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THEMED ISSUE REVIEW

Anticoagulation reversal (vitamin K, prothrombin complex concentrates, idarucizumab, andexanet-α, protamine)

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Bleeding events are common in patients prescribed anticoagulants and can have devastating consequences. Several specific and nonspecific agents have been developed to reverse the effects of anticoagulant drugs or toxins. Vitamin K, as the oldest of these antidotes, specifically counteracts the effects of pharmaceuticals and rodenticides designed to deplete stores of vitamin K-dependent factors. In cases of life-threatening bleeding, the addition of prothrombin complex concentrates (PCCs) allows for the immediate replacement of coagulation factors. While the use of PCCs has been extended to the non-specific reversal of the effects of newer direct oral anticoagulants, the specific agents idarucizumab, targeting dabigatran and andexanet-α, binding factor Xa inhibitors, have recently been developed and are being preferentially recommended by most guidelines. However, despite having rapid effects on correcting coagulopathy, there is to date a lack of robust evidence establishing the clear superiority of direct oral anticoagulant-specific reversal agents over PCCs in terms of haemostatic efficacy, safety or mortality. For andexanet-α, a potential signal of increased thromboembolic risks, comparatively high costs and low availability might also limit its use, even though emerging evidence appears to bolster its role in intracranial haemorrhage. Protamine is the specific agent for the reversal of unfractionated heparin anticoagulation used mainly in cardiovascular surgery. It is much less effective for low molecular weight heparin fragments and is usually reserved for cases with life-threatening bleeding.

KEYWORDS
andexanet, anticoagulation, antidotes, idarucizumab, protamine, prothrombin complex concentrates, vitamin K

1 | INTRODUCTION

Anticoagulants are a drug class consisting of various medications that act by inhibiting specific steps of the coagulation cascade. Common indications include prophylaxis and therapy of thrombotic disorders and their complications. Targeting the fairly downstream factors **Xa** and/or **IIa (thrombin)** in the coagulation pathway is a common feature of anticoagulants in clinical use. While older agents such as vitamin K antagonists (VKAs) and unfractionated heparin (UFH) target several additional coagulation factors, the newer direct oral anticoagulants (DOACs) were designed to specifically inhibit factor Xa or factor IIa. A summary of some currently commonly used anticoagulants and their

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pharmacological characteristics is provided in Table 1, the mechanism of action of DOAC and their reversal agents is provided in Figures 1 and 2.

Bleeding events are the main adverse effects driving morbidity and mortality associated with anticoagulant therapy and a leading cause of emergency department visits.[3] Reversal of anticoagulation might be required in some patients, especially when life-threatening haemorrhage occurs. Antidotal strategies may include counteracting or bypassing the toxin's effects,[4] this is the case when replenishing vitamin K stores depleted by VKA or when substituting several coagulation factors using prothrombin complex concentrates (PCCs). Another type of reversal molecule binds directly to the toxin,[4] thus interfering with its effects, as is the case with protamine, which forms complexes with heparin, and with the newer DOAC-specific reversal agents. Among antidotes, agents for the reversal of anticoagulation occupy a somewhat particular role, typically not given to poisoned patients, but rather to counteract or prevent bleeding complications in patients on therapeutic-dosed anticoagulants.[5,6] This has been exacerbated in recent years, as there has been a trend towards prescribing the more targeted DOAC such as the direct factor IIa (thrombin) inhibitor (**dabigatran**) and the factor Xa inhibitors (**apixaban**, **rivaroxaban**, **edoxaban**), at the expense of indirectly acting VKA. While vitamin K has an established role in clinical toxicology as an antidote to pharmaceutical or rodenticidal VKA, the newer DOAC-specific reversal agents **idarucizumab** and **andexanet-α** are reserved to severe bleeding and not commonly required in overdose.[7,8] Although limited evidence is available to guide the use of anticoagulation reversal agents in typical clinical situations, some controversy remains, especially regarding the role of newer DOAC-specific antidotes in relation to nonspecific reversal strategies. Additionally, there is some uncertainty about the appropriate dose for specific reversal agents such as the DOAC antidotes and protamine in the somewhat uncommon context of anticoagulant overdose with life-threatening bleeding. For those antidotes, given to approximate a 1:1 stoichiometric ratio, conventional regimens might lead to underdosing in the presence of several fold higher drug exposure than in the therapeutic setting, yet the risks of thromboembolic complications when using higher off-label doses are unknown.[5] In this review, we focused on commonly used reversal agents and their role in the care of anticoagulated patients, after providing a brief overview of general management considerations.

2 | PATIENT ASSESSMENT, INVESTIGATIONS AND NONANTIDOTAL TREATMENTS

For patients presenting with suspected excessive anticoagulation, the initial assessment includes an evaluation for the presence and severity of bleeding as well as a careful history.[9] Considering the time course, especially the timing of last drug intake, is essential to inform anticoagulation reversal decisions, since benefits are reduced in late-presenting patients, and would potentially even be absent if the anticoagulant has mostly cleared, which is often the case for DOAC, considering their comparatively short half-lives of 5–17 h (Table 1). Investigations should include a blood count, measurements of liver and renal function, as well as general coagulation tests (typically international normalized ratio [INR], activated partial thromboplastin time, fibrinogen). For older anticoagulants, general coagulation tests are appropriate for monitoring their effects, as activated partial

TABLE 1 Pharmacodynamic and pharmacokinetic characteristics of selected commonly used anticoagulants.[1,2]

Anticoagulant agent/route of administration	Factors inhibited/ mechanism	Tmax	Metabolism	Elimination half-life	Therapeutic monitoring	Remarks
Vitamin K antagonists (e.g., warfarin, phenprocoumon, rodenticides)/PO	II, VII, IX, X/inhibition of vitamin K epoxide reductase	1–4 h (depending on the substance)	Mainly CYP3A4/2C9 (depending on the substance)	Warfarin: 20–60 h Phenprocoumon: 6–7 days Brodifacoum:16–62 days	INR required for dose adjustments	Effect of dose changes may take days Prolonged anticoagulation in case of rodenticides overdose
Heparins (UFH, LMWH)/SC (both), IV (UFH)	Mainly Xa (both), IIa (UFH)/binding to antithrombin III	UFH: minutes; LMWH: 3–6 h	No CYPs involved	UFH: 30–120 min; LMWH: 2–7 h	aPTT for UFH; for LMWH not required but possible	Preferred therapy during pregnancy
Direct oral anticoagulants/ PO	Xa (e.g., rivaroxaban, apixaban, edoxaban), IIa (dabigatran)/direct inhibition	1–4 h (depending on the substance)	All P-gp substrates, rivaroxaban and apixaban additionally CYP3A4 substrates	Dabigatran 12–17 h; Rivaroxaban 5–13 h; Apixaban 8–15 h; Edoxaban 10–14 h	Anti-Xa levels: not required but possible	Effects in overdose generally of short duration

Abbreviations: aPTT, activated partial thromboplastin time; CYP, cytochrome P450 enzyme; INR, international normalized ratio; IV, intravenous route; LMWH, low molecular weight heparin; P-gp, P-glycoprotein; PO, oral route; SC, subcutaneous route; Tmax, time to reach the maximum plasma concentration; UFH, unfractionated heparin.

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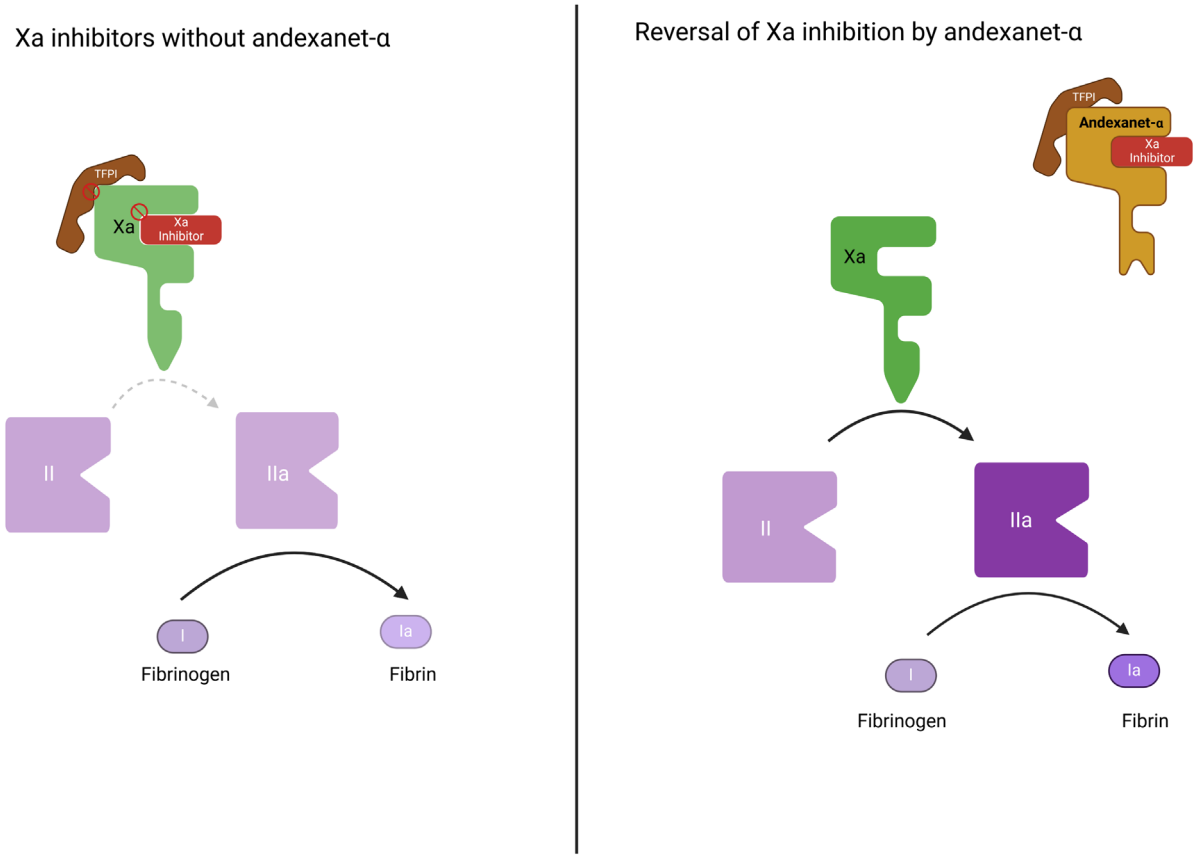

FIGURE 1 Effects of factor Xa inhibitors on the common pathway of coagulation with and without andexanet-α. left: inhibition of factor Xa (Xa) by pharmaceutical factor Xa inhibitors such as apixaban, rivaroxaban and edoxaban. The endogenous tissue factor pathway inhibitor can also inhibit Xa, among other anticoagulant effects. Right: andexanet-α, a modified Xa molecule lacking the catalytic activity of the native factor, acts as a decoy competitively sequestering Xa inhibitors (restoring thrombin generation) and binds to tissue factor pathway inhibitor (potentially increasing thrombogenicity). II: prothrombin, IIa: thrombin. TFPI: tissue factor pathway inhibitor. Created with BioRender.com.

thromboplastin time reflects UFH-associated anticoagulation and the INR estimates vitamin-K antagonist effects. These tests, however, are less useful to assess DOAC-associated coagulopathy, as they might be abnormal, but usually do not allow a quantitative assessment of DOAC effects.[10] Anticoagulant-specific assays, such as measurement of plasma concentrations for factor Xa inhibitors, typically using a chromogenic anti-Xa assay, or the dilute thrombin time for dabigatran, should be considered whenever available.[9] As patient history might be unreliable and drug accumulation can be present, for instance in concomitant renal impairment, specific tests can give valuable insights to guide DOAC antidote use. Anti-Xa assays are increasingly being deployed, with appropriate turnaround time to affect clinical management in emergent situations.[10] Viscoelastographic methods are being proposed by some authors to complement coagulation assessment in medication-induced coagulopathy, but their role is not yet sufficiently well defined.[11] Apart from considering reversing anticoagulation in bleeding patients, supportive measures also play a crucial role in management. Such interventions might include, if appropriate, discontinuation of any anticoagulant or antiplatelet drugs, bleeding site management, transfusion support, activated charcoal, as well as general haemostatic agents such as antifibrinolytics, fibrinogen and/or desmopressin. Extracorporeal removal might be considered for refractory bleeding in selected anticoagulants, such as haemodialysis for dabigatran or plasmapheresis for danaparoid.[9]

3 | VITAMIN K

Vitamin K designates a group of similar fat-soluble compounds involved as cofactors in the γ-carboxylation of glutamate residues of specific proteins, most importantly of precursor forms of some coagulation factors: factors II (prothrombin), VII, IX and X. The antidote for reversal of coagulopathy associated with VKA is vitamin K1 (phytomenadione), which is also the form present in leady greens and cruciferous vegetables, while vitamin K2 is found in animal sources.[12] The γ-carboxylation reaction leads to the formation of vitamin K epoxide and of γ-carboxylglutamate residues on clotting factors, which are able to chelate calcium and bind to negatively charged phospholipids on the membranes of platelets at the site of injury, both promoting coagulation.[13] Since mammals are unable to synthesize vitamin K de novo, vitamin K epoxide is recycled back to vitamin K by vitamin K epoxide reductase, which is the enzyme inhibited by

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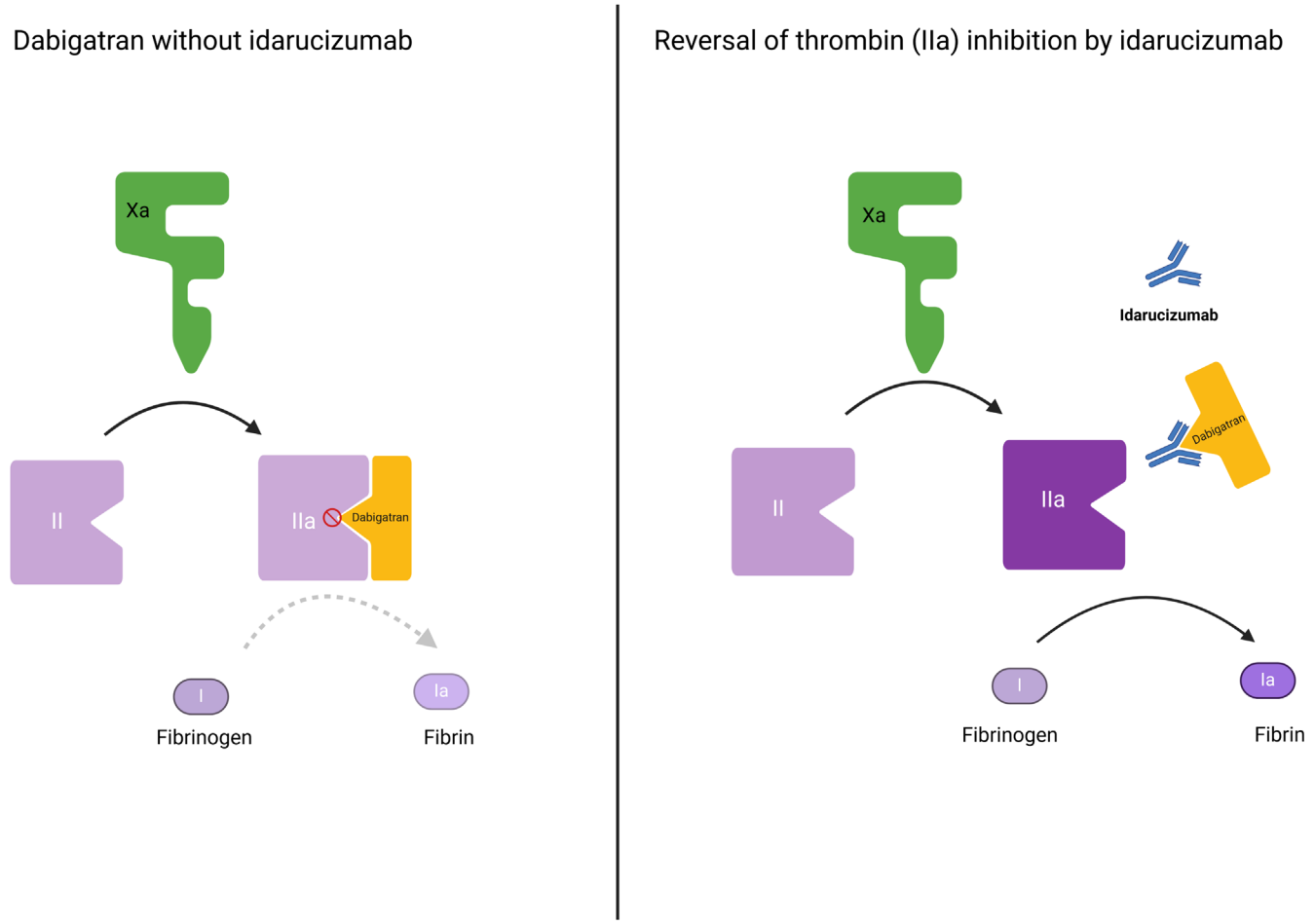

FIGURE 2 Effect of the direct thrombin inhibitor dabigatran on the common pathway of coagulation with and without idarucizumab. Left: inhibition of thrombin (factor IIa) by dabigatran. Right: high-affinity binding of the monoclonal antibody fragment idarucizumab to dabigatran, preventing its binding to factor IIa thus restoring thrombin activity. Xa: factor Xa. II: prothrombin. IIa: thrombin. Created with BioRender.com.

pharmaceutical or rodenticidal VKA (coumarins). These agents thus lead to a vitamin K-depleted state. Replenishment of vitamin K stores by antidotal vitamin K is crucial in counteracting coumarin-associated anticoagulation, but it is a comparatively slow process, as reversal of coagulopathy begins within 1 or 2 h after intravenous infusion,[14] with a maximum effect after 4–6 h.[15] Thus, in the context of life-threatening VKA-associated bleeding, an agent with a more rapid onset such as PCC or, if unavailable, fresh frozen plasma should be given as well.

Vitamin K can be administered orally or intravenously. Enteral absorption of vitamin K is facilitated by micelle formation with bile acids in the small intestine, the bioavailability is around 50% with high interindividual variability,[12] and its terminal elimination half-life is approximately 14 (±6) h following intravenous administration. In enterocytes vitamin K is incorporated into chylomicrons and enters the systemic circulation via the lymphatic system before being taken up by hepatocytes.

As an antidote, vitamin K is used in the context of VKA-associated bleeding or coagulopathy. Typically, oral doses of 1–10 mg are used, depending on the degree of coagulopathy as measured by the INR or the prothrombin time (Table 2). In bleeding patients or when urgent reversal of anticoagulation is needed, vitamin K should be started intravenously. By this route, vitamin K has been associated with anaphylactoid reactions, although this has become exceedingly rare with newer formulations.[20] To further reduce this risk, parenteral vitamin K should be administrated slowly over 30 min. High-dose vitamin K or overcorrection of coumarin-induced coagulopathy was associated with transient resistance to VKA.[21,22]

In rodenticide poisoning, vitamin K is given at higher doses, ranging from 25 up to 600 mg/day in case reports.[23] Treatment over several months can be necessary in case of long-acting rodenticides such as brodifacoum, a lipophilic compound accumulating in adipose tissue, with a half-life ranging from 16 to 62 days in case reports.[24] There is currently no consensus on the optimal monitoring and treatment strategy in the case of poisoning with anticoagulant rodenticides. Typically, INR measurements guide the duration of vitamin K therapy in these patients.[13] Increasingly, additional measurements of rodenticide plasma concentrations are being recommended to estimate its pharmacokinetics,[24,25] but blood levels might not reflect tissue levels.[13]

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TABLE 2 Indications, suggested dose and adverse reactions for commonly used antidotes in the management of anticoagulated patients.[14,16–19]

Reversal agent	Anticoagulant to be reversed	Indication and dose		Main adverse reactions of interest
		Coagulopathy/overdose without severe bleeding	Life-threatening bleeding/urgent procedure	
Vitamin K	-Vitamin K antagonists (pharmaceuticals, rodenticides)	-INR < 5: usually not required -INR 5–10: 1–2.5 mg PO -INR > 10: 5–10 mg PO -Higher doses in rodenticide poisoning	10 mg vitamin K IV (over 30 min)	-Low risk of anaphylactoid reactions when given quickly IV -Risk of INR overcorrection with high doses
4F-PCC	-Vitamin K antagonists -DOAC (factor IIa inhibitor, factor Xa inhibitors)	Usually not indicated	-Vitamin K antagonists: • INR 2–4: 25 units/kg IV • INR 4–6: 35 units/kg IV • INR > 6: 50 units/kg IV -DOAC: 25–50 units/kg IV	3–8% rate of thromboembolic events
Idarucizumab	-Factor IIa inhibitor (dabigatran)	Usually not indicated	2 infusions of 2.5 mg each, IV over 10 min (may be repeated in case of dabigatran rebound)	4–5% rate of thromboembolic events
Andexanet-α	-Factor Xa inhibitors (apixaban, rivaroxaban)	Usually not indicated	-Low dose[a]: 400-mg bolus, followed by 480 mg over 2 h IV -High dose[a]: 800-mg bolus, followed by 960 mg over 2 h IV	10–14% rate of thromboembolic events
Protamine	-UFH -LMWH (enoxaparin, dalteparin, nadroparin)	Individual risk–benefit consideration	-Should be given over at least 10 min IV -No more than 50 mg -Usually not required after 3 h (UFH) resp. 12 h (LMWH) -UFH: 1 mg/100 units UFH, typical adult dose in emergency: 25 mg -LMWH: • Enoxaparin: 1 mg protamine/1 mg enoxaparin (if <8 h)[b] • Dalteparin, nadroparin: 1 mg protamine/100 units of dalterparin or nadroparin	-Immunoallergic reactions (vasodilatory shock, pulmonary vasoconstriction) -Paradoxical increase in anticoagulation at doses >50 mg, especially in case of inadequate LMWH reversal

Abbreviations: 4F-PCC, 4 factor prothrombin concentrate; INR, international normalized ratio; IV, intravenous route; LMWH, low molecular weight heparin; PO, oral route; UFH, unfractionated heparin.

[a]Indication for low dose andexanet-α: apixaban 5 mg or rivaroxaban 10 mg or last dose >8 h before presentation; high dose andexanet-α: apixaban >5 mg or rivaroxaban >10 mg, provided last dose <8 h before presentation.

[b]If enoxaparin exposure 8–12 h prior: 0.5 mg protamine/1 mg enoxaparin.

4 | PCCS

PCCs are a mix of coagulation factors available as 3 factor PCC (containing factors II, IX and X), 4 factor PCC (additionally containing factor VII) and activated 4 factor PCC (partly containing activated factors, primarily activated factor VII). Four factor PCC is the preferred agent in most clinical scenarios when reversal of anticoagulation is needed.[14] Their main indication is the immediate replacement of vitamin K dependent coagulation factors in life-threatening VKA-associated bleeding. In cases of overdose with high INR (>10) but no bleeding, the American College of Chest Physicians 2012 guidelines recommend the use of vitamin K, while PCC is recommended in case of major bleeding independent of the INR.[20] They are also given off-label for reversal of DOAC-associated bleeding, but their presumed mechanism of action is not fully elucidated in this context. The amount of factors II or X present in PCC is insufficient to antagonize the DOAC directly, in a 1:1 ratio. Instead, PCC is thought to work primarily by compensatory actions, increasing concentrations of several unactivated factors, which can get activated at the site of injury, potentially bypassing or overwhelming the effect of factor Xa or IIa inhibition and thus restoring thrombin generation.[26,27] Evidence for the use of PCC in DOAC associated bleeding stems from preclinical and volunteer studies, observational data and some prospective clinical investigations. Randomized controlled trials have not yet been conducted to definitively assess the efficacy and safety of PCC for DOAC reversal in target populations, and, crucially, direct

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head-to-head comparisons to specific reversal agents (idarucizumab, andexanet-α) are lacking so far.[26] Still, while indirect comparisons have inherent limitations, available evidence indicates similar efficacy of PCC compared to specific agents overall (Table 3).[28] Specific reversal agents might, however, prove superior in subgroups of patients, such as those suffering from intracranial haemorrhage, as preliminary data suggest for andexanet-α.[16]

Reversal of anticoagulation with PCC appears to be associated with an approximately 3–8% risk of thromboembolic complications, although this appears to correspond to the underlying thrombotic risk in patients requiring anticoagulation (Table 3).[26] Additionally, PCC may cause allergic reactions and there is an increased risk of heparin-induced thrombocytopenia for preparations containing heparin.[31]

5 | IDARUCIZUMAB

Idarucizumab, a monoclonal antibody fragment, is a highly specific immunotherapeutic antidote binding to the thrombin (factor IIa) inhibitor dabigatran with 350 times higher affinity compared to dabigatran's binding to thrombin. The binding occurs in a 1:1 stoichiometric ratio to free and thrombin-bound dabigatran (Figure 2). Idarucizumab decreases the unbound dabigatran concentration in the vascular compartment, thus leading to back diffusion of tissue-bound dabigatran to plasma, where it can be further neutralized by the antibody, provided it is present in excess.[32] After intravenous infusion, idarucizumab exhibits a volume of distribution of approximately 9 L, reflecting limited extravascular distribution. Idarucizumab is primarily excreted by the kidneys and its elimination is considerably decreased in renal insufficiency. This is likely to prove beneficial for anticoagulation reversal, as dabigatran also accumulates in this context. Dose adjustment is not required in renal impairment, in fact, some authors even advocate for higher doses in renal failure, as dabigatran is likely to be disproportionately increased, but evidence for this practice is lacking.[33]

In healthy volunteer studies, idarucizumab showed no effect in the absence of dabigatran, while providing rapid-onset reversal in dabigatran pretreated subjects, as measured by specific coagulation tests, with immediate reduction in the diluted thrombin time and the ecarin clotting time, paralleling the decrease in unbound dabigatran, with normalization of the activated clotting time occurring within 30 min. These effects on coagulation parameters were sustained for over 72 h after infusion.[32] Approval of idarucizumab was granted on the basis of the REVERSE-AD trial, in effect a hard to interpret prospective observational study, since it crucially lacked randomization and a control group.[34] The reversal agent was administered both in patients with major bleeding and in those in need of urgent reversal of anticoagulation for procedures. The primary outcome was the maximum percentage reversal of dabigatran anticoagulation, as measured by the dilute thrombin time and the ecarin clotting time. While reversal of anticoagulation was seen in all patients, the clinical relevance of this surrogate endpoint is unclear. As a secondary endpoint, the time to cessation of bleeding was reported to be 2.5 h, but this is hard to interpret in uncontrolled data. Subsequent observational studies have shown a mixed picture when comparing the efficacy of idarucizumab to PCC, systematic reviews and meta-analyses concluded that no difference could be shown between these reversal agents to date in terms of haemostatic efficacy, safety or mortality.[28,30] Still, most guidelines recommend the first-line use of specific agents for reversal of DOAC-associated anticoagulation, mainly based upon suggestive evidence from surrogate endpoints and the assumption that specifically designed antidotes are expected to be of superior efficacy compared to nonspecific agents such as PCC.[35]

Idarucizumab is administered in a dose of 5 g split into 2 infusions over 5–10 min each (Table 2). As there might be a secondary dabigatran increase due to redistribution from tissues, the 5 g infusion can be repeated.

Anticoagulation reversal by idarucizumab appears to be associated with a roughly 4–5% risk of thromboembolic complications

TABLE 3 Efficacy and safety of specific and nonspecific agents for reversal of direct anticoagulation in various bleeding contexts in systematic reviews.

	Indication	Haemostatic efficacy	Mortality	Thromboembolic events
Gómez-Outes *et al.*[28] 60 studies 4735 patients (AXA: 936; IDA: 1111; PCC: 2688)	Severe bleeding[a]	AXA: 80.7% IDA: 76.7% PCC: 80.1%	AXA: 18.9% IDA: 17.4% PCC: 17.4%	AXA: 10.7% IDA: 3.8% PCC: 4.3%
Jaspers *et al.*[29] 21 studies 1824 patients (AXA: 396; PCC: 1428)	Major bleeding[b]	AXA: 83% PCC: 77%	AXA: 15% (range 13.9–24.0%) PCC: NA[c] (range 13.6–63.6%)	AXA: 11% PCC: 3%
Chaudhary *et al.*[30] 32 studies 1832 patients	Intracranial haemorrhage	AXA: 75% IDA: 82% PCC: 77%	AXA: 24% PCC: 26% IDA: 11%	AXA: 14% IDA: 5% PCC: 8%

Abbreviations: AXA, andexanet-α; IDA, idarucizumab; PCC, prothrombin complex concentrates.
[a]Severe bleeding: potentially life-threatening bleeding with signs or symptoms of haemodynamic compromise; major bleeding associated with a fall in haemoglobin >2 g/dL; or bleeding in a critical area or organ.
[b]Major bleeding as defined in included studies (variable definitions).
[c]Not available (NA) but range provided.

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(Table 3), which does not appear to differ from the intrinsic risk of clot formation in this patient population.[26,28] The antibody has a low immunogenic potential, hypersensitivity reactions have not been commonly observed.[32] Even though dabigatran is much less used than factor Xa inhibitors, 60–80% of US hospitals have included idarucizumab on their formularies, compared to 11–35% for andexanet-α.[36,37] Costs for 1 treatment dose are estimated to reach $4000 in the USA and €3100 in the EU as of 2023, which is comparable to the cost of PCC and markedly lower compared to andexanet-α.[38]

6 | ANDEXANET-A

Andexanet-α acts as a decoy molecule sequestering factor Xa inhibitors. It is a recombinant factor Xa molecule, modified to include mutations in the active site and in the membrane binding domain, thus lacking proteolytic activity and the ability to form the prothrombinase complex.[16] In contrast to idarucizumab, factor Xa inhibitors bind andexanet-α with comparable affinity to native factor Xa; this reversal agent thus acts as a competitive and reversible antidote, which might contribute to its short duration of action.[16,39] The volume of distribution is close to the blood volume. It is hypothesized to be metabolized in an analogous manner to factor X by proteases in plasma, the renal and hepatic elimination is thought to be negligible. Andexanet-α has a terminal half-life of 5–7 h, but its effective half-life is markedly shorter at approximately 1 h. Due to the corresponding rapid cessation of effect and recurrence of anticoagulation upon discontinuation, a 2-h infusion of andexanet-α is recommended after the initial bolus.[16]

Andexanet-α is approved for the reversal of apixaban or rivaroxaban anticoagulation in the context of life-threatening bleeding. It is also being used off label in the management of haemorrhagic complications associated with edoxaban; available data, though sparse, suggests similar efficacy and safety compared to the reversal of apixaban and rivaroxaban anticoagulation.[40] Sparse data from single case reports also show a potential role for its use in overdose complicated by intracranial haemorrhage.[41] In healthy volunteers pretreated with apixaban or rivaroxaban, andexanet-α showed an over 90% reduction in anti-factor Xa activity and restoration of thrombin generation within 5 min, although this effect was transient.[42] The ANNEXA-4 trial was conducted in the target population and led to the conditional approval of andexanet-α, yet it suffered from similar methodological flaws as the REVERSE-AD trial for idarucizumab, mainly the lack a control group. Eligibility criteria for ANNEXA-4 were more stringent than in the REVERSE-AD trial for idarucizumab, requiring a history of recent DOAC exposure and excluding patients with a poor prognosis (Table 4), the latter limiting generalizability. In patients with major bleeding, andexanet-α rapidly reduced anti-factor Xa activity by 92% at the end of the bolus, and prespecified criteria of haemostatic efficacy were reached in 82% of patients at 12 h, outcomes that are, however, challenging to interpret in absence of a control group. Furthermore, the reduction in factor Xa activity did not predict haemostatic efficacy, except in the subset of patient with intracranial haemorrhage. As a result, controversy surrounds the use of andexanet-α in patients on direct factor Xa inhibitors.[26] For haemorrhage in general, there is no convincing evidence to date that andexanet-α is superior to PCC in terms of haemostatic efficacy or mortality, as several systematic reviews and meta-analyses concluded,[28,30] with potential downsides in terms of thromboembolic safety according to some studies.[28] Building on insights from the ANNEXA-4 trial concerning patients with intracranial haemorrhage, however, emerging evidence suggests that andexanet-α might be advantageous in patients with life-threatening intracranial haemorrhage. While prospective data comparing specific to nonspecific reversal agents are lacking for most situations, it was recently announced that the ANNEXA-I trial conducted in patients with intracranial haemorrhage and comparing andexanet-α to usual care, which involved PCC in the majority of cases, was prematurely stopped because the andexanet-α group achieved significantly higher rates of haemostatic efficacy related to haematoma expansion in an interim analysis.[44] These provisional, not yet peer-reviewed findings should be interpreted with caution, as trials stopped early for superior efficacy often overestimate the true treatment effect.[45] Of interest, the comparatively high rate of thromboembolic events reported in several studies seemed confirmed in these preliminary findings with approximately 10 *vs.* 6% thromboembolic events in the active and control group, respectively ($P = 0.048$)[46]; importantly, these figures are not definitive, and might be updated in the final study report. Despite

TABLE 4 Inclusion and exclusion criteria from the ANNEXA-4 study (andexanet-α approval study).[43]

Inclusion criteria	Exclusion criteria
• Age ≥18 years • Presented with acute major bleeding[a] • Had received within 18 h apixaban, rivaroxaban, or edoxaban at any dose or enoxaparin at a dose of ≥1 mg/kg body weight/day	• Planned surgery within 12 h after andexanet treatment (with the exception of minimally invasive operations or procedures) • Intracranial haemorrhage in a patient with a score of <7 on the Glasgow Coma Scale or an estimated haematoma volume of >60 mL • Expected survival of <1 month • The occurrence of a thrombotic event within 2 weeks before enrolment • Use of any of the following agents within the previous 7 days: vitamin K antagonist, dabigatran, prothrombin complex concentrate, recombinant factor VIIa, whole blood, or plasma

[a]Acute major bleeding was defined as: potentially life-threatening bleeding with signs of haemodynamic compromise (severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained); bleeding associated with a decrease in the haemoglobin level of at least 2 g/dL (or a haemoglobin level of ≤8 g/dL if no baseline haemoglobin level was available); and bleeding in a critical area or organ (e.g., retroperitoneal, intraarticular, pericardial, epidural, or intracranial or intramuscular bleeding with compartment syndrome).

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conflicting and inconclusive data, many guidelines such as the 2020 American College of Cardiology or the 2019 Anticoagulation Forum guidelines recommend the specific antidote andexanet-α to be preferred over unspecific reversal agents such as PCC in life-threatening bleeding associated with apixaban or rivaroxaban.[6,47–52] The 2018 American Society of Hematology recommended reversal but did not issue a preference for either PCC or andexanet-α in light of the scarcity of comparative data.[53] In the United Kingdom, the 2021 National Institute for Health and Care Excellence guidance recommends the use of andexanet-α in life-threatening gastrointestinal bleeding, but restricts the use in intracranial haemorrhage to research and recommended against its use in other types of bleeding.[54] In contrast, a more recent guideline from the Working Party Hemostasis of the Swiss Society of Hematology from 2023, recommends use of this specific agent in patients with intracranial haemorrhage, provided fulfilment of selected eligibility criteria from ANNEXA-4 (Table 4), while recommending PCC in other types of life-threatening bleeding.[16]

Two dose regimens are approved for the use of andexanet-α (Table 2), the low-dose regimen is indicated for patients exhibiting life-threatening bleeding on 5 mg apixaban or 10 mg rivaroxaban, as well as for delayed presentations (after 8 h). The high dose is recommended if higher or unknown doses of apixaban or rivaroxaban have been ingested, provided the last DOAC dose was taken <8 h prior to presentation.[14] Combination of andexanet-α with nonspecific reversal agents such as PCC is controversial as little is known about thromboembolic risks. Because of the short duration of action of andexanet-α, the use of additional procoagulant agents may, however, be considered in the context of ongoing bleeding after completion of the andexanet-α infusion.[16]

A potentially concerning off-target effect of andexanet-α is its binding to the tissue factor pathway inhibitor, an endogenous anticoagulant, which mainly works by inhibiting factor Xa (Figure 1), with additional effects on the factor VIIa/tissue factor complex and tissue factor signalling pathways.[55] This effect is hypothesized to contribute to the comparatively high rate of thromboembolic events following the use of andexanet-α.[26] An overview of systematic reviews and meta-analysis indirectly comparing efficacy and safety of specific reversal agents as well as PCC is provided in Table 3. Overall, the approximately 10–14% rate of thrombotic complications associated with andexanet-α appears consistently higher when compared to the thromboembolic rates observed with idarucizumab (4–5%), PCC (3–8%) or the expected intrinsic rate in this patient population (4–5%).[26] Even though head-to-head comparisons between andexanet-α and PCC are lacking, the potential signal of increased thromboembolic risk should be factored into risk–benefit considerations for andexanet-α.[28]

Mainly because of the limited effectiveness of protamine in low molecular weight heparin (LMWH) associated bleeding and regional variations in protamine availability, andexanet-α is being considered by some authors as an alternative reversal agent for this indication, but evidence for this practice is primarily derived from in vitro data.[56] Results from the ANNEXA-4 trial, which included a small subset of patients on enoxaparin, appear to support these findings, which need to be confirmed in larger trials.[43]

The high price of andexanet-α also constitutes a barrier to its use, since as of 2023 a high dose is estimated to cost around $50 000 in the USA or €32 000 in Europe, which is 5–10 times more onerous compared to PCC or idarucizumab.[38] Accordingly, many hospitals have opted not to stock andexanet-α to date, limiting the availability and use of this reversal agent in emergencies.[36,37] In hospitals including andexanet-α on their formulary, a recent survey in the UK revealed a wide range of practices surrounding its use, especially showing variable and limited consideration of the ANNEXA-4 eligibility criteria.[57] The authors concluded that in light of high-costs and limited evidence, well-designed protocols taking into account these inclusion and exclusion criteria would be desirable (Table 4).

7 | PROTAMINE

Protamine is a specific reversal agent derived from fish sperm and designed to neutralize the anticoagulant effect of UFH. It is a polycationic compound able to bind the negatively charged heparin molecule and to displace antithrombin III from its binding site, forming stable salts with UFH.[45] Its role in reversal of UFH anticoagulation has been established in several volunteer studies and observational data, but its efficacy is considerably lower for the reversal of LMWH anticoagulation, due to decreased binding of protamine to the shorter heparin fraction. While the anti-factor II activity is fully reversed, the anti-factor X activity is only partly antagonized, up to about 60% for enoxaparin, for instance.[58] Protamine's effectiveness is dependent on the molecular weight of the specific LMWH and its sulphate charge density.[59] It is considered mainly for reversal of enoxaparin or dalteparin, while the effects from the LMWH-like anticoagulant fondaparinux are not thought to be adequately reversible by protamine, activated factor VII or activated PCC are the preferred agents in this case.[9,14,60] After intravenous application, protamine has a volume of distribution of approximately 12 L and gets eliminated with a very short half-life of 5–7 min, with predominantly renal excretion.[61–63]

Protamine is mainly used to reverse the effects of high-dose UFH in cardiovascular surgery. In other clinical scenarios, reversal is seldom needed for excessive or inadequate UFH anticoagulation, since heparin's short half-life of 60–90 min usually obviates its use.[26] Because of the longer half-life of LMWH, reversing its anticoagulation acutely might be of greater clinical relevance. However, owing to reduced effectiveness and lack of robust evidence, the role of protamine in LMWH overdose is less clearly defined. While it is usually recommended in life-threatening bleeding due to the lack of established alternatives, prophylactic reversal of LMWH anticoagulation should only be considered if the expected benefits outweigh the efficacy and safety disadvantages of protamine in this situation.[64]

Traditionally, empiric dosing strategies have been used to reverse heparin anticoagulation (Table 2), but these schemes might lead to excessive protamine exposure with increased risks of associated toxicities. To optimize dosing several pharmacokinetic model-based dosing schemes have been proposed, mainly for the use in cardiovascular surgery.[31] For reversal of LMWH anticoagulation, agent-specific empiric

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dosing regimens have been suggested (Table 2). Protamine should be infused slowly over at least 10 min since immunoallergic reactions ranging from hypotension to vasodilatatory shock have been associated with rapid application. A complement-mediated hypersensitivity with pulmonary vasoconstriction and right heart failure has also been described.[14,65] Of potential concern are paradoxical anticoagulant effects of protamine, which could outweigh the procoagulant effects in LMWH reversal. This is thought to occur through inhibition of factor V at high doses and facilitation of fibrinolysis, weakening clot structure.[14,61]

8 | CONCLUSION

Various antidotal agents are available for the reversal of anticoagulation in case of major bleeding. For most substances, reversal is usually not indicated in case of overdose in the absence of bleeding. Vitamin K is given in case of coagulopathy, overdose or bleeding associated with the use of pharmaceutical or rodenticidal VKA. In contrast, the newer DOAC specific reversal agents idarucizumab and andexanet-α are typically reserved for life-threatening DOAC associated bleeding; however, their superiority to PCC has not yet been convincingly established. For andexanet-α, emerging evidence suggests added haemostatic benefit to usual care in selected patients with intracranial haemorrhage, but high costs, safety concerns and a lack of evidence-based protocols could constitute barriers to its use. Protamine is a specific antidote targeting UFH, mainly used in cardiovascular surgery, with some safety concerns. Protamine is less effective for reversal of LMWH-associated anticoagulation, but is usually recommended in case of life-threatening bleeding.

8.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to Pharmacology 2019/20 (Alexander *et al.*).[66]

AUTHOR CONTRIBUTIONS

Elias Bekka and Evangelia Liakoni performed the literature review, and wrote and reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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