantages over vitamin K antagonists: a more rapid onset and offset of action, a lower propensity for food and drug interactions, and a predictable anticoagulant effect that allows fixed-dose administration without routine coagulation monitoring.[2] Their elimination half-lives in patients with a normal renal function are as follows: 14–17 h (dabigatran), 7–11 h (rivaroxaban), 8–14 h (apixaban), and 5–11 h (edoxaban).[2] About 80%, 50%, 33%, and 27% of dabigatran, edoxaban, rivaroxaban, and apixaban, respectively, are cleared unchanged via the kidneys.[2]

The direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban have received regulatory approval for the following clinical indications: prevention of venous thrombosis after major orthopaedic surgery, prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF), and treatment and secondary prevention of symptomatic venous thrombosis. In addition, rivaroxaban is approved in Europe for secondary prevention after an acute coronary syndrome.

Information needed for emergency care in patients on NOACs

When a patient is known or suspected to be on NOAC treatment presents for emergency care, careful medical history taking is required to determine which NOAC, if any, is taken, which dose regimen is used, and when the last dose was taken (i.e. whether the drug level is pre- or post-peak).[3] It is also essential to identify co-morbidities and concomitant treatments associated with an increased risk of bleeding. As the half-lives of NOACs are influenced by renal function (see Table 1)[3] and patients with renal failure will be at increased risk of bleeding complications as a result of the faulty renal elimination, assessment of creatinine clearance is important to evaluate when restoration of haemostasis can be expected after cessation of NOAC treatment. Measuring the anticoagulant effect of NOACs may also be helpful to guide emergency care.

Effect of NOACs on coagulation tests

Non-specific coagulation tests include the prothrombin time (PT), the activated partial thromboplastin time (aPTT) and point-of-care coagulation tests such as rotational

Table 1 Effect of renal function on estimated half-lives of NOACs (from Heidbuchel and colleagues[3]). CrCl, creatinine clearance

	Dabigatran (h)	Rivaroxaban (h)	Apixaban (h)	Edoxaban (h)
CrCl >80 ml min^{-1}	12–17	5–9	12	10–14
CrCl 50–80 ml min^{-1}	~17	~8.7	~14.6	~8.6
CrCl 30–50 ml min^{-1}	~19	~9.0	~17.6	~9.4
CrCl 15–30 ml min^{-1}	~28	~9.5	~17.3	~16.9
CrCl ≤15 ml min^{-1}	–	–	–	–

thromboelastometry (ROTEM™) and thromboelastography (TEG®). In contrast, specific assays provide information on the effect of anticoagulants on individual coagulation factors. The effect of NOACs on coagulation tests is summarized in Table 2.[4]

Direct thrombin inhibitor (dabigatran)

PT and the international normalized ratio are not appropriate tests to assess the anticoagulant effect of dabigatran.[5] The aPTT may be helpful to detect the presence of the drug (if other causes of an elevated aPTT are excluded), but it cannot be used to quantify the anticoagulant effect of dabigatran, especially at high plasma levels.[5] A normal aPTT does not always exclude the presence of clinically important levels of dabigatran, particularly when a relatively insensitive reagent is used.[6,7] Point-of-care viscoelastic coagulation tests such as TEG[8–10] or ROTEM[11–13] may provide a quick and reliable assessment of the anticoagulant effect of dabigatran. However, clinical studies are warranted to evaluate the benefits and limitations of viscoelastic coagulation tests in the acute care setting.[14]

Thrombin time (TT) is useful for detecting minimal dabigatran levels; a normal TT excludes the presence of clinically important levels of dabigatran.[6] The dilute thrombin time (dTT) performed with dabigatran calibrators is suitable for determining the anticoagulant activity and calculating plasma levels of dabigatran above the lower limit of detection (30–45 ng ml^{-1}).[6,15,16] The ecarin clotting time (ECT) and the ecarin chromogenic assay are closely and linearly correlated with dabigatran plasma levels even at very low levels.[5,16] However, these tests are hampered by lack of standardization and limited availability.[17] The development of commercial kits is expected to improve the availability and ease of use of these tests.

Direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban)

The PT is generally increased in response to factor Xa inhibitor treatment, but its sensitivity is much higher for edoxaban and rivaroxaban than for apixaban.[18–20] Large variations are observed according to the thromboplastin reagent used, and a normal PT does not exclude the presence of the drugs at clinically relevant levels. Although the aPTT may be prolonged in the presence of direct factor Xa inhibitors, its sensitivity is insufficient to exclude the presence of clinically relevant drug levels.[7,20] TEG[8] and (modified) ROTEM[13,21,22] assays might permit rapid point-of-care determination of the anticoagulant effect of rivaroxaban or apixaban.

Determination of the anti-factor Xa activity is the preferred test for all direct factor Xa inhibitors. However, this test is not routinely available in all laboratories, and it needs to be calibrated specifically for these drugs.[23] Chromogenic anti-factor Xa assays with calibration for the specific agent are available in specialized laboratories, but turnaround times may preclude their use in emergency situations.[24]

Therapeutic options for NOAC reversal or removal

Therapeutic options for reversing the anticoagulant effect of NOACs include non-specific prohaemostatic agents, therapies aimed at reducing drug exposure, and reversal agents targeted at dabigatran (idarucizumab), direct factor Xa inhibitors

Table 2 Effect of direct oral anticoagulants on coagulation tests (modified from Siegal and Cuker[4]). aPTT, activated partial thromboplastin time; CFT, clot formation time; CT, clotting time; dTT, dilute thrombin time; ECT, ecarin clotting time; K, coagulation time; lowTF–ROTEM®, low–tissue factor activated ROTEM®; MA, maximum amplitude; MCF, maximum clot firmness; MRTG, maximum rate of thrombus generation; PT, prothrombin time; R, reaction time; t,MaxVel, time to maximum velocity; TT, thrombin time

	PT	aPTT	TT	dTT	ECT	Anti-Xa activity	Point-of-care viscoelastic tests (TEG®/ROTEM™)
Dabigatran	↑ or unchanged (low sensitivity, varies with reagent)	↑ (varies with reagent)	↑	↑ (preferred test)	↑	–	TEG®: ↑ R, K, and MRTG with dose response correlation, ↑ or unchanged α angle and MA (kaolin test); ↑ ACT with dose-response correlation, ↑ or unchanged K, α angle and MRTG (rTEG test) ROTEM™: ↑ CT (INTEM and EXTEM), ↑ or unchanged CFT, no effect on MCF
Rivaroxaban	↑ or unchanged (not sensitive at low levels, varies with reagent)	↑ or unchanged (less sensitive than PT)	–	–	–	↑ (preferred test)	TEG®: ↑ R, K, α angle, and MRTG (kaolin test) only at higher levels; ↑ ACT with dose-response correlation, K, unchanged α angle and MRTG (rTEG test) ROTEM™: ↑ or unchanged EXTEM CT and INTEM CT Modified ROTEM™: ↑ CT and t,MaxVel (lowTF–ROTEM™), with wide variability
Apixaban	↑ or unchanged (limited sensitivity, may vary with reagent)	↑ or unchanged (limited sensitivity, may vary with reagent)	–	–	–	↑ (preferred test)	TEG®: ↑ R time, K time, α angle, MRTG (kaolin test); ↑ ACT, unchanged K time, α angle and MRTG (rTEG test) ROTEM™: ↑ EXTEM CT, ↑ or unchanged INTEM CT Modified ROTEM™: ↑ CT and t,MaxVel (lowTF–ROTEM™), with wide variability
Edoxaban	↑ (may vary with reagent)	↑ (may vary with reagent)	–	–	–	↑ (preferred test)	–

(andexanet alfa), and both NOACs and heparin-based anticoagulants (ciraparantag).

Non-specific prohaemostatic agents

The efficacy and safety of non-specific prohaemostatic agents in restoring haemostasis in patients treated with NOACs have not been evaluated in clinical studies. At present, the evidence supporting their use is limited to case reports or series, studies in healthy human volunteers, animal models, and *in vitro* experiments, which all carry important limitations.[25]

Fresh frozen plasma

Fresh frozen plasma (FFP) is obtained by freezing plasma that is removed from a whole blood donation or collected by apheresis. Plasma transfusion is associated with significant risks, including circulatory overload, allergic reactions, transfusion-related acute lung injury, and potential for transmission of blood-borne infections.[26] Because of the likely need to use large volumes to overcome the inhibition of thrombin or factor Xa, FFP is not recommended to rapidly reverse the anticoagulant effect of NOACs.[27,28]

Non-activated prothrombin complex concentrates

Prothrombin complex concentrates (PCCs) are highly purified concentrates of vitamin K-dependent coagulation factors prepared from pooled normal plasma (see Table 3).[29] All PCCs undergo a viral inactivation procedure. The level of clotting factors is approximately 25 times higher than in plasma, allowing rapid factor substitution with small volumes.[30] PCCs can be administered rapidly, without cross-matching, and are not associated with risks of circulatory overload and acute lung injury.[29,31] PCCs have been associated with a low (1.4%) but non-negligible risk of thromboembolic adverse events.[32]

The evidence for the use of PCCs in restoring haemostasis in patients treated with NOACs has been reviewed recently.[33,34] Preclinical and healthy volunteer studies suggest that non-activated PCCs may be helpful in this setting, but the efficacy of different PCC preparations appears to vary and there is a lack of correlation between the effects of PCCs on haemostasis and their influence on coagulation tests. Rapid reversal of coagulopathy after administration of a 4-factor PCC was reported in a dabigatran-treated elderly patient presenting with severe gastrointestinal haemorrhage.[35] In a patient with life-threatening rectal bleeding on dabigatran treatment, bleeding cessation was achieved after administration of two doses of 4-factor PCC, whilst coagulation parameters remained abnormal.[36] In an apixaban-treated patient with severe traumatic bleeding refractory to blood product support, 4-factor PCC failed to restore haemostasis.[37] Favourable outcomes after 4-factor PCC administration were reported in six of 18 patients with intracranial haemorrhage who were receiving rivaroxaban or apixaban.[38]

Administration of non-activated PCCs may be considered in clinical situations where urgent reversal of NOACs is required.[27,34] As a result of the lack of clinical data, there is currently no consensus regarding PCC dosing.[33] An initial dose of 50 IU kg^{-1}, followed by an additional dose of 25 IU kg^{-1} if clinically indicated, has been suggested.[3] Considering the strong thrombin generating push induced by PCC and the pre-existing thrombogenic diathesis, careful titration of up to 25 IU kg^{-1}, with repeated doses in cases of ongoing bleeding, has also been proposed.[27]

Activated PCC

Activated PCC (aPCC), or factor VIII inhibitor bypassing agent (FEIBA, Baxter, Deerfield, IL, USA), was developed as a prohaemostatic agent for the management of patients with haemophilia and inhibitors to coagulation factors VIII or IX.[26] aPCC is a surface-activated PCC containing small quantities of FIXa, FXa, and thrombin, and larger amounts of FVIIa. A vapour heat treatment procedure is used for inactivation of blood-borne viruses.[39] Pharmacovigilance assessments indicate that the incidence of thromboembolic events after administration of FEIBA in patients with haemophilia is very low.[40] However, the safety profile of FEIBA in non-haemophiliac patients with risk factors for thrombosis is unknown.

Successful management of dabigatran-associated life-threatening bleeding episodes with aPCC was reported in one patient[41] and in a series of four patients.[42] aPCC was reported to correct all thrombin generation parameters *in vitro* in plasma from healthy volunteers who were taking rivaroxaban or apixaban, and to reduce blood loss in animal models after administration of rivaroxaban or edoxaban.[43] From the perspective of practicability and safety, aPCC has the disadvantage of not being used routinely in perioperative medicine whilst PCC is commonly included in treatment algorithms.

Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) is a recombinant protein originally developed to treat or prevent bleeding in patients with haemophilia A or B with inhibitors to factor VIII or IX.[44] Clinical trials and post-marketing data indicate that the incidence of thromboembolic events after administration of rFVIIa in approved indications is low.[45] In randomized controlled trials evaluating rFVIIa in off-label indications, the risk of arterial thrombosis was significantly increased compared with placebo (5.5% *vs* 3.2%).[46]

In animal models, rFVIIa improved some haemostasis-related parameters but failed to reduce blood loss after administration of dabigatran or rivaroxaban.[47–50] In a cell-based model of haemostasis, rFVIIa improved parameters of thrombin generation in the presence of therapeutic but not supratherapeutic dabigatran levels.[51] Considering the strong thrombin generating push induced by rFVIIa and the pre-existing thrombogenic diathesis, rFVIIa should only be regarded as a last-resort option in life- or organ-threatening bleeding, especially in patients with acute ischaemic events.

Antifibrinolytic agents

Antifibrinolytic agents include tranexamic acid and epsilon-aminocaproic acid, which preserve haemostasis through plasmin inhibition, and aprotinin, which inhibits multiple serine proteases. Antifibrinolytics have been shown to reduce bleeding and transfusion requirements in the perioperative setting.[52] In a large randomized trial, tranexamic acid reduced mortality in bleeding trauma patients.[53] There are currently no clinical data supporting the use of antifibrinolytic agents to improve haemostasis in patients treated with a NOAC; however, they may be used as adjuvant therapy in patients with

Table 3 Coagulation factor content of the most commonly used non-activated prothrombin complex concentrates (adapted from Grottke and Levy[29]). N/A, information not available

Product	Availability	Coagulation factors (IU ml^{-1})			
		Factor II	Factor VII	Factor IX	Factor X
3-factor PCCs					
Prothromplex TIM 3 (Baxter)	Europe	25	N/A	25	25
Cofact/PPSB SD (Sanquin/CAF)	Europe	≥15	≥5	≥20	≥15
Bebulin VH (Baxter)	USA	24–38	<5	24–38	24–38
Profilnine SD (Grifols)	USA	1.5 IU/IU factor IX	0.35 IU/IU factor IX	100 U	1 IU/IU factor IX
4-factor PCCs					
Beriplex P/N, Confidex or Kcentra (CSL Behring)	Europe, Canada, USA	20–48	10–25	20–31	22–60
Octaplex (Octapharma)	Europe, Canada	14–38	9–24	25	18–30
Prothromplex Total/S-TIM 5 (Baxter)	Europe	30	25	30	30

NOAC-associated bleeding.[3,54] Antifibrinolytics should not be used in patients with prior acute coronary syndromes or cerebral ischaemic events because of the risk of secondary thromboembolic events.

Therapies aimed at reducing drug exposure

Therapies aimed at reducing drug exposure include measures to reduce drug absorption and to remove the drug from the blood.

Activated charcoal

Activated charcoal is a processed form of carbon that can bind to oral drugs and reduce absorption from the gastrointestinal tract. *In vitro* data indicate that dabigatran etexilate can be successfully adsorbed by activated charcoal therapy[5] and a study in healthy volunteers showed that administration of activated charcoal up to 6 h after a single 20-mg dose of apixaban reduced apixaban exposure and facilitated drug elimination.[55] A woman who presented to the emergency department after ingesting 11.25 g of dabigatran in a suicide attempt was successfully managed with gastric lavage and activated charcoal therapy.[56] The use of activated charcoal to reduce absorption may be considered in case of a recent overdose with any NOAC, using a standard dosing scheme of 30–50 g for adults.[3] The contraindications and side effects of charcoal should be considered.

Haemodialysis

Dabigatran can be removed from the circulation through dialysis because of its relatively low plasma protein binding (~35%). In patients with end-stage renal disease, 50–60% of active dabigatran was removed after 4 h of haemodialysis.[57] Haemo(dia)filtration is suggested to be efficacious in removing dabigatran after an application of more than 4 h.[27] A systemic review identified 35 cases of dabigatran-associated bleeding in which haemodialysis was used for dabigatran removal and the effect of haemodialysis on bleeding was reported.[58] There were significant reductions in dabigatran levels after haemodialysis, but a rebound of dabigatran level was observed in some patients after cessation of dialysis. Haemostasis was achieved in 24 patients and 10 patients died as a result of bleeding.

Haemodialysis may be considered in dabigatran-treated patients who present with life-threatening bleeding or require emergency surgery, particularly in case of renal impairment. Disadvantages include the long duration until removal of dabigatran by renal replacement therapy, complications associated with extracorporeal circulation and anticoagulation in the critical event of severe or massive bleeding, and the requirement of intensive care resources.

As rivaroxaban and apixaban are highly protein bound, it is unlikely that they can be removed by haemodialysis.[26] In patients with end-stage renal disease treated with edoxaban, haemodialysis resulted in a minor decrease in drug levels, suggesting that haemodialysis is not an effective option for removal of edoxaban from the blood.[59]

Targeted reversal agents

Three targeted reversal agents are currently being evaluated: idarucizumab, a humanized murine monoclonal antibody fragment directed specifically at dabigatran; andexanet alfa, a recombinant modified decoy factor Xa that binds to factor Xa inhibitors; and ciraparantag, a small molecule that binds to factor Xa and thrombin inhibitors and to heparin-based anticoagulants through charge interaction.[60]

Idarucizumab

Idarucizumab (Praxbind®, Boehringer Ingelheim, Ingelheim, Germany) is a humanized Fab antibody fragment that binds specifically and with high affinity to dabigatran.[61] In healthy volunteers, idarucizumab administered alone as a 1-h or 5-min infusion was safe and well tolerated, and had no effect on coagulation parameters.[62,63] When administered in healthy volunteers treated with dabigatran etexilate, idarucizumab immediately reversed dabigatran-induced anticoagulation in a dose-dependent manner, with a complete and sustained effect over 72 h for doses of 2 g or greater.[64] Rapid and sustained reversal of dabigatran-induced anticoagulation was also observed after administration of idarucizumab (5 g or 2×2.5 g) in male and female healthy volunteers who were middle-aged (45–64 yr) or elderly (65–80 yr), and in patients with mild or moderate renal impairment (creatinine clearance of 60 to <90 and 30 to <60 ml min^{-1}, respectively).[65] Effective dabigatran anticoagulation can be re-established 24 h after administration of idarucizumab.[66]

The efficacy and safety of idarucizumab (5 g administered as two 50 ml bolus infusions no more than 15 min apart) for the reversal of the anticoagulant effects of dabigatran in patients with uncontrollable or life-threatening bleeding and in those requiring an urgent surgical or invasive procedure have been investigated in the Study of the REVERSal Effects of idarucizumab in patients on Active Dabigatran (RE-VERSE AD™), a global Phase 3 prospective cohort study.[67] The full cohort analysis included 503 patients (301 with serious bleeding and 202 requiring an urgent procedure). Amongst 461 patients with an elevated dTT or ECT at baseline, the median maximum percentage reversal was 100% [95% confidence interval (CI), 100–100]. After administration of idarucizumab, levels of unbound dabigatran decreased to 20 ng ml^{-1} or below in all but three of the patients who could be assessed; within 24 h after idarucizumab administration, dabigatran levels above this threshold were observed in 23% of the assessed patients, mainly after 12 h. Amongst 203 patients with serious bleeding for whom the time to cessation of bleeding could be ascertained, 134 (67.7%) had confirmed bleeding cessation within 24 h and median time to haemostasis was 2.5 h. Amongst the 197 patients who underwent an urgent procedure, normal haemostasis was reported in 184 (93.4%). Thrombotic events were reported in 24 patients (4.8%) within 30 days after treatment.

The pharmacology of idarucizumab and clinical data on its use to reverse the anticoagulant activity of dabigatran have been reviewed recently.[68] Idarucizumab has been approved by the United States Food and Drug Administration and the European Commission for use in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required: (i) for emergency surgery/urgent procedures; and (ii) in life-threatening or uncontrolled bleeding. Information on the practical use of idarucizumab is provided in Table 4.

Andexanet alfa

Andexanet alfa (AndexXa®, Portola Pharmaceuticals, South San Francisco, CA, USA) is a modified, human recombinant factor Xa that is catalytically inactive but retains high-affinity binding to direct factor Xa inhibitors and heparin-antithrombin III complexes.[69] The safety and efficacy of andexanet alfa in reversing the anticoagulant effects of apixaban and rivaroxaban in healthy older volunteers has been evaluated in two parallel randomized, double-blind, placebo-controlled Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors (ANNEXA) Phase III studies.[70] In the ANNEXA-A study, participants received 5 mg of apixaban twice daily for 3.5 days and andexanet alfa was administered i.v. as a 400-mg bolus or as a 400-mg bolus followed by a continuous infusion of 4 mg min^{-1} for 120 min. In the ANNEXA-R study, participants received 20 mg of rivaroxaban once daily for 4 days and andexanet alfa was administered i.v. as an 800-mg bolus or as an 800-mg bolus followed by a continuous infusion of 8 mg min^{-1} for 120 min. Andexanet alfa rapidly and completely reversed the anticoagulant effect of rivaroxaban and apixaban, respectively, with a maximal effect within 2–5 min after administration of the bolus. Reversal was sustained after administration of a bolus plus a continuous infusion, but not after administration of a bolus alone. Anti-Xa activity returned to placebo levels within 1–3 h after the administration of the infusion. No serious adverse or thrombotic events were reported.

Table 4 Practical use of idarucizumab for dabigatran reversal

Presentation	**Two vials containing each 2.5 of idarucizumab in a 50 ml solution**
Mode of administration	I.V. administration as two consecutive infusions over 5–10 min each or as a bolus injection
Dosing	The recommended dose is 5 g (2×2.5 g) Administration of a second dose of 5 g may be considered if clinically indicated No dose adjustment is required in patients with renal impairment or hepatic impairment and those aged 65 yr and above
Restarting antithrombotic therapy after idarucizumab administration	Treatment with dabigatran etexilate or other antithrombotic agents, can be re-initiated 24 h after administration of idarucizumab if the patient is clinically stable and adequate haemostasis has been achieved Absence of antithrombotic therapy exposes patients to the thrombotic risk of their underlying disease or condition
Precautions for use	*Hypersensitivity* The risk of using idarucizumab in patients with known hypersensitivity to idarucizumab or to any of the excipients should be weighed cautiously against the potential benefit. If an anaphylactic reaction or other serious allergic reaction occurs, administration of idarucizumab should be discontinued immediately and appropriate therapy initiated *Hereditary fructose intolerance* The recommended dose of idarucizumab contains 4 g sorbitol as an excipient. In patients with hereditary fructose intolerance, parenteral administration of sorbitol has been associated with serious adverse events and death. The risk of treatment with idarucizumab should be weighed against the potential benefit in such patients. If idarucizumab is administered, intensified medical care during exposure and within 24 h of exposure is required
Urinary protein testing	I.V. administration of idarucizumab causes transient proteinuria as a physiologic reaction to renal protein overflow. This transient proteinuria is not indicative of renal damage, which should be taken into account for urine testing
Interactions with other drugs	No interactions with volume expanders, coagulation factor concentrates (activated and non-activated prothrombin complex concentrates, recombinant factor VIIa), or anticoagulants other than dabigatran etexilate have been reported

The prospective, open-label, single-group ANNEXA-4 study is currently evaluating the efficacy and safety of andexanet alfa in patients with factor Xa inhibitor-associated acute major bleeding. The first 67 patients enrolled in the study have been included in an interim report.[71] Andexanet alfa was administered as a bolus (15–30 min) followed by a 2-h infusion. A bolus dose of 400 mg and an infusion dose of 480 mg were used for patients on apixaban or known to have taken rivaroxaban more than 7 h before administration of andexanet alfa, whereas patients on enoxaparin or edoxaban and those who had taken rivaroxaban 7 h or less before administration of andexanet alfa or at an unknown time received a bolus dose of 800 mg and an infusion dose of 960 mg. The two co-primary efficacy outcomes were the percent change in anti-factor Xa activity and the rate of excellent or good haemostatic efficacy 12 h after the infusion. Median anti-factor Xa activity decreased by 89% (95% CI, 58–94) amongst rivaroxaban-treated patients and by 93% (95% CI, 87–94) amongst apixaban-treated patients. Clinical haemostasis 12 h after the infusion was rated as excellent or good in 79% (95% CI, 64–89) of the 47 patients included in the efficacy analysis. Thrombotic events occurred in 12 patients (18%) during the 30-day follow-up.

Ciraparantag

Ciraparantag (Perosphere Pharmaceuticals, Danbury, CT, USA) is a small, synthetic, water-soluble, cationic molecule which reverses unfractionated heparin, low-molecular-weight heparin and fondaparinux through non-covalent hydrogen binding and charge–charge interactions, and NOACs through non-covalent hydrogen binding.[72] In thromboelastographic studies and animal models, ciraparantag was shown to reverse the anticoagulant effect of all NOACs. In healthy volunteers, a single i.v. dose of ciraparantag within 3 h after administration of 60 mg of edoxaban decreased whole-blood clotting time to within 10% above the baseline value in 10 min or less.[72]

Management of bleeding in patients treated with NOACs

In the absence of high-quality evidence from randomized trials to guide clinical practice, current recommendations for the management of bleeding in patients treated with NOACs are based on expert opinion and limited clinical experience (Fig. 1). The European Heart Rhythm Association has published a practical guide on the use of NOACs in patients with NVAF, updated in 2015, which includes a section on bleeding management.[3] Practical guidance has also been provided by several expert groups.[27,54,73–76]

The management of bleeding in patients on NOAC therapy should be tailored according to the severity and location of the haemorrhage. Medical history taking is required to identify comorbidities and concomitant treatments associated with an increased bleeding risk and to assess which NOAC is taken, which dose regimen is used, and when the last dose was taken. A renal function test is important to evaluate when

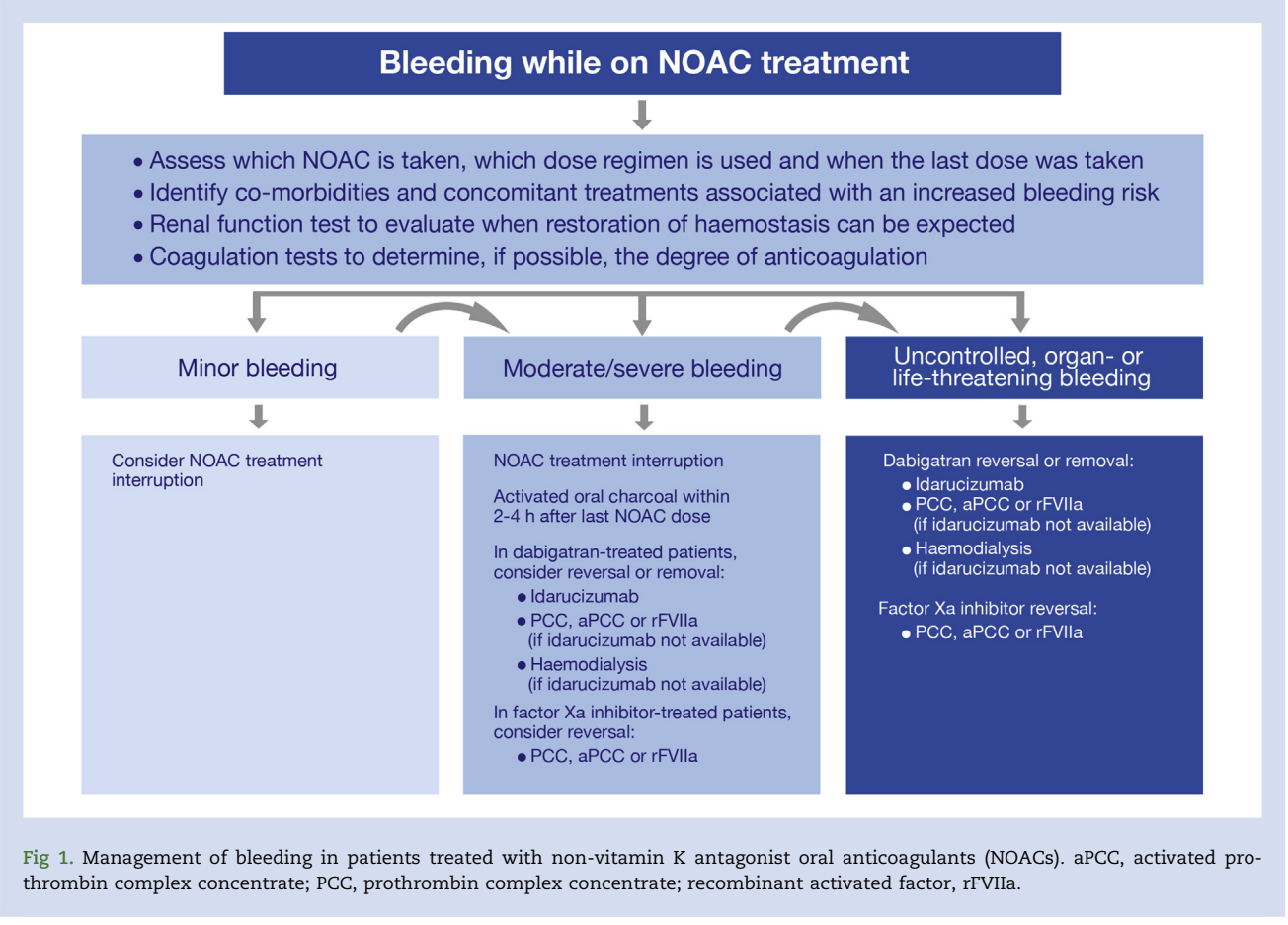

Fig 1. Management of bleeding in patients treated with non-vitamin K antagonist oral anticoagulants (NOACs). aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; recombinant activated factor, rFVIIa.

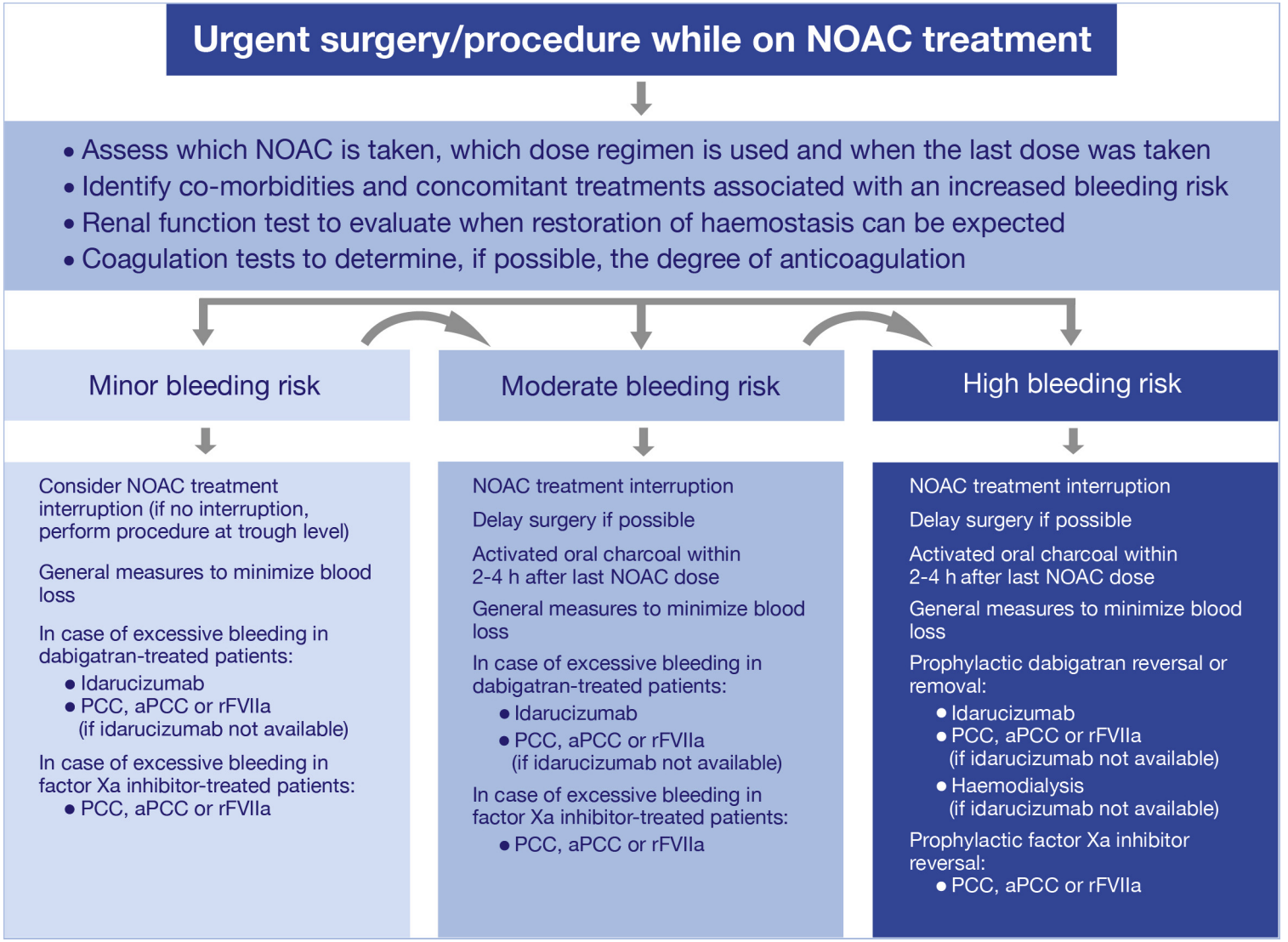

Fig 2. Management of non-vitamin K antagonist oral anticoagulant (NOAC)-treated patients who require an emergency surgical or invasive procedure. aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; recombinant activated factor, rFVIIa.

restoration of haemostasis can be expected after cessation of treatment. Adequate diuresis should be maintained to facilitate renal elimination of the NOAC.

In patients with mild bleeding, treatment discontinuation, local haemostatic measures and clinical observation may be sufficient. In case of ongoing, severe bleeding, coagulation monitoring is helpful to assess the anticoagulant effect of the drug and potentially secondary bleeding disorders. Specific tests should not delay the application of supporting measures such as fluid resuscitation, red blood cell transfusion, platelet transfusion, antifibrinolytic agents, and invasive haemostatic methods (surgical and radiological/endovascular interventions). Hypothermia, acidosis, and hypocalcaemia should be avoided or corrected if present. Activated oral charcoal may be administered to reduce drug absorption within 2–4 h after the last NOAC dose was taken. NOAC reversal or removal cannot be recommended for all patients with moderate-to-severe bleeding, but may be considered based on clinical judgement and interdisciplinary consultation.

In case of uncontrolled, organ-threatening or life-threatening bleeding, NOAC reversal is recommended. In dabigatran-treated patients, idarucizumab should be considered as the first-line option. In direct factor Xa inhibitor-treated patients (and in dabigatran-treated patients if idarucizumab is not available), administration of PCC (25 or 50 IU kg^{-1}, followed by additional 25 IU kg^{-1} doses in case of ongoing bleeding) should be considered; alternatively, administration of aPCC (50 U kg^{-1}; maximum daily dose 200 U kg^{-1}) or rFVIIa (90 μg kg^{-1}) may be considered. These therapeutic options should only be used after a careful benefit/risk assessment. FFP should not be used as a reversal agent unless no coagulation factor concentrate is available. Haemodialysis may be considered in dabigatran-treated patients, particularly in case of impaired renal function, if idarucizumab is not available. The roles of andexanet alfa and ciraparantag in reversing the anticoagulant activity of factor Xa inhibitors require further evaluation.

Management of NOAC-treated patients who require an urgent surgical or invasive procedure

Many patients on long-term oral anticoagulation will at some point require a surgical or invasive procedure (Fig. 2). One-third of the patients enrolled in the ROCKET AF trial required at least one treatment interruption, of whom 40% experienced treatment interruption for a surgical or invasive procedure.[77] In the RE-LY trial, 2% of the study participants underwent an urgent surgical or invasive procedure.[78] Amongst close to 2200 patients enrolled in the Dresden NOAC registry, 595 (27.3%) underwent a total of 863 surgical or interventional procedures, of which 10% were classified as major.[79] Interventions associated with a major bleeding risk include thoracic and abdominal surgery, major orthopaedic surgery, transurethral prostate resection, kidney and liver biopsy, or catheter ablation of simple left-sided supraventricular tachycardia.[3] Several working groups[3,27,73–76] have provided guidance for the management of NOAC-treated patients requiring urgent procedures, and the European Society of Anaesthesiology has published recommendations on regional anaesthesia and antithrombotic therapy[80] and the management of severe perioperative bleeding.[81]

If an emergency intervention is required, assessment of coagulation and renal function should be performed to evaluate the anticoagulant effect of the NOAC and its time of elimination. The risk of bleeding associated with the type of procedure, the patient's condition, and the level of anticoagulant activity have to be weighed against the risk of delaying the procedure. If possible, interventions with a moderate-to-high bleeding risk should be delayed by at least 24 h and, in case of impaired renal elimination, up to 96 h. NOAC treatment interruption is recommended in case of moderate or high bleeding risk and may be considered in case of minor bleeding risk (if treatment is not interrupted, the procedure should be performed at trough level).

If the procedure cannot be delayed and the patient's coagulation status indicates a high risk of bleeding, NOAC reversal should be considered before the procedure. In dabigatran-treated patients, idarucizumab is the preferred option. In direct factor Xa inhibitor-treated patients (and in dabigatran-treated patients if idarucizumab is not available), administration of PCC (alternatively, aPCC or rFVIIa) should be considered (see the section on Management of bleeding in patients treated with NOACs). In dabigatran-treated patients, haemodialysis may be considered if the intervention can only be postponed by less than 12 h and idarucizumab is not available. If the estimated risk of bleeding is minor or moderate, reversal agents may not be administered prophylactically but should be available in case abnormal bleeding occurs.

Conclusion

The development of NOACs has opened a new era in the prevention and treatment of thromboembolic events. Whilst the favourable benefit-risk profile of NOACs is well recognized, the lack of specific reversal agents has made the management of some patients problematic. The availability of specific reversal agents will provide further reassurance and is expected to help streamline the management of NOAC-treated patients in whom rapid reversal of anticoagulation is required. The practical guidance provided in this article aims to help clinicians make appropriate use of available therapeutic options in daily clinical practice.

Authors' contributions

Participated in two expert meetings during which presentations were delivered by J.W.E., S.K.L., and A.E. and the topics covered in the manuscript were discussed: all authors.
Prepared a draft version of this manuscript: A.K., F.C.
Reviewed several revisions of the manuscript and approved the final version for submission: all authors.

Declaration of interest

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Appendix A. Supplementary data

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