REVIEW ARTICLE

Antidotes for Anticoagulation Reversal

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SUMMARY

The global rise in anticoagulant use has increased the number of major bleeding events that warrant timely and effective pharmacologic reversal. Reversal strategies should be informed by the pharmacodynamic and pharmacokinetic features of the anticoagulant and antidote, regulatory indications, quality of evidence, patient-specific factors, and availability of treatment options. Protamine sulfate neutralizes unfractionated heparin, whereas no specific antidotes exist for low-molecular-weight heparins or fondaparinux. Four-factor prothrombin complex concentrates effectively reverse vitamin K antagonists. Idarucizumab specifically reverses dabigatran, although delayed dabigatran rebound can occur. Andexanet alfa targets direct oral factor Xa inhibitors, but uncertainties regarding the efficacy–safety balance, monitoring, rebound, perioperative use, and cost have prompted off-label use of four-factor prothrombin complex concentrates, for which stronger evidence is needed. Key challenges remain, including determination of appropriate dosing, standardization and validation of laboratory monitoring, mitigation of thrombotic risk, and development of guidelines for perioperative treatment. Emerging agents aim to broaden targets and improve safety. Building high-quality evidence remains essential to advancing global, patient-centered anticoagulant and hemostatic care.

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The global use of oral anticoagulant drugs has risen substantially over recent decades, driven by embolic-stroke prevention in atrial fibrillation and treatment or prevention of venous thromboembolism (VTE). This trend reflects heightened awareness of VTE-related burden and a near doubling of the prevalence of atrial fibrillation worldwide, from 33.5 million in 2010 to more than 59 million in 2019, with further growth projected by 2050.[1] Use of parenteral anticoagulants, particularly unfractionated heparin, has also increased, driven by expanding invasive cardiovascular procedures and cardiopulmonary bypass surgeries. The global market for unfractionated heparin is projected to grow by 4.2% annually through 2030,[2] contingent on the sustainable availability of sources.[3]

Despite their proven antithrombotic efficacy, all anticoagulants carry an intrinsic risk of bleeding.[4] In major trials and registries of atrial fibrillation (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), the rate of major bleeding events ranges from 1.4 to 6 per 100 patient-years across the spectrum of oral anticoagulants. Oral anticoagulant–associated intracranial hemorrhage, the bleeding event associated with the highest mortality and disability, accounts for up to 25% of all cases of intracranial hemorrhage and has poorer outcomes than intracranial hemorrhage that is not associated with the use of oral anticoagulants.[5] The rate of intracranial hemorrhage is approximately 0.3 per 100 person-years with direct oral anticoagulants (DOACs) and approximately 0.8 per 100 patient-years with vitamin K antagonists. The risk of major bleeding events increases with age, kidney or liver disease, frailty, and polypharmacy, regardless of anticoagulant type. With the expanding use of anticoagulants, the absolute num-

ber of major bleeding events that lead to pharmacologic intervention is rising. Timely and effective pharmacologic reversal of anticoagulation remains critical for events of major bleeding, emergency surgery, and high-risk procedures.

Several antidotes with distinct pharmacodynamic features are available (Table 1).[6] Specific antidotes (e.g., idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors) directly neutralize the anticoagulant by means of molecular-specific recognition and selective binding to the agent. Nonspecific functional antidotes, including prothrombin complex concentrate, restore hemostasis by supplementing the substrate (i.e., coagulation factors) in a way that is not dependent on the pharmacodynamic features of the anticoagulant (Fig. 1).

This review outlines the pharmacologic aspects, rationale, and evidence supporting antidotes to parenteral and oral anticoagulants. Figure 1 depicts antidote targets and effects within the coagulation cascade, and Table 1 outlines the chemical and pharmacologic properties, dosing, and approved and off-label uses of antidotes to anticoagulants, including whether the antidotes can be used during pregnancy.

SPECIFIC ANTIDOTES

PROTAMINE SULFATE AND HEPARINS

The highly cationic protamine sulfate peptide (protamine) neutralizes the anionic unfractionated heparin mixture (Table 1) and is widely used in cardiopulmonary bypass surgery, vascular procedures, and other clinical contexts that pose a high risk of bleeding.[7] Protamine incompletely neutralizes low-molecular-weight heparins, primarily targeting their antithrombin activity, although it is ineffective against fondaparinux and danaparoid.[8] Protamine dosing should be individualized on the basis of the unfractionated heparin dose, pharmacologic factors, patient characteristics, and available monitoring assays.

The dose of intravenous protamine is guided by the amount and timing of unfractionated heparin administered, with the ratio of protamine to unfractionated heparin not to exceed 1:1 (Table 1). Excess protamine may paradoxically impair hemostasis through multiple mechanisms, increasing bleeding and transfusion amounts.[8,9] Whether protamine doses should be based on the loading or total (loading plus intraoperative) unfractionated heparin dose remains a subject of debate.[9] Proposed dose-adjustment strategies incorporate the pharmacokinetic features of intravenous unfractionated heparin, particularly its half-life (approximately 30 to 90 minutes, dose-dependent with nonlinear kinetics) and patient-specific characteristics, including age, sex, height, platelet count, and body weight.[9,10] Fixed-dose regimens may simplify use and improve efficacy and safety, although definitive evidence is lacking.[11-13]

Assessing the adequacy of unfractionated heparin neutralization after protamine infusion remains challenging. Procedure-associated coagulopathy, coexisting conditions, and the intrinsic anticoagulant effects of protamine can affect available assays. Chromogenic anti–factor Xa assays most accurately quantify residual unfractionated heparin activity but are not routinely available. The routinely used activated partial-thromboplastin time (aPTT) and activated clotting time assays detect low and high unfractionated heparin levels, respectively, yet correlate poorly, even across different devices for testing activated clotting time.[14,15]

In the hours after protamine infusion, the reappearance of circulating free unfractionated heparin (the unfractionated heparin rebound), typically less than 0.2 IU per milliliter of anti–factor Xa activity and undetectable on an activated clotting time test, may occur, but the clinical relevance and management remain unclear.[8,16-19] Point-of-care whole-blood assays, such as protamine titration and viscoelastic tests, can accurately detect low unfractionated heparin activity but lack outcome validation.[16,17]

Protamine-associated, hemodynamic adverse events are relatively common (Table 1) and arise from direct toxic or indirect, immune-mediated mechanisms (or both).[8,9] Risks can be reduced by slow infusion through a peripheral intravenous catheter.[9] Risk factors include previous vasectomy (owing to antisperm antibodies), fish allergy (limited evidence), and exposure to protamine-containing insulins.[8] In patients with clear contraindications to protamine (e.g., documented allergy) or unfractionated heparin (e.g., heparin-induced thrombocytopenia), bivalirudin is a preferred alternative to argatroban in cardiac surgery owing to its shorter half-life,[9] although it lacks a specific antidote; modified ultrafiltration has been used to decrease bivalirudin levels after

separation from cardiopulmonary bypass.[19] Off-label prothrombin complex concentrates may be used, if needed.

ANDEXANET AND DIRECT AND INDIRECT FACTOR XA INHIBITORS

Andexanet is a recombinant inactive factor Xa decoy that is engineered to neutralize direct factor Xa inhibitors and antithrombin-associated indirect factor Xa inhibitors (Table 1). Andexanet also inhibits tissue factor pathway inhibitor for up to 14.5 hours, with tissue factor pathway inhibitor levels returning to baseline within 72 hours after administration.[20] Tissue factor pathway inhibitor suppression may transiently enhance thrombin generation, sustaining a prothrombotic milieu (Fig. 1),[20] as reflected by transient, above-baseline increases in prothrombin fragment 1+2 and D-dimer levels[21] and nearly doubled endogenous thrombin potential levels early after infusion in 163 participants in the ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors) trial.[22]

In the single-group ANNEXA-4 trial, andexanet was administered to 352 patients who had major bleeding associated with rivaroxaban, apixaban, edoxaban, or enoxaparin.[23,24] Postbolus anti–factor Xa activity decreased by 92% in patients who had received a direct factor Xa inhibitor (234 patients, 10 of whom had received edoxaban) and by 75% in those who had received enoxaparin (16 participants) (Table 2).[22,23] A partial factor Xa inhibitor rebound, assessed by anti–factor Xa activity, occurred within 4 hours after completion of infusion in most patients who had received DOACs, as shown by anti–factor Xa activity remaining inhibited by 32% (with apixaban) and 42% (with rivaroxaban). This rebound may reflect the dissociation of the andexanet–DOAC complexes and the fact that the half-life of andexanet is shorter than that of each factor Xa inhibitor (Table 1). At 12 hours, 82% of the patients had good or excellent hemostasis. Thirty-day mortality was 14% (49 patients); the incidence of major thrombotic events was 10% (34 patients), predominantly within 14 days after infusion. The lack of a comparator, small trial size, and short follow-up time limit the interpretation of the ANNEXA-4 trial results.[24]

In the ANNEXA-I trial,[36] 452 patients with factor Xa inhibitor–associated intracranial hemorrhage were assigned to receive andexanet or standard care (prothrombin complex concentrates in 85.5%). The trial was stopped at the first interim analysis (prespecified after enrollment of the first 450 patients) on the basis of a prespecified criterion of reaching a P value of 0.031 for the primary end point (a change in the hematoma volume of 20% or less [excellent hemostasis] or of 35% or less [good hemostasis] within 12 hours after baseline, an increase in the National Institute of Health Stroke Scale score of <7 points at 12 hours, and receipt of no rescue therapies within 3 to 12 hours after randomization). Andexanet showed superior hemostatic efficacy to standard care at 12 hours (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003), a finding that was largely driven by a reduction in hematoma volume of 35% or less. However, growth of larger hematomas (≥12.5 ml), 30-day neurologic deterioration, and mortality were similar in the two groups, whereas the incidence of thrombotic events, mostly ischemic stroke, was nearly twice as high with andexanet (10.3% vs. 5.6%; P=0.048) (Table 2). Of note, an increase in endogenous thrombin potential and reduction in anti–factor Xa activity early after andexanet treatment were associated with both reduced hematoma expansion and increased thrombosis,[22] which suggests a tight link between restoring hemostasis and provoking thrombosis. Long-term outcomes were not collected. Despite the superior hemostatic efficacy of andexanet, mostly in reducing hematoma expansion, the neutral effect on larger hematomas and mortality[36,37] together with the higher risk of major and life-threatening thromboses that have been consistently reported in observational studies (Table 2) arouse concern.

As of December 22, 2025, andexanet has been voluntarily withdrawn from the U.S. market as a result of safety concerns raised by the Food and Drug Administration (FDA).[38] Andexanet holds conditional approval by the European Medicines Agency (EMA),[39] subject to additional monitoring,[40] only for reversal of apixaban and rivaroxaban — not for edoxaban, low-molecular-weight heparin, or fondaparinux — in cases of major uncontrolled and life-threatening bleeding (Table 1). Neither the ANNEXA-4 trial nor the ANNEXA-I trial included patients who were undergoing emergency surgery. Accordingly, andexanet is not approved perioperatively and carries a warning against

Table 1. Characteristics of Available and Emerging Antidotes to Anticoagulant Agents.*

Antidote	Composition and Pharmacodynamic Features	Pharmacokinetic Features†	Administration	Approved Indications	Risks and Warnings	Reference Assay
Specific						
Protamine sulfate	Polycationic arginine-rich peptides (approx. 32 AA; MW, approx. 4.5 kDa) Selective binding to UFH forming inert complexes Partial LMWH neutralization (anti-FIIa activity)	Vd: approx. 60 ml/kg Onset: <5 min Half-life: 5–7 min Clearance: hepatic for heparin–protamine complexes, renal for free drug, but no dose adjustment required in kidney disease	Slow IV infusion: ≤1 mg per 100 IU (or 1 mg) UFH considering UFH half-life (30–90 min, nonlinearly dose-dependent)	UFH reversal (FDA, EMA) Not approved for LMWH	Risks: hypotension (1.8–12.4%), pulmonary hypertension (0.6–15.8%), anaphylaxis (0.14–0.7%), fatal ventricular arrhythmias (<0.1%) Prothrombotic effect at high doses Caution with previous exposure and in pregnancy	ACT (high UFH levels) aPTT–anti-FXa (low UFH levels) Viscoelastic assays under study
Vitamin K1	Naphthoquinone (MW, approx. 450.7 Da) Selective competition with VKA at VKORC1 (Kd, ≤10 nM; warfarin Ki, approx. 5 nM) restoring γ-carboxylation of vitamin K–dependent factors	Vd: approx. 290 ml/kg Onset of reversal dependent on coagulation factor, not antidote half-life Half-life: approx. 2 hr Clearance: renal and fecal	IV (5–10 mg) or oral (1–10 mg), depending on INR and bleeding	VKA-associated bleeding or high INR (EMA, FDA)	IV route: risk of anaphylactoid reactions Use the lowest effective dose Avoid intramuscular route Safe in pregnancy	INR Vitamin K–dependent factor levels
Andexanet alfa	Recombinant, modified, FXa decoy (S419A + GLA domain deletion, MW, approx. 40 kDa) Reversible binding of direct FXaI (similar Kd for native and decoy FXa) Binds heparin–AT complex Off-target binding to TFPI	Vd: approx. 75 ml/kg Onset: ≤5 min Half-life: approx. 4–7 hr Clearance: hepatic	IV bolus + 2-hr infusion Dose based on FXaI type, dose, and timing since last intake	Uncontrolled or life-threatening bleeding with apixaban, rivaroxaban (EMA conditional authorization, withdrawn from the U.S. market)‡ No approval for edoxaban, LMWH, fondaparinux	Thromboembolic risk Transient UFH resistance Early FXaI rebound Not recommended in pregnancy	Interferes with commercial anti-FXa assays Point-of-care viscoelastic assays under study
Idarucizumab	Humanized mouse Fab fragment (MW, approx. 47.8 kDa) Specific for dabigatran (Kd approx. 2 pM; Kd of dabigatran for thrombin 0.7 nM)	Vd: 60 ml/kg (dabigatran Vd higher than that with idarucizumab by approx. factor of 6) Onset: <5 min Half-life: approx. 10 hr Clearance: renal with prolonged half-life if renal disease	IV: 5 g (2×2.5 g boluses)	Uncontrolled or life-threatening bleeding or emergency surgery with receipt of dabigatran (EMA, FDA)	Late dabigatran rebound (from 24 hr) Contraindicated in pregnancy	ECT dTT aPTT (less sensitive)

Nonspecific						
4-Factor PCC	Plasma-derived concentrate restoring vitamin K–dependent FII, FVII, FIX, FX Protein C, protein S, UFH, AT may be present Final plasma coagulation factor levels up to 1.5 times that of the physiologic concentrations	Vd: variable, from 45±10.7 ml/kg of FVII to 114.3±54.6 ml/kg of FIX Onset: INR correction detectable by 30 min after infusion Half-life: variable (FVII 5±1.9 hr, FIX 42.4±41.6 hr, FX 31.8±8.7 hr, FII 60.4±21.5 hr) Clearance: hepatic	Approved IV dose: 25–50 FIX IU/kg adjusted on INR (max 5000 IU) Fixed dose under investigation	VKA reversal (EMA, FDA) in major bleeding and before surgery or procedures Off-label for DOACs	UFH-containing preparations contraindicated if history of HIT or in DIC Caution if recent (3 mo) major thrombotic event Pregnancy and lactation: only if benefits outweigh risks	INR (VKA) Coagulation factor levels PT (FXaI, depending on reagents) aPTT (dabigatran only) Thrombin generation (all FXaI)
Activated PCC	Plasma-derived concentrate of FVIIa (approx. 1 IU/mg) + FII, IX, X Bypasses intrinsic pathway by FX activation Plasma FVIIa levels increased by a factor of 25 to 100 (based on 50 IU/kg dose in a 70-kg person)§	Vd: 45–114 ml/kg Onset: 10–30 min Half-life: variable according to the single components Clearance: hepatic	IV Usual dose, 500 IU for INR <5 and 1000 IU for INR ≥5 for VKA reversal; 10–50 IU/kg for DOAC reversal	Off-label for all anticoagulants	High risk of major thrombosis, especially >200 IU/kg/day or in high-risk patients Avoid in pregnancy	INR (for VKA) PT (reagent dependent) aPTT (dabigatran only) Thrombin generation (FXaI)
Recombinant FVIIa	Recombinant FVIIa (MW, approx. 50 kDa) Direct activation of FX FVIIa levels increase by a factor of up to 1500 (dose of 90 μg/kg in a 70-kg person)	Vd: 103 ml/kg Onset: within minutes Half-life: 2.3 hr in patient with bleeding Clearance: hepatic	IV Off-label dose ≤90 μg/kg	Off-label for all anticoagulants	High dose-dependent risk of thrombosis, reduced if <20 IU/kg Avoid in pregnancy	PT (reagent-dependent for FXaI)
Ciraparantag	Synthetic cationе based on the arginine ring (MW, 512 Da) Electrostatic binding to UFH, LMWH, and DOACs	Vd: approx. 300 ml/kg Onset: within minutes Half-life: 12–19 min Clearance: renal	IV, dose under investigation	In development	Off-target binding to proteins and relevant drug interactions possible Safety to be established	Whole-blood clotting time (experimental)
VMX-C001	Modified, recombinant, human FX (MW, approx. 63 kDa) Selective restoration of FX activity independent of FXaI	Vd: approx. 130 ml/kg Onset: within minutes Half-life: 20.5–30.2 hr Clearance: possibly hepatic	IV, dose under investigation	In development	Safety not yet established	Diluted PT Diluted Russell viper venom time

* Plus–minus values are means ±SD. The letter "a" denotes activated, AA amino acids, ACT activated clotting time, aPTT activated partial-thromboplastin time, AT antithrombin, DIC disseminated intravascular coagulation, DOAC direct oral anticoagulants, dTT dilute thrombin time, ECT ecarin clotting time, EMA European Medicines Agency, F factor, FDA Food and Drug Administration, FXaI activated factor X inhibitors, HIT heparin-induced thrombocytopenia, INR international normalized ratio, IV intravenous, Kd dissociation constant, Ki inhibition constant, LMWH low-molecular-weight heparin, MW molecular weight, PCC prothrombin complex concentrate, PT prothrombin time, TFPI tissue factor pathway inhibitor, UFH unfractionated heparin, and VKA vitamin K antagonists.

† Volume of distribution (Vd) values are reported at a steady state in a 70-kg healthy adult.

‡ Andexanet alfa is no longer manufactured or sold in the United States as of December 22, 2025, on voluntary withdrawal of Biologics Licensing Application from the applicant on the basis of safety concerns raised by the FDA (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/update-safety-andexxa). Use is subject to additional monitoring by the EMA according to the summary of product characteristics updated on November 15, 2025 (https://www.ema.europa.eu/en/documents/product-information/ondexxya-epar-product-information_en.pdf).

§ One IU produces activity to correct clotting time of FVIII inhibitor plasma by 50%.

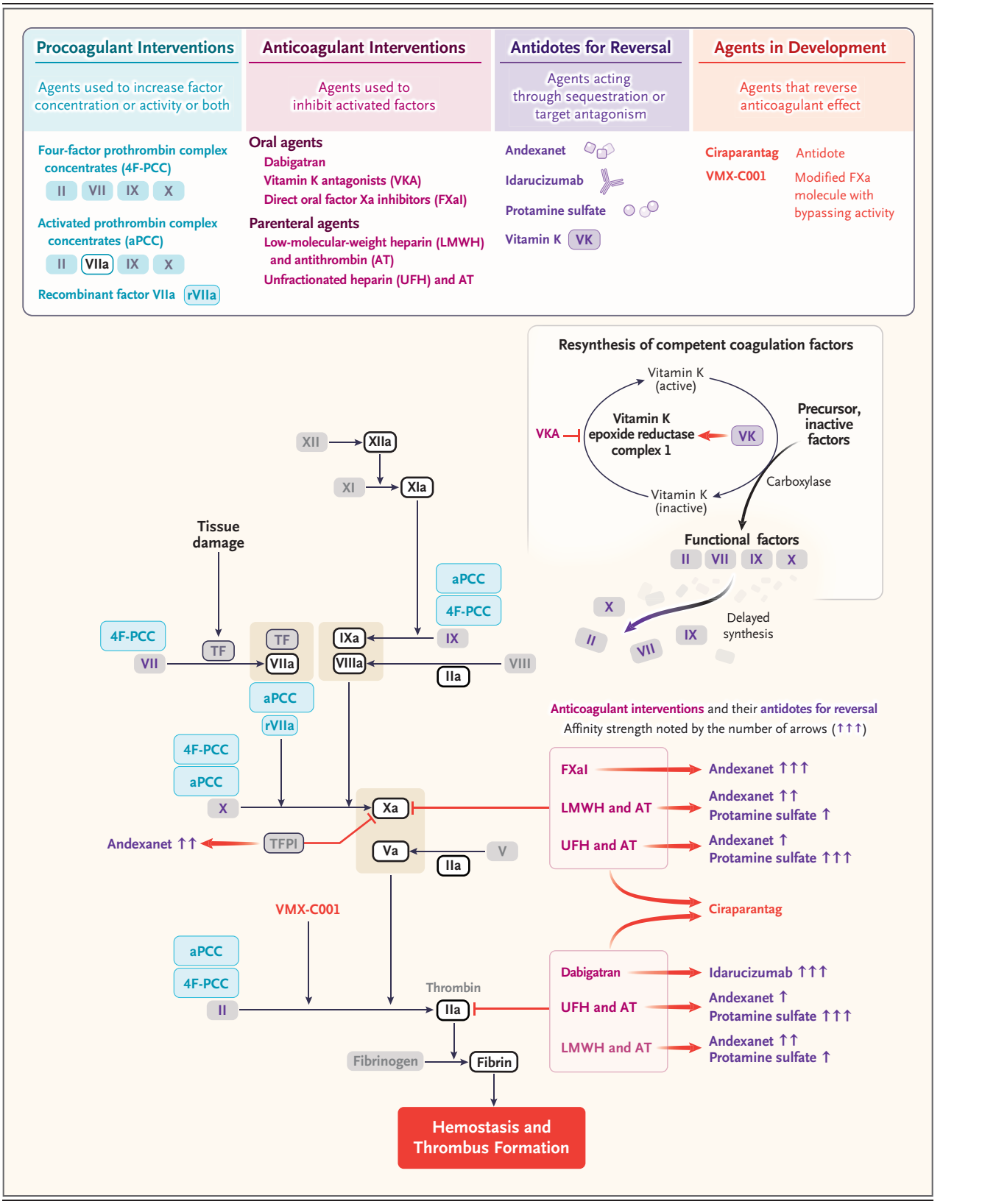


Figure 1 (facing page). Mechanisms of Action of Specific and Nonspecific Antidotes to Anticoagulant Drugs.

Specific antidotes directly neutralize anticoagulants by means of molecular-specific recognition and selective binding to the agents, whereas nonspecific functional antidotes, including prothrombin complex concentrate, restore hemostasis in a way that is not dependent on the pharmacodynamic features of the anticoagulant. Four-factor prothrombin complex concentrates (4F-PCCs) restore coagulation by supplementing vitamin K–dependent coagulation factors (II, VII, IX, and X), resulting in a variable support of hemostasis, regardless of the anticoagulant's pharmacodynamics; activated 4F-PCCs contain factor VII in the activated form (FVIIa), with bypassing activity through direct, tissue-factor–dependent activation of factor X (FX) and factor IX (FIX), resulting in a rapid burst of thrombin generation; recombinant FVIIa has a similar bypassing activity. As shown on the right side of the figure, anticoagulant drugs have different competing affinities for their coagulation targets and for their specific antidotes. Vitamin K competes with vitamin K antagonists for the vitamin K epoxide reductase complex 1 binding site, enabling gradual resynthesis of competent coagulation factors and correction of the international normalized ratio (INR). Direct factor Xa inhibitors (FXaIs) have higher affinity for andexanet alfa than for factor Xa; the heparin–antithrombin complex also binds andexanet and induces transient heparin resistance. Andexanet binding and inhibition of tissue factor (TF) pathway inhibitor (TFPI) may increase thrombin generation and prothrombotic risk; however, andexanet is no longer marketed in the United States as of December 22, 2025.[38] Unfractionated heparin (UFH) has a very high chemical affinity for protamine sulfate, whereas low-molecular-weight heparin (LMWH) has a low affinity. Dabigatran has a higher affinity for idarucizumab than for thrombin. Ciraparantag, currently in development, can bind multiple oral and parenteral drugs with high affinity. VMX-C001 is a bypassing agent in development.

administration in patients undergoing cardiac surgery[40,41] (Table 1). By binding to antithrombin–unfractionated heparin complexes, andexanet induces transient unfractionated heparin resistance,[42] seriously complicating perioperative treatment with unfractionated heparin, and it has been associated with clinically significant circuit thrombosis, a condition that compromises pump flow and poses life-threatening risk for patients during cardiopulmonary bypass.[43] Higher doses of unfractionated heparin or preemptive antithrombin supplementation[42,43] may overcome resistance if andexanet has already been administered, but clinical validation is lacking.

Measuring anti–factor Xa levels before andexanet infusion, if feasible, may guide appropriate use (see Table S2 for on-therapy ranges). Unlike with the specific assay used in the ANDEXA-4 trial to quantify anticoagulant reversal, andexanet interferes with exogenous factor Xa added to commercial chromogenic routine anti–factor Xa assays.[44] Thus, postinfusion monitoring is an unreliable support for decision making in cases of rebleeding.[44] Although viscoelastic and new point-of-care assays appear to be promising, they still lack validation.[45,46] Thus, routine laboratory assays for measuring anti–factor Xa activity of factor Xa inhibitors after andexanet infusion are currently lacking.

Given its thrombogenicity, lack of monitoring, undefined long-term clinical effect, regulatory concerns,[38-40] and high costs (Table 2), andexanet should be reserved only for selected patients, with strict adherence to approved indications (i.e., life-threatening or uncontrolled bleeding) when rapid reversal outweighs risks and surgery is not anticipated (Fig. 2). Combining andexanet with a prothrombin complex concentrate should be avoided owing to a theoretical additive thrombogenicity.[47]

IDARUCIZUMAB AND DABIGATRAN

Idarucizumab is a humanized monoclonal antibody fragment that selectively binds dabigatran at the light–heavy chain interface (Fig. 1 and Table 1).[48] Preclinical and phase 1 studies showed no intrinsic procoagulant activity.[49,50] In healthy volunteers, dabigatran prolongs ecarin clotting time (ECT), diluted thrombin time, and aPTT proportionally to unbound plasma concentrations up to approximately 600 ng per milliliter.[48] These anticoagulant effects were rapidly and completely reversed for 24 hours in patients who had received idarucizumab at a dose of at least 2.5 grams.[51]

The single-group Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study enrolled 503 patients who were treated with dabigatran and had life-threatening bleeding (group A) or were undergoing emergency surgery (group B) (Table S3).[51] Idarucizumab was associated with rapid, 100% reversal of ECT and diluted thrombin time across various demographic groups. Confirmed bleeding cessation within 24 hours, a secondary end point, was reached in 67.7% of the evaluable patients in group A and

Table 2. Andexanet Alfa as Compared with PCC.*

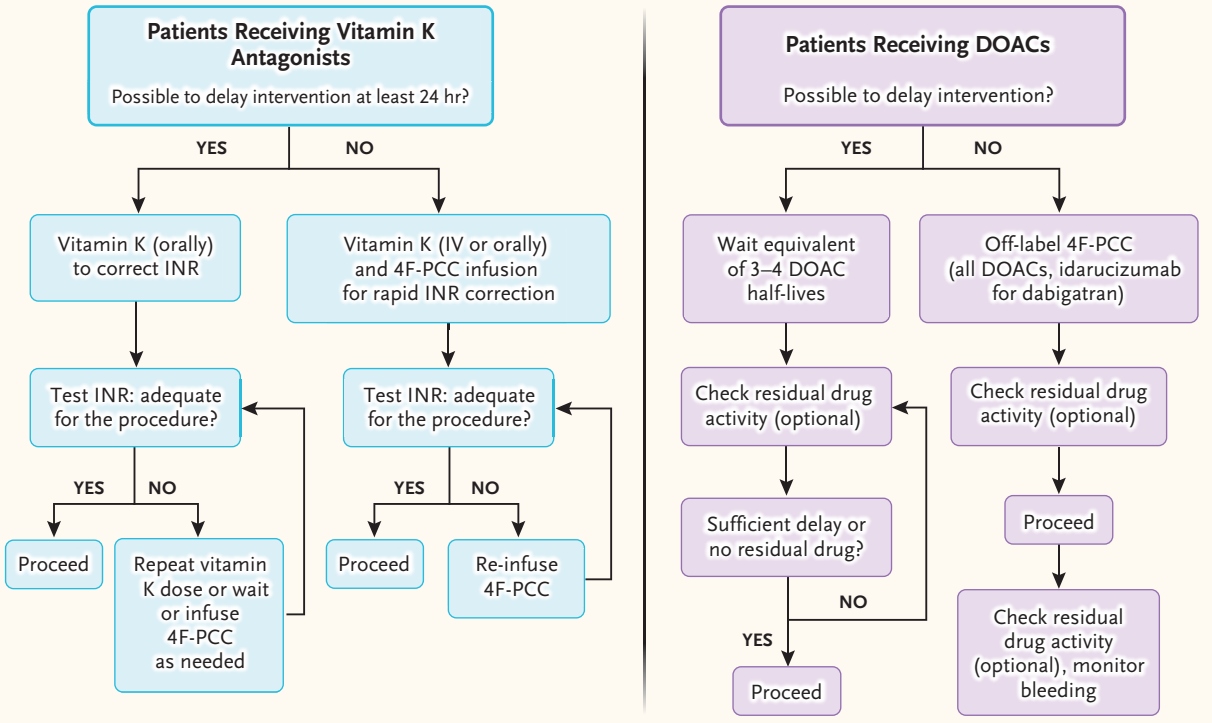
Study or Trial and Year	Design	Population and Intervention	End Points	Key Results
Diener et al., 2025[25]	Single-group, prospective	137 patients with ICH (47.4% men; mean age, 80 yr; 65.7% apixaban, 34.3% rivaroxaban) Andexanet	Primary: hematoma volume change within 12–72 hr; hematoma growth ≤33% within 12–72 hr Secondary: mortality and in-hospital TEE	Mean hematoma expansion 2.3 ml (95% CI, 0.4–4.2); approx. 90% with hematoma growth ≤33% In-hospital mortality, 21.9% 90-Day mortality, 36.7% In-hospital TEE, 8%
Tsivgoulis et al., 2025[26]	Meta-analysis of 18 studies	Andexanet (1567 patients) or study-defined usual care (1969 patients)	Primary: hematoma expansion ≤35% or ≤6 ml (good hemostasis) Secondary: hematoma expansion ≤20% (excellent hemostasis), functional outcomes (modified Rankin Scale score 0–3), mortality, and TEE	Good hematoma control: higher with andexanet (RR, 1.16; 95% CI, 1.06–1.26) No significant difference in excellent hemostasis, function, mortality, or TEE
Sarhan et. al., 2025[27]	Meta-analysis of 16 studies	2977 patients (58% men; mean age, 77 yr) with ICH PCC (1560 patients) or andexanet (1417 patients)	Primary: anticoagulation reversal, mortality, and TEE Secondary: length of hospital and ICU stay, hematoma expansion	Associated with andexanet: Higher anticoagulant reversal (RR, 1.10; 95% CI, 1.01–1.20; P=0.02) More TEE (RR, 1.47; 95% CI, 1.01–2.15; P=0.046) Longer hospital stay (mean difference in days, 0.64; 95% CI, 0.07–1.22; P=0.03) No meaningful difference in ICU stay, mortality, or hematoma expansion
Ovesen et al., 2025[28]	Systematic review of 2 RCTs	534 patients with FXaI-related critical bleeding PCC, FFP, or andexanet	Mortality TEE Trial-defined hemostatic efficacy Functional outcomes	PCC vs. FFP Faster INR correction (RR, 0.41; 95% CI, 0.32–0.52) Hemostasis nonsignificantly better (RR, 0.68; 95% CI, 0.44–1.06; P=0.09) Similar all-cause mortality and TEE (RR, 3.14; 95% CI, 0.14–72.92) PCC vs. andexanet Lower hemostatic efficacy (RR, 1.46; 95% CI, 1.15–1.85; P=0.002) Similar all-cause mortality and functional outcomes Lower TEE (RR, 0.55; 95% CI, 0.30–1.00; P=0.052)
Connolly et al., 2024[36]	RCT	452 patients with ICH (mean age, 78.9 yr; approx. 55% men; ≤15 hr since the last FXaI dose) Andexanet (263 patients) or usual care (267 patients; 85.5% received PCC preparations)	Primary: hemostatic efficacy on the ANNEXA-A scale Secondary: 30-day mortality, TEE	Hemostatic efficacy: andexanet, 67.0%; usual care, 53.1% (adj. difference, 13.4 percentage points; 95% CI, 4.6–22.2; P=0.003) 30-Day mortality: andexanet, 27.8%; usual care, 25.5% (P=0.51) 30-Day TEE: andexanet, 10.3%; usual care, 5.6% (P=0.048)
White et al., 2024[29]	Meta-analysis of 18 studies†	1725 patients with FXaI-associated major bleeding (mean age, 72 yr; 54% men) Andexanet (645 patients) or PCC products at a dose of 25–50 IU/kg (1080 patients)	Effective hemostasis (study-defined scales, mostly ISTH) TEE 30-Day mortality All studies considered to be at high risk of bias	Associated with andexanet: Higher effective hemostasis (OR, 1.36; 95% CI, 1.01–1.84) Lower 30-day mortality (OR, 0.53; 95% CI, 0.37–0.76) Similar TEE

Dobesh et al., 2023[30]	Retrospective	4395 patients (57% men; mean age, 66 yr) with major bleeding with rivaroxaban or apixaban (1328 ICH, 2567 gastrointestinal bleeding, 500 bleeding in critical compartment or other type) Andexanet (2122 patients) or 4F-PCC (2273)	Effective hemostasis In-hospital stay In-hospital mortality Rate of DOAC restart	Effective hemostasis: andexanet, 73.8%; 4F-PCC, 58.8% (P=0.05) In-hospital mortality: andexanet, 6.0%; 4F-PCC, 10.6% (OR, 0.50; 95% CI, 0.39–0.65) Similar in-hospital stay duration and rate of DOAC restart
Chaudhary et al., 2022[31]	Meta-analysis of 36 studies	1832 patients with ICH (57% men; mean age, 74 yr) while taking DOACs (1123 dabigatran, 180 apixaban, 110 rivaroxaban) 4F-PCC (967 patients), andexanet (525), or idarucizumab (340)	Primary: anticoagulation reversal (mostly ISTH criteria) Secondary: all-cause mortality, TEE	Anticoagulation reversal: PCC, 77%; andexanet, 75%; idarucizumab, 82% All-cause mortality: PCC, 26%; andexanet, 24%; idarucizumab, 11% TEE: PCC, 8%; andexanet, 14%; idarucizumab, 5% 4F-PCC vs. andexanet: no significant difference in anticoagulation reversal, mortality, or TEE
Costa et al., 2022[32]	Observational (propensity-score–weighted analysis)	202 patients with ICH while taking rivaroxaban or apixaban Andexanet (107 patients; 96.6% received low dose) or 4F-PCC (95 patients; 79.3% received 25 U/kg)	Hemostatic effectiveness and 30-day mortality	Hemostatic effectiveness: andexanet, 85.8%; 4F-PCC, 68.1% (OR, 2.73; 95% CI, 1.16–6.42) 30-Day mortality: andexanet, 7.9%; 4F-PCC, 19.6% (OR, 0.36; 95% CI, 0.13–0.98); Similar hematoma growth
Gómez-Outes et al., 2021[33]	Meta-analysis of 60 studies (2 RCTs)	4735 patients (55% men; mean age, 70 yr) with major bleeding (55% ICH) while taking DOACs (dabigatran, 1111 patients; FXaI, 2688 patients) 4F-PCC (25–50 IU/kg) (2688 patients), idarucizumab (1111), or andexanet (936)	Overall mortality Effective hemostasis (ANNEXA-4, ISTH, or Sarode scale) TEE	Differences in death rates and effective hemostasis not significant across reversal agents TEE: andexanet, 10.7%; 4F-PCC, 4.3%; idarucizumab, 3.8% (4F-PCC and idarucizumab, P=0.03 vs. andexanet) Risk of death significantly associated with failure to achieve effective hemostasis (RR, 3.63; 95% CI, 2.56 to 5.16; I^2 = 0%)
Nederpelt et al., 2021[34]	Meta-analysis of 21 studies	1726 patients (53% men; mean age, 70 yr) with FXaI-related bleeding Andexanet (438 patients) or PCC preparations (1278)	Hemostatic effectiveness (Sarode or ISTH scales) at 12 hr and 24 hr TEE In-hospital mortality	Similar hemostatic effectiveness At 12 hr — andexanet, 82%; PCC, 88% At 24 hr — andexanet, 71%; PCC, 76% 30-Day TEE: andexanet 10.7%, PCC 3.1% In-hospital mortality: andexanet 23.3%, PCC 15.8%
Jaspers et al., 2021[35]	Meta-analysis of 21 studies	1428 patients treated with PCC and 396 with andexanet Separate analyses and indirect comparison	Hemostatic effectiveness (ANNEXA-4 criteria) TEE In-hospital mortality	Hemostatic effectiveness: PCC, 85% (95% CI, 80–90); andexanet, 82% (95% CI, 0.78–0.87) TEE: PCC, 3% (95% CI, 0.02–0.04); andexanet, 11% (95% CI. 0.04–0.18)
Connolly et al., 2019[23]	Open-label, single-group (ANNEXA-A)	352 patients (66% men; mean age, 77 yr) with major uncontrolled bleeding (64% with ICH) while taking apixaban (194 patients), rivaroxaban (128), enoxaparin (20), or edoxaban (10) Andexanet	Primary: percent change in anti–FXa activity, hemostatic efficacy at 12 hr Secondary: 30-day TEE and mortality	92% reduction in anti-FXa activity 82% excellent or good hemostasis 14% 30-day mortality 10% TEE

* Studies are listed in order from the most recent to the oldest. CI denotes confidence interval, 4F-PCC four-factor prothrombin complex concentrate, FFP fresh frozen plasma, ICH intracranial hemorrhage, ICU intensive care unit, ISTH International Society of Thrombosis and Hemostasis, OR odds ratio, RCT randomized, controlled trial, RR relative risk, and TEE thromboembolic events.

† All studies included in the meta-analysis were considered to be at high risk for bias.

A Decision Algorithms for Reversal of Oral Anticoagulants in Patients Undergoing Surgery or Major Invasive Procedures



B Reversal Strategies for Patients Presenting with Major Bleeding while Receiving an Oral Anticoagulant

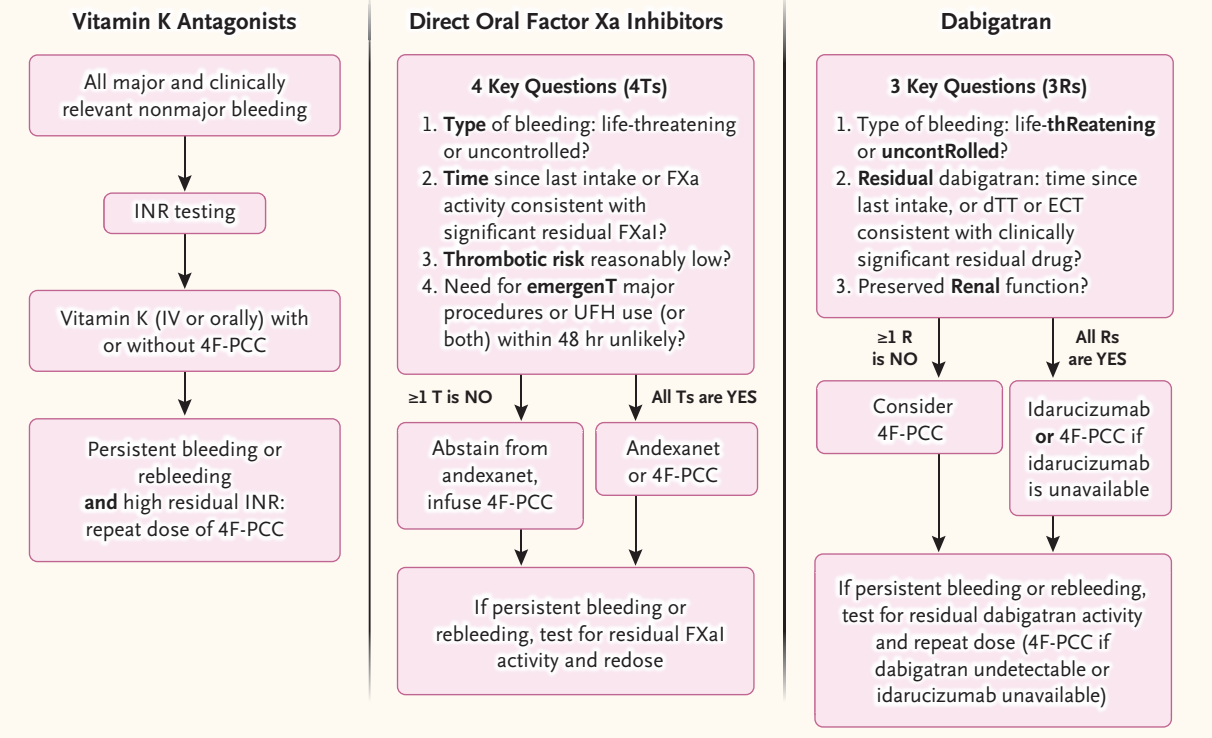


Figure 2 (facing page). Suggested Reversal Strategies of Oral Anticoagulant Use for Major Bleeding and before Emergency Surgery.

As shown in Panel A, reversal management depends on the urgency of surgery or the invasive procedure. Reversal management includes administration of oral or intravenous (IV) vitamin K with or without 4F-PCC, depending on the timing of the procedure (emergency or urgent), baseline international normalized ratio (INR) value, and presence (or absence) of active bleeding. For patients receiving direct oral anticoagulants (DOACs), the decision also depends on time to surgery. Decision making is informed by DOAC type, time since last dose, half-life, presence (or absence) of active bleeding, and renal function tests to estimate residual drug activity. Laboratory assays (if available) can inform reversal before (and after, in the case of dabigatran) infusion of antidotes. Surgery is considered to be safe in selected patients who are not actively bleeding and in whom DOAC levels are less than 30 ng per milliliter or less than 50 ng per milliliter, depending on the type of surgery. Panel B shows reversal strategies for patients presenting with major bleeding while receiving an oral anticoagulant. The reversal strategy of vitamin K antagonists includes vitamin K given intravenously or orally, combined with 4F-PCC and INR testing. Management of anticoagulant reversal of direct oral FXaIs is based on four key factors (shown as the 4Ts): type of bleeding, timing of the last dose, thrombotic risk, and need for invasive procedures in the next 48 hours that would result in the administration of UFH. These factors may facilitate the use of specific (e.g., andexanet alfa) or nonspecific (e.g., 4F-PCC) antidotes. The reversal of dabigatran is informed by three clinical variables (shown as the 3Rs) — the type of bleeding, time of the last dose of dabigatran, and preserved renal function. Andexanet is no longer marketed in the United States as of December 22, 2025,[38] and it is not approved for edoxaban-related major uncontrolled and life-threatening bleeding. Andexanet interferes with routine anti-Xa assays.

93.4% of the patients in group B. Delayed rebound of dabigatran in plasma (to levels of ≥20 ng per milliliter) occurred in approximately 20% of the patients at 24 hours, an effect that probably indicates that dabigatran reenters the peripheral circulation from the extravascular compartment, which would be consistent with its broader volume of distribution relative to that of idarucizumab (Table 1); it also indicates saturation of the circulating antidote. Bleeding persisted or recurred in 1.9% (10 patients); 3 patients received a second dose. Thrombotic events occurred in 4.8% (24 patients) at 30 days and in 6.8% (34 patients) at 90 days. Thirty-day mortality was similar in the two groups (group A, 13.5%; group B, 12.6%). Anti-idarucizumab antibodies, detected in 5.6% of the patients, remain of unknown clinical relevance. These findings have been corroborated by meta-analyses, pharmacovigilance, and real-world studies (Table 2).

Limitations of the RE-VERSE AD study include the lack of a comparator (e.g., four-factor prothrombin complex concentrate), small sample size, and reliance on surrogate laboratory primary end points without clinical validation. Of note, some participants received idarucizumab more than 96 hours after the last dabigatran dose. Moreover, approximately 20% of participants had a creatinine clearance of less than 30 ml per minute — a level that, according to the EMA, contraindicates dabigatran. This factor may have contributed to drug accumulation, as suggested by the high baseline dabigatran concentrations and rebound fraction (50%) observed in those participants.[52] A recent meta-analysis showed that 2.8% of patients received idarucizumab inappropriately, and 3% had undetectable dabigatran at baseline.[53] Measuring residual unbound dabigatran on the basis of diluted thrombin time, ECT, or even standard thrombin time may guide appropriate use of idarucizumab before and after infusion if bleeding persists or relapses (Fig. 2), with the concentration ranges during treatment in phase 3 trials used as reference.[54-56]

Idarucizumab is a rapid, complete, dabigatran-specific antidote without apparent intrinsic thrombogenicity. However, close clinical follow-up for rebleeding and laboratory monitoring to test for anticoagulant rebound is necessary, especially in renal impairment.

VITAMIN K ANTAGONISTS

Vitamin K antagonists inhibit the vitamin K–dependent γ-carboxylation of hepatic factors VII, IX, X, and II. This action impairs the activation and hemostatic function of the factors, as reflected by the prolongation of the prothrombin time, expressed in the international normalized ratio (INR). Vitamin K1 specifically antagonizes binding of vitamin K antagonists to vitamin K epoxide reductase complex subunit 1 (Fig. 1 and Table 1).[57] In case of major or life-threatening bleeding associated with vitamin K antagonists, intravenous administration of vitamin K1 offers a faster onset of action than the oral route (see Table S4 and Section 3.1 in the Supplementary Appendix for details). In less-urgent situations,

oral administration is preferable owing to the possibility of adverse reactions associated with intravenous infusion, either alone or combined with four-factor prothrombin complex concentrate, with the dose dependent on the INR value; presence, site, and severity of bleeding; or need for emergency surgery or invasive procedures (Fig. 2; also see the Supplementary Appendix).

NONSPECIFIC ANTIDOTES

PROTHROMBIN COMPLEX CONCENTRATES AND ORAL COAGULANTS

Plasma-derived three-factor and four-factor prothrombin complex concentrates contain concentrated vitamin K–dependent clotting factors (Fig. 1 and Table 1). Only four-factor prothrombin complex concentrates are approved for reversal of vitamin K antagonists (Table S5). Meta-analyses, mostly of observational studies, consistently show that four-factor preparations lead to target INR (≤1.3 or ≤1.5) approximately 3.5 times faster than three-factor formulations,[58,59] a result that reflects the presence of factor VII in the four-factor preparation, which replenishes all four vitamin K–dependent factors. Some four-factor prothrombin complex concentrates contain amounts of unfractionated heparin that are well below the therapeutic doses that are not known to impair hemostasis; however, safety concerns include heparin-induced thrombocytopenia and ongoing disseminated intravascular coagulation (Table 1).

Prothrombin Complex Concentrate for Vitamin K Antagonists

As compared with fresh-frozen plasma, four-factor prothrombin complex concentrates are associated with faster INR correction, superior hemostatic effectiveness, less need for transfusion, fewer adverse events, less hematoma expansion, shorter time to surgery,[60-62] and possibly lower all-cause mortality (Table S6).[60] The incidence of thromboembolic events appears to be similar between the two approaches.[60,62] Pharmacoeconomic simulations also favor prothrombin complex concentrate.[61]

Although three- and four-factor prothrombin complex concentrates appear to be similar in terms of the incidence of thromboembolic complications (four-factor formulation, 5.7%; three-factor formulation, 4.2%)[59] and with regard to in-hospital mortality,[58,59] the quality and heterogeneity of studies limit the reliability of these safety data. The faster reversal onset and INR correction (crucial in intracranial hemorrhage[63] and emergency surgery[64]), widespread availability, and broader factor profile are among the features that make four-factor prothrombin complex concentrates the preferred option. Combining the three-factor formulation with fresh-frozen plasma is unlikely to increase the factor VII concentrations substantially and would expose patients to the risks associated with fresh-frozen plasma. The coadministration of three-factor prothrombin complex concentrate with recombinant factor VIIa to mimic the four-factor formulation should be avoided owing to a thrombotic risk nearly four times that associated with four-factor prothrombin complex concentrate.[65]

Results of indirect comparison[66] and one noninferiority trial[67] suggest similar efficacy and safety across different preparations of four-factor prothrombin complex concentrate. Approved doses of four-factor prothrombin complex concentrate for reversing vitamin K antagonists are based on body weight (factor IX at a dose of 25 to 50 IU per kilogram of body weight) and INR (Table 1). This formula may lead to overdose in patients with severe obesity, because blood volume does not scale linearly with weight, which elicits safety concerns[68,69]; thus, appropriate doses remain undefined.

Fixed-dose four-factor prothrombin complex concentrate regimens, typically at doses between 750 and 3000 IU (depending on the site of bleeding), have been studied as an alternative to standard adjusted doses to simplify administration, reduce delays, and improve efficacy, safety, and cost-effectiveness (Table 3). A meta-analysis of observational studies encompassing a total of 2055 patients who had been treated with vitamin K antagonists reviewed standard-dose regimens as compared with fixed-dose regimens. Despite differences in fixed-dose amounts, INR targets, reversal indications, hemostatic effectiveness criteria, and follow-up duration,[72] fixed-dose regimens were associated with significantly shorter delays, lower total doses, and lower cost than standard-dose regimens. Achievement of a target INR less than 2, in-hospital mortality, and incidence of thrombosis were similar between fixed-dose and standard-dose regimens. Repeated doses were more frequent, and fewer patients had INR within the target range of less than 1.6

(Table 3). However, when fixed doses delivered at least 20 IU per kilogram or at least 2000 IU, the two regimens were similar with regard to all INR targets and outcomes. In the PROPER-3 (Prothrombin Complex Concentrate Prospective Evaluation and Rationalization, Number 3) randomized noninferiority trial, a fixed dose of 1000 IU led to a significant reduction in door-to-needle time, with INR correction similar to that with a standard dose.[75] However, owing to early termination for poor enrollment, the trial was underpowered. Further trials are needed to refine fixed-dose strategies across various scenarios of bleeding events and emergency interventions.

A pharmacovigilance analysis conducted from 1996 to 2022 included both approved (reversal of vitamin K antagonists) and off-label (reversal of DOACs) uses of prothrombin complex concentrate.[62] Overall, 614 adverse events and 233 thromboembolic complications were reported in the trial over a total of more than 2 million standard infusions (approximately 2500 IU each) delivered in the same time interval. Thromboembolic complications were similarly distributed in the on-label–use and off-label–use groups.[62] An analysis of retrospective studies that were conducted during the same time interval showed a wide range of incidence of thromboembolic events when prothrombin complex concentrates were used for reversal of vitamin K antagonists (1.0 to 11.5%) and when they were used to reverse DOACs (2.1 to 11.4%).[62]

Although INR remains the standard assay after prothrombin complex concentrate infusion (Table 1 and Fig. 2), results are influenced by several variables (e.g., transfusion and infusion volume). Thrombin generation may more reliably measure coagulation recovery, but it is not routinely available yet and lacks clinical validation.[79,80]

Prothrombin Complex Concentrates for DOACs

Among patients who have been treated with DOACs, the off-label use of prothrombin complex concentrates, primarily four-factor formulations, is common when anticoagulant reversal is needed (e.g., for uncontrolled major bleeding, an emergency invasive procedure, or surgery); however, evidence is limited and appropriate dosing is undefined (Table 2). Administration of four-factor prothrombin complex concentrates in DOAC-related bleeding is independent of the pharmacodynamic features of the specific DOAC and aims to provide substrates for coagulation (Fig. 1). The effect of infusion of the four-factor formulation on hemostatic efficacy may be limited, because thrombin generation is partially, but not completely, restored.[80] No randomized trial has yet compared nonspecific four-factor prothrombin complex concentrates with specific antidotes across different clinical scenarios. The control group of the ANNEXA-I trial provided limited insights, because 85% of the patients in the standard-care group received heterogeneous treatments that included prothrombin complex concentrates predominantly along with activated prothrombin complex concentrates and recombinant factor VIIa with no standardized protocol, thereby limiting interpretability.[36]

Current data derive from low-quality, heterogeneous, small observational studies (Table 2). Typically, doses of four-factor prothrombin complex concentrate for patients who have been treated with DOACs range from 25 to 50 IU per kilogram, with some data supporting the highest dose for intracranial hemorrhage.[81] Definitions of hemostatic efficacy include laboratory measures and various clinical assessments, each with a different duration of follow-up.[82] Consequently, meta-analyses yield conflicting results: some show that prothrombin complex concentrate and andexanet are associated with similar mortality and hemostatic effectiveness,[31] whereas others favor one over the other (Table 2).[29,32] However, andexanet is consistently associated with a higher incidence of thromboembolic events and higher costs across different studies, despite heterogeneous thrombosis definitions, event rates, and follow-up times (Table 2).

Laboratory monitoring of DOAC reversal with prothrombin complex concentrate remains problematic. INR is unsuitable, and prothrombin time and aPTT do not linearly reflect on-treatment factor Xa inhibitor concentrations.[54] Anti–factor Xa activity assays quantify residual anti–factor Xa activity, but their use is not yet routine. The clinical relevance of thrombin generation and global coagulation (viscoelastic) assays remains investigational.[22,44]

Despite those limitations, four-factor prothrombin complex concentrate is widely available and is less expensive and possibly safer than andexanet, whereas its efficacy as compared with specific antidotes needs further study.[83] Thus, the four-factor preparation is commonly used for

Table 3. Fixed vs. Standard Doses of 4F-PCC for Reversal of VKA and DOAC.*

Study or Trial and Year	Design	Population and PCC Dose	End Points	Key Findings
Alwakeal et al., 2024[70]	Meta-analysis of 19 studies (3 RCTs)	323 patients in RCTs, 1912 in observational studies (approx. 55% men, age approx. 73 yr) 4F-PCC at fixed dose of 750–3000 IU, mean approx. 1500 IU (858 patients) or standard dose (1054 patients)	INR <1.5 In-hospital mortality TEEs Hemostatic effectiveness (ISTH criteria in 4 studies) Additional doses	Fixed vs. standard dose: INR <1.5: OR, 0.3; 95% CI, 0.1–0.8 Order-to-needle time, 39 vs. 72 min Total PCC dose, 22.1 vs. 27.7 IU/kg PCC-to-INR time, 147.4 vs. 192.5 min Higher clinical hemostasis: OR, 1.7; 95% CI, 1.0–2.8 Additional doses: OR, 8.6; 95% CI, 3.0–24.6 INR <1.5: OR, 0.3; 95% CI, 0.1–0.8 Mortality and TEE similar among the RCTs Subgroup analysis: improved effectiveness with fixed dose ≥2000 IU
Brett et al., 2024[71]	Retrospective, single-center study	173 patients with FXaI-related bleeding Fixed dose of 2000 IU or 5000 IU (72 patients) or standard dose of 50 IU/kg (101 patients)	Primary: time between drug order and administration Secondary: total PCC dose, postadministration procedures, hemostasis, 30-day mortality, length of hospitalization	Fixed vs. standard dose: Shorter administration time with fixed dose (4.5 min faster) Hemostasis similar for fixed and standard doses (79.2% and 71.3%) (RR, 1.11; 95% CI, 0.94–1.32) Similar incidence of postsurgery bleeding (fixed dose, 29.2%; standard dose, 36.7%) (RR, 0.80; 95% CI, 0.51–1.24) Similar mortality (fixed dose, 26.4%; standard dose, 35.6%) (RR, 0.73; 95% CI, 0.46–1.17)
Condeni et al., 2024[72]	Meta-analysis of 23 studies (2 RCTs)	2055 patients (63.5% men, median age 77 yr) Fixed dose of ≥1000 IU or standard dose Excluded studies that used <1000 IU and those that involved patients who had obesity	Target INR TEE Time to PCC Survival Cost	Fixed vs. standard dose: Similar percentages of patients had INR <2, TEE, and in-hospital mortality Percentage of patients with INR <1.6 was lower with fixed dose, unless dose was ≥2000 IU or >20 IU/kg Shorter administration time with fixed dose Suggested cutoff of 80 kg for an additional 500-IU fixed dose Cost savings, $581 to $1,657 per patient
Chiasakul et al., 2022[73]	Meta-analysis of 25 observational studies	1760 patients with FXaI-associated major bleeding received PCC Fixed dose of 1500–2000 IU, mean 2025 IU (228 patients), or standard dose of 20–25 IU/kg (1532 patients)	Primary: study-defined clinical hemostatic effectiveness Secondary: mortality, TEE, 4F-PCC use, in-hospital and ICU length of stay, time to 4F-PCC infusion	Fixed vs. standard dose: Similar hemostatic effectiveness (fixed dose, 74%; standard dose, 79%), mortality (fixed dose, 16%; standard dose, 21%), and TEE (fixed dose, 2.9%; standard dose, 4.1%) Longer hospitalization: fixed dose, 7.4 days; standard dose, 5.9 days (P<0.001) Lower mean initial 4F-PCC dose/kg: standard dose 38 IU/kg (95% CI, 32–44), fixed dose 27 IU/kg (95% CI, 26–28) (P<0.001)

Bajdas et al., 2022[74]	Retrospective	265 patients (approx. 60% men) with major, non-ICH bleeding or emergency procedures received 4F-PCC Fixed dose of 1500 IU (90 patients) or standard dose (175 patients)	Primary: hemostatic efficacy at 48 hr (ISTH criteria) Secondary: INR ≤1.5, in-hospital mortality, time to 4F-PCC, cost	Fixed vs. standard dose: Lower hemostatic efficacy (21.7% vs. 37.8%) (P<0.005) Shorter administration time Lower cost (mean reduction, $1,881/patient) Similar in-hospital mortality and INR ≤1.5
Abdoellakhan et al., 2021[75]	Randomized, multicenter, open-label, noninferiority trial (PROPER3)	199 patients with major non-ICH bleeding received 4F-PCC Fixed dose of 1000 IU or standard dose	Primary: noninferior ISTH hemostatic efficacy between 4 hr and 48 hr Secondary: INR at 1 hr and 24 hr, time to PCC, in-hospital TEE, 30-day all-cause mortality	Underpowered trial owing to early termination for low recruitment Shorter infusion time with fixed dose than standard (difference, 33 min) Similar INR after infusion, in-hospital TEE (1.2% fixed dose vs. 2.3% standard dose), and mortality (4.7% fixed dose vs. 8.1% standard dose)
Elsamadisi et al., 2021[76]	Retrospective	44 patients who had obesity (≥100 kg) received 4F-PCC Fixed dose of 2000 IU vs. standard dose	INR <2 (extracranial bleeding) or <1.5 (ICH) Additional doses Time to PCC 7-Day TEE Mortality Cost	Fixed vs. standard dose: Post-treatment INR: fixed dose, 1.6 (IQR, 1.5–1.9); standard dose, 1.3 (IQR, 1.2–1.5) (P<0.01) Percentage of patients with INR <2, frequency of repeated doses, incidence of TEE, and mortality similar in the two groups Lower costs with fixed dose (savings of $2,419–3,411 per patient)
Mohammadi et al., 2021[77]	Meta-analysis of 10 observational studies and 1 RCT	988 patients with ICH, extracranial hemorrhage, or emergency surgery Fixed dose (mean dose of 1360 IU, approx. 16 IU/kg) or standard dose (approx. 25 IU/kg)	Mortality TEE Target INR Need for a repeat dose Time elapsed for INR reversal Order-to-needle time Length of hospitalization	Fixed vs. standard dose: Lower mortality with fixed dose (RR, 0.65; 95% CI, 0.47–0.90) except for patients with ICH Order-to-needle time 68 min shorter with fixed dose More repeat doses but lower total dose Higher postinfusion INR values Fewer patients with INR <1.5 (RR, 0.87; 95% CI, 0.78–0.96) Similar incidence of TEE and hospitalization
Yohe et al., 2019[78]	Retrospective, single-center	114 patients with major bleeding (42% ICH, 54% men, mean age 75 yr) 4F-PCC at standard dose	Primary: characterize relationship between 4F-PCC and postinfusion INR Secondary: TEE, events ≤10 days after treatment, death from any cause in hospital	Weak linear relationship between 4F-PCC dose and postreversal INR (R^2 = 0.06) Each additional 500-IU dose of 4F-PCC dose (in FIX IU) was associated with INR decrease of 0.02 Body weight and baseline INR value not correlated with postreversal INR

* Studies are listed in order from the most recent to the oldest. IQR denotes interquartile range.

managing factor Xa inhibitor–associated major bleeding or for perioperative reversal, given the lack of an approved agent for factor Xa inhibitors (Fig. 2). In case of contraindications to prothrombin complex concentrate, alternatives include fresh-frozen plasma or recombinant factor VIIa.

Randomized, head-to-head trials comparing four-factor prothrombin complex concentrates and current or emerging specific antidotes, with suitable clinical end points and appropriate follow-up, are needed to establish appropriate dosing, efficacy, and safety in specific clinical settings involving patients who have received direct factor Xa inhibitors. Ongoing trials are comparing the efficacy and safety of different doses of four-factor preparations in factor Xa inhibitor–associated major bleeding[84] and for perioperative use.[85] Until robust data emerge, the use of four-factor prothrombin complex concentrate (when available) should be individualized on the basis of bleeding severity, site and urgency, thrombotic risk, and timing since the last DOAC dose.

Activated Prothrombin Complex Concentrate, Recombinant Factor VIIa, and DOACs

Plasma-derived activated prothrombin complex concentrate contains factor VIIa with other vitamin K–dependent factors (Fig. 1 and Table 1). It is used off-label to treat patients with life-threatening bleeding or who must undergo emergency procedures; it is considered to be a second-line agent owing to limited supporting data and is more often used for DOAC-associated bleeding than for bleeding associated with vitamin K antagonists.[86] Further details and rationale for use are provided in the Supplementary Appendix.

Recombinant factor VIIa binds tissue factor, activating factor X and factor IX and leading to thrombin burst and clot formation (Fig. 1 and Table 1). Off-label use of recombinant factor VIIa in patients with oral-anticoagulant–related bleeding should be avoided, given its high risk of arterial thrombosis, which is probably related to the very high supraphysiologic systemic factor VIIa levels associated with its preparation (see the Supplementary Appendix).[87]

Antidotes in Development

Antidotes that are in preclinical and early clinical development and hemoadsorption devices that are currently under investigation are described in the Supplementary Appendix. Two strategies that are being tested in trials involving humans are ciraparantag, a small-molecule antidote that broadly binds and neutralizes multiple agents, and VMX-C001, a modified factor Xa molecule that is not bound by — and bypasses — factor Xa inhibitors (Fig. 1 and Table 1). Further clinical development of ciraparantag is uncertain. Its potential to bind endogenous molecules and drugs may lower safety; it binds to anticoagulant molecules in vitro (EDTA and sodium citrate tubes) and thus impairs routine coagulation assays. VMX-C001 was granted fast-track designation by the FDA for a phase 3 study in the perioperative context with or without the use of unfractionated heparin.[88]

Conclusions

The use of an antidote for oral or parenteral anticoagulant reversal should be informed by the pharmacodynamic (Fig. 1) and pharmacokinetic factors of both the antidote and the anticoagulant (Table 1), approved indications, quality of evidence, patient-specific factors, local availability, and cost-effectiveness. Suggested algorithms are summarized in Figure 2.

For unfractionated heparin, protamine remains the standard, specific antidote, although appropriate dosing strategies (fixed dose vs. adjusted dose), monitoring, and rebound effects require further evidence. Antidotes to low-molecular-weight heparin, fondaparinux, and danaparoid remain unmet therapeutic needs.

In patients treated with vitamin K antagonists who have major bleeding or must undergo emergency procedures, four-factor prothrombin complex concentrate combined with vitamin K provides safer, faster, and possibly more hemostatically effective reversal than fresh-frozen plasma. Four-factor formulations are preferred over off-label use of three-factor prothrombin complex concentrate.

For DOAC-associated life-threatening or uncontrolled bleeding, idarucizumab is the specific, approved antidote for dabigatran. Andexanet is still under conditional approval by the EMA for rivaroxaban and apixaban reversal,[39] because in the ANNEXA-4 trial it was administered to only a few patients who had received edoxaban and low-molecular-weight heparin.[24,89] Substantial concerns remain regarding the efficacy of andexanet

weighed against its safety profile and cost-effectiveness; it was recently withdrawn from availability in the United States owing to safety concerns raised by the FDA.[38] Perioperative treatment remains a profound unmet therapeutic need. This need is reflected in some heterogeneity in the recommendations with regard to factor Xa inhibitor reversal issued by major scientific societies (Table S7). The importance of addressing unmet therapeutic needs related to factor Xa inhibitors is increased by the fact that direct factor Xa inhibitors are the most-used oral-anticoagulant class worldwide.[90] In practice, four-factor prothrombin complex concentrates are often used off-label for reversal despite low-quality evidence.

Ideally, each antidote should undergo a formal cost-effectiveness analysis. For reversal of vitamin K antagonists, four-factor prothrombin complex concentrates are more cost-effective than fresh-frozen plasma and possibly three-factor preparations. No cost-effectiveness analysis exists for idarucizumab. Before the ANNEXA-I trial, a study suggested andexanet as cost-effective for use in patients with intracranial hemorrhage, as compared with prothrombin complex concentrate, but this analysis is outdated.[91]

Central to decision making is balancing the urgency of bleeding control and the risk of clinical deterioration against the potential complications of the specific antidote, particularly thrombosis. To improve assessment of bleeding risk and instruct antidote choice, rapid assays that are available at any time for measuring clinically relevant DOAC concentrations and activity would be valuable both before and after antidote administration (Fig. 2). Idarucizumab carries a small risk of delayed dabigatran rebound, detectable by ECT or diluted thrombin time and partially detectable by aPTT. The clinically meaningful thresholds of those assays and the clinical effect of repeat doses of the antidote to prevent rebleeding remain to be defined. In advanced renal disease, dabigatran rebound can be greater and contribute to recurrent bleeding.[52] In contrast, data on andexanet indicated that an antidote with a half-life shorter than that of the target drug can generate an earlier rebound of anti–factor Xa activity, within a few hours after administration. Another clinical challenge is the fact that the effect of this antidote cannot be monitored with routine laboratory tests, leaving its therapeutic effect uncertain. Maximizing laboratory monitoring of anticoagulant activity and clarifying clinically relevant thresholds remain unmet needs. This knowledge may substantially improve patient treatment, supporting decisions regarding repeat treatment or alternative strategies when bleeding persists but the anticoagulant activity is no longer meaningful or detectable. Meanwhile, given laboratory limitations — especially for oral factor Xa inhibitors — clinical assessment of hemostatic efficacy remains essential, particularly with regard to intracranial hemorrhage, in which hematoma expansion is an imperfect surrogate for long-term disability or death in patients who have been treated with oral anticoagulants.[92]

The clinical interpretation of recent phase 3 trials of specific antidotes is limited by design weaknesses, namely the lack of comparators, reliance on biomarker-based primary end points with no previous clinical validation, small sample sizes, nonstandardized bleeding classifications, heterogeneous and nonvalidated efficacy criteria, and short follow-up times.[93] These limitations should instruct and improve the design of future trials of both established and emerging reversal agents. Emerging antidotes, such as ciraparantag and modified factor Xa decoys, are being developed to address current therapeutic gaps in safety and efficacy, thus widening the breadth of anticoagulant reversal.

However, the prevention of major bleeding by control of risk factors (e.g., hypertension, drug interactions, liver and kidney function, and gastrointestinal bleeding) and appropriate use of anticoagulant agents are priorities for reducing the need for antidotes. Periodic assessment — at least annually — of the appropriate doses of oral anticoagulants, adherence, risk factors, and coexisting conditions is essential, given the increasing number of older, frail, ill, and polymedicated persons worldwide. Recently developed predictive risk scores for DOACs may aid in this process.[94]

When anticoagulant reversal is needed, the right antidote must be delivered to the right patient in a timely, appropriate, safe, effective way, balancing the need for effective hemostasis and bleeding control against the risk of a life-threatening thrombosis and the burden of cost. Although the ideal antidote, like the ideal anticoagulant, remains largely elusive, the scientific and medical communities have the responsibility to build stronger evidence and refine tools to ad-

KEY POINTS

ANTIDOTES FOR ANTICOAGULATION REVERSAL

- Protamine remains the unfractionated heparin–specific antidote; however, a determination of appropriate dosing and monitoring requires further studies. No antidotes are approved for neutralizing low-molecular-weight heparins, fondaparinux, or danaparoid.
- In bleeding associated with vitamin K antagonists, four-factor prothrombin complex concentrates with vitamin K achieve faster correction of the international normalized ratio than three-factor formulations and fresh-frozen plasma, with better hemostasis and safety than fresh-frozen plasma. The efficacy and safety of fixed doses as compared with standard doses of four-factor prothrombin complex concentrates remain uncertain.
- Idarucizumab and andexanet alfa provide specific, rapid, nearly complete pharmacodynamic reversal of uncontrolled or life-threatening bleeding with dabigatran and factor Xa inhibitors, respectively. Andexanet elicits regulatory concerns owing to early thrombosis risk and is not approved for perioperative use, with a warning regarding cardiac surgery. Off-label use of four-factor prothrombin complex concentrates provides safe hemostatic support to the reversal of bleeding associated with factor Xa inhibitors. Head-to-head comparisons of four-factor prothrombin complex concentrates with each specific antidote are lacking.
- The priorities for future study include the development of safer antidotes; standardized, clinically validated laboratory assays; and enhanced understanding of rebound effects. Randomized studies with clinical end points and adequate follow-up are needed.

vance patient-centered, global anticoagulant and prohemostatic care.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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