

Chapter 13

Anticoagulation Reversal Guide and Reversal Agents



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Abbreviations

3F-PCC	Three-factor prothrombin complex concentrate
4F-PCC	Four-factor prothrombin complex concentrate
aPCC	Activated prothrombin complex concentrate
ASCO	American Society of Clinical Oncology
CAT	Cancer-associated thrombosis
CrCl	Creatinine clearance
CVC	Central venous catheter
DOACs	Direct oral anticoagulants
DVT	Deep vein thrombosis
FEIBA	Factor eight inhibitor bypassing activity
FFP	Fresh frozen plasma
INR	International normalized ratio
IU	International unit
LMWH	Low-molecular-weight heparin
NCCN	National Comprehensive Cancer Network
PCC	Prothrombin complex concentrate
PE	Pulmonary embolism
PTT	Partial thromboplastin time
rFVIIa	Recombinant activated factor VII

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S/D	Solvent and detergent
U	Unit
UFH	Unfractionated heparin
VH	Vapor heat
VTE	Venous thromboembolism
WFI	Water for injection

Introduction

Pharmaceutical anticoagulants disrupt the process of normal hemostasis directly by inhibiting clotting factor activity, indirectly by depleting vitamin K–dependent clotting factors, or by amplifying native anticoagulant pathways through anti-thrombin [1].

Coagulation Reversal Guide

In the context of active bleeding with or without over-dosage of the anticoagulant medications or when an urgent state of hemostasis is required due to an eminent surgery, anticoagulation reversal becomes a necessity. Figure 13.1 is a practical anticoagulation reversal guide.

Anticoagulant agent	Half-life	Reversal approach
Unfractionated heparin infusion [2].	60–90 minutes	<p><i>Non-urgent:</i> Holding infusion for 4–6 hours results in a near-complete reversal</p> <p><i>Emergent/urgent:</i> <i>Protamine sulfate</i> 1 mg/80–100 U UFH if within 15 minutes of UFH infusion 0.5 mg/80–100 U within 60 minutes or 0.25 mg/80–100 U within 2 hours Maximum 50 mg dose</p>
Enoxaparin [2]	~4–8 hours	<p><i>Non-urgent:</i> Time-dependent, ~24 hours</p> <p><i>Emergent/urgent:</i> PCC at 20 U/kg Partial reversal with protamine, but degree unclear If dosed ≤8 hours: 1 mg/1 mg enoxaparin If dosed >8 hours: 0.5 mg/1 mg enoxaparin</p> <p><i>Experimental:</i> Ciraparantag 300 mg IV</p>

Fig. 13.1 The different anticoagulant agents, their half-lives, and their reversal approach

Anticoagulant agent	Half-life	Reversal approach															
Nadroparin [3]	3.5 hours	<p><i>Non-urgent:</i> Time-dependent, ~24 hours</p> <p><i>Emergent/urgent:</i> The dose of protamine should be equal to the dose of nadroparin used, on a mg to mg basis. A second infusion of 0.5 mg protamine per 1 mg nadroparin may be administered if the aPTT measured 2–4 hours after the first infusion remains prolonged</p>															
Tinzaparin [4]	3–4 hours	<p><i>Non-urgent:</i> Time-dependent, ~24 hours</p> <p><i>Emergent/urgent:</i> Transfusion of FFP may be used 1 mg of protamine sulfate neutralizes the effect of 100 anti-Xa IU tinzaparin (effective in 3 hours)</p>															
Fondaparinux [2]	~17–21 hours	<p><i>Non-urgent:</i> Time-dependent, ~24 hours</p> <p><i>Emergent/urgent:</i> 4F-PCC at 20 U/kg Protamine has not been shown to be effective</p>															
Argatroban [5]	39–51 minutes	<p><i>Non-urgent:</i> Time-dependent: full reversal in ~4–6 hours</p> <p><i>Emergent/urgent:</i> No effective means of reversal has been established</p>															
Warfarin [2, 6]	40 hours	<p><i>Non-urgent:</i> Time: Hold for 5 d, INR normalization variable depending on age, dose, and drug/enzyme interactions If not bleeding and INR >10 Oral vitamin K (1–5 mg)</p> <p><i>Emergent/urgent:</i></p> <table border="1"> <tr> <td>Weight/INR</td> <td>1.6–1.9</td> <td>2.0–2.9</td> <td>3.0–5.0</td> <td>>5</td> </tr> <tr> <td><100 Kg</td> <td>500 U</td> <td>1000 U</td> <td>2000 U</td> <td>3000 U maximum</td> </tr> <tr> <td>>100 Kg</td> <td>1000 U</td> <td>1500 U</td> <td>2500 U</td> <td>3000 U maximum</td> </tr> </table> <p>3F-PCC could be used in conjunction with plasma or vitamin K Repeat INR 15 minutes after PCC infusion is completed</p> <p><i>INR and weight known</i> Vitamin K 10 mg in 50 mL NS IV STAT Administer PCC 2000 IU Repeat INR 15 minutes after PCC infusion is completed</p> <p><i>NB:</i> If 4F-PCC is not available, use plasma 10–15 mL/kg aPCC not effective</p>	Weight/INR	1.6–1.9	2.0–2.9	3.0–5.0	>5	<100 Kg	500 U	1000 U	2000 U	3000 U maximum	>100 Kg	1000 U	1500 U	2500 U	3000 U maximum
Weight/INR	1.6–1.9	2.0–2.9	3.0–5.0	>5													
<100 Kg	500 U	1000 U	2000 U	3000 U maximum													
>100 Kg	1000 U	1500 U	2500 U	3000 U maximum													

Fig. 13.1 (continued)

Anticoagulant agent	Half-life	Reversal approach
Dabigatran [7]	7–9 hours in young adults 12–14 hours in older adults [8]	<p><i>Non-urgent:</i> Time-dependent, ~24 hours</p> <p><i>Emergent/urgent:</i> Administer 5 g idarucizumab IV (typically provided as two separate vials, each containing 2.5 g/50 mL) If idarucizumab is not available, administer 4F-PCC or aPCC 50 units/kg IV Consider activated charcoal for known recent ingestion (within 2–4 hours)</p> <p>NB: Plasma not effective</p>
Rivaroxaban [7]	5–9 hours in young adults 11–13 hours in older adults [8]	<p><i>Non-urgent:</i> Time-dependent, ~24 hours</p> <p><i>Emergent/urgent:</i> <i>Last dose >10 mg or unknown <8 hours ago or unknown:</i> High dose of andexanet alfa Initial IV bolus 800 mg at a target rate of 30 mg/min Follow-on IV infusion: 8 mg/min for up to 120 minutes</p> <p><i>Last dose <10 mg or <8 hours:</i> Low dose of andexanet alfa Initial IV bolus: 400 mg at a target rate of 30 mg/min Follow-on IV infusion: 4 mg/min for up to 120 minutes If andexanet alfa is not available, administer 4F-PCC 50 units/kg IV or aPCC 50 units/kg IV Consider activated charcoal for known recent ingestion (within 2–4 hours)</p> <p>NB: Idarucizumab, plasma not effective</p> <p><i>Experimental:</i> Ciraparantag 100–300 mg IV</p>
Apixaban [2, 7]	~12 hours	<p><i>Non-urgent:</i> Time-dependent, ~24 hours</p> <p><i>Emergent/urgent:</i> <i>Last dose >5 mg or unknown <8 hours ago or unknown:</i> High dose of andexanet alfa Initial IV bolus 800 mg at a target rate of 30 mg/min Follow-on IV infusion: 8 mg/min for up to 120 minutes</p> <p><i>Last dose <5 mg or <8 hours:</i> Low dose of andexanet alfa Initial IV bolus: 400 mg at a target rate of 30 mg/min Follow-on IV infusion: 4 mg/min for up to 120 minutes If andexanet alfa is not available, administer 4F-PCC 50 units/kg IV or aPCC 50 units/kg IV Consider activated charcoal for known recent ingestion (within 2–4 hours)</p> <p>NB: Idarucizumab, plasma not effective</p> <p><i>Experimental:</i> Ciraparantag 100–300 mg IV</p>

Fig. 13.1 (continued)

Anticoagulant agent	Half-life	Reversal approach
Edoxaban [2, 7]	1–3 hours	<p><i>Non-urgent:</i> Time-dependent, ~24 hours</p> <p><i>Emergent/urgent:</i> Administer 4F-PCC 25–50 units/kg IV Second line if 4F-PCC is not available, administer aPCC 50 units/kg IV For all patients, consider activated charcoal for known recent ingestion (within 2–4 hours)</p> <p>NB: Idarucizumab, plasma, not indicated</p> <p><i>Experimental:</i> Ciraparantag 100–300 mg IV</p>
Multiple agents LMWH, anti-Xa, anti-IIa	Variable	<p><i>Experimental:</i> Ciraparantag 100–300 mg IV</p>

Fig. 13.1 (continued)

Coagulation Reversal Agents

Vitamin K

(a) Mechanism of Action

Vitamin K administration repletes the warfarin-induced depletion of functional vitamin K and promotes the synthesis of clotting factors VII, IX, X, and II.

(b) Indication

Vitamin K administration is suitable for reversal of vitamin K antagonists, warfarin, and Coumadin.

(c) Dose and Administration

For minor bleeds with any elevation of the INR: vitamin K 2.5–5 mg orally; monitor INR; if INR remains elevated at 24 hours, repeat dose of vitamin K may be given [9].

For major bleeds: If INR 1.6–5.0, vitamin K 5 mg (in 50 mL normal saline) IV; if INR > 5.0, vitamin K 10 mg (in 50 mL, normal saline).

In the setting of severe bleeding, administer 4-factor prothrombin complex concentrate and vitamin K 5–10 mg IV [10].

(d) Warnings/Precautions

Severe allergic reactions, including anaphylactic reactions, can occur as a result of intravenous or intramuscular administration of vitamin K.

In severe bleeding, it may be combined with PCC or plasma.

Protamine Sulfate

Since its discovery and FDA approval, protamine sulfate has occupied an important therapeutic niche as perhaps the only viable option for reversing the anticoagulant effect of heparin use for over 77 years [11, 12].

(a) Mechanism of Action

When administered alone, protamine has an anticoagulant effect. However, when it is given in the presence of heparin (which is strongly acidic), a stable salt is formed and the anticoagulant activity of both drugs is lost. Neutralization of heparin occurs within 5 minutes after intravenous administration of an appropriate dose of protamine sulfate.

It is supplied as a solution containing 10 mg of protamine sulfate/ml (50 mg in 5 ml).

(b) Indication

Protamine sulfate can be used to reverse the anticoagulant effect of unfractionated heparin and for incomplete reversal of low-molecular-weight heparin anticoagulant effect.

(c) Adult Dose and Administration

- UFH reversal: protamine sulfate 1–1.5 mg IV per 100 units of heparin
 - Maximum dose: 50 mg/dose; maximum rate: 5 mg/min.
 - Dose based on the amount of heparin remaining in the body; for intravenous heparin infusion, calculate heparin dose based on infusion rate for prior 2 hours.
 - Dose may be adjusted based on time from heparin admin; if 0–30 minutes, give 1–1.5 mg/100 units; if 30–60 minutes, give 0.5–0.75 mg/100 units; if >2 hours, give 0.25–0.375 mg/100 units.
- LMWH reversal
 - Less than 8 hours since the last LMWH dose:
 - Protamine sulfate 1 mg IV per 100 anti-Xa units LMWH; max: 50 mg/dose; rate: 5 mg/min; info: may give additional 0.5 mg IV per 100 anti-Xa units LMWH if bleeding continues; protamine incompletely neutralizes LMWH effects; 1 mg enoxaparin = 100 anti-Xa units
 - Greater than 8 hours since last LMWH dose:
 - Protamine sulfate 0.5 mg IV per 100 anti-Xa units LMWH; max: 50 mg/dose; rate: 5 mg/min; info: may repeat dose x1 if bleeding continues; protamine incompletely neutralizes LMWH effects; 1 mg enoxaparin = 100 anti-Xa units

(d) Warnings and Precautions

Protamine sulfate can cause rare but severe adverse effects that include systemic hypotension, pulmonary hypertension, liver and kidney tissue damage, and anaphylactic reaction [13].

Fresh Frozen Plasma (FFP)

For the reversal of VKA action, if other products are not available, FFP could be administered at a dose of 10–15 ml/kg.

Three-Factor (3F-PCC)/Four-Factor Prothrombin Complex (4F-PCC) and Activated Prothrombin Complex Concentrate (aPCC)

Three- and 4-factor prothrombin complexes are plasma-derived products used to revert the action of warfarin and stop bleeding. They have the potential for inducing allergic reactions. Being plasma-derived and virally inactivated, their potential for transmission of blood-borne infections is minimal. They are, however, potentially thrombogenic.

Three-Factor Prothrombin Complex Concentrates (3F-PCC) (Bebulin VH [14, 15], Profilnine SD [16])

Three-factor prothrombin complex concentrates (Bebulin, Profilnine) have historically been used to control and/or prevent bleeding associated with hemophilia B.

3-F PCC contains plasma-derived factors II, IX, and X, as well as low/nontherapeutic levels of factor VII. For this reason, four-factor PCC is typically preferred for reversal of warfarin effect.

Figure 13.2 illustrates the difference between Bebulin/Immunine VH and Profilnine SD.

(a) Indication

Three-factor prothrombin complex concentrates can be considered for off-label use in the reversal of severe/life-threatening bleeding associated with warfarin. Due to low factor VII content, concomitant administration of fresh frozen plasma or factor VII could be considered.

Name	Bebulin VH/Immunine VH	Profilnine SD
Source	Plasmatic	Plasmatic
Viral inactivation	Vapour heat, Tween 80	Solvent/detergent
Dose based on	Units of factor IX activity	Units of factor IX activity
Prothrombin content	24–38 IU/ml	150 IU/100 fIX IU
Factor VII	<5 IU/ml	<35 IU/100 fIX IU
Factor IX	24–38 IU/ml	100 IU
Factor X	24–38 IU/ml	100 IU/100 fIX IU
Heparin	0.15 IU/1 fIX IU	None

Fig. 13.2 Differences between commercial preparations of 3F-PCC

(b) Dose and Administration

An average dose of 25–50 IU/kg is usually administered.

Co-administer vitamin K (phytonadione) 5–10 mg by slow IV infusion [10, 17, 18]; vitamin K may be repeated every 12 hours if INR is persistently elevated.

(c) Warnings and Precautions

Due to viral inactivation, the potential for transmission of blood-borne infections is minimal.

Three-factor prothrombin complex concentrations have thrombogenic potential. Patients should be monitored for thrombotic sequelae following administration of these concentrates.

Allergic reactions have been reported.

Four-Factor Prothrombin Complex Concentrate (4F-PCC)

(a) Mechanism of Action

Four-factor PCC contains coagulation factors II, VII, IX, and X together with the endogenous inhibitor proteins S and C and is indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA with bleeding or in the urgent perioperative prophylaxis context to revert the action of VKA. Doses are usually individualized based on severity of disorder, extent and location of bleeding, and clinical status of patient. -Four-factor PCC may result in superior efficacy compared to the use of 3F-PCC [18, 19].

Three preparations are available in North America including Kcentra [20]/ Beriplex [21] and Octaplex [22]. Figure 13.3 illustrates the differences between the available formulations.

(b) Indications

Four-factor PCC is indicated for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonists in patients who are bleeding or who require invasive procedures on an urgent basis. In this setting, 4F-PCC may result in superior efficacy compared to the use of 3F-PCC [19].

Brand names	Octaplex	Kcentra/Beriplex
Formulation	Freeze-dried	Freeze-dried
Viral inactivation	Solvent and detergent treated	Chromatographic, heat-treated, nano-filtration
Diluent	20 mL/40 mL of WFI	20 mL/40 mL of WFI
Vial size	500 IU	20–31 Factor IX units/mL after reconstitution. The actual potency for 500 unit vial ranges from 400 to 620 units/vial. The actual potency for 1000 unit vial ranges from 800 to 1240 units/vial
Factor II	280–760 IU	380–800 IU
Factor VII	180–480 IU	200–500 IU
Factor IX	280–760 IU	400–620 800–1240
Factor X	360–600 IU	500–1020 IU
Protein C	140–620 IU	420–820 IU
Protein S	140–640 IU	240–680 IU
Others	Heparin	Heparin: 8–40 IU AT 4–30 IU

Fig. 13.3 Differences between the available 4F-PCC formulations [23]

Empiric dosage				
Pretreatment INR	INR <3.0	INR 3.0–5.0	INR >5.0	
Dose of prothrombin complex	40 mL (1000 IU)	80 mL (2000 IU)	120 mL (3000 IU)	
Weight-adjusted dosage				
Pretreatment INR	INR 2–2.5	INR 2.5–3	INR 3–3.5	INR >3.5
Dose IU/Kg	22.5–32.5 IU/Kg	32.5–40 IU/Kg	40–47.5 IU/Kg	>47.5 IU/Kg maximum dose: 3000 IU (120mL)

For Kcentra® as per FDA approval:

Pretreatment INR	2-<4	4–6	>6
Dose	25 units of F IX/ Kg body weight	35 units of F IX/ Kg body weight	50 units of F IX/ Kg body weight
Maximum dose** (Units of factor IX)/kg body weight	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

Fig. 13.4 Dose of Octaplex/Beriplex as per Canadian Blood Services recommendation and dose of Kcentra as per FDA approval

(c) Dose and Administration

Dosing of prothrombin complex concentrate should be based on the INR as per Fig. 13.4 with empiric treatment based on INR or a weight-adjusted dosage.

Notes regarding administration:

- 4F-PCC must be administered intravenously; it may be administered by direct IV push, syringe pump, or minibag
- Maximal infusion rates, as per the manufacturer's recommendations:
 - Octaplex: 3 mL/min
 - Beriplex P/N: 8 mL/min
- Reconstituted Kcentra is administered at a rate of 0.12 mL/kg/min (~3 units/kg/min) up to a maximum rate of 8.4 mL/min (~210 units/min) [20]

A 4F-PCC reversal strategy is efficacious in INR reversal and provides lower thromboembolic risk as compared to 3F PCC with rFVIIa [24].

Activated Prothrombin Complex Concentrate (aPCC)

(a) Mechanism of Action

Activated prothrombin complex concentrate (factor eight inhibitor bypassing activity [FEIBA]/Autoplex) contains plasma-derived precursor and activated forms of coagulation factors II, IX, X, and VII [25].

(b) Indications

FEIBA is approved by the FDA to control spontaneous bleeding episodes and to prevent bleeding with surgical interventions in hemophilia A patients with factor VIII inhibitors.

Recent data have also suggested that FEIBA may be used off-label as an anticoagulant reversal agent [26].

(c) Dose and Administration

Dosage and duration of treatment depend on the location and extent of bleeding and clinical condition of the patient.

Determination of the optimal dosing of aPCC for the purpose of anticoagulant reversal has primarily been determined in the setting of intracranial hemorrhage (ICH) associated with non-vitamin K antagonist anticoagulants administered within three to five drug half-lives (off-label use) [27]:

- Oral direct factor Xa inhibitor-mediated bleeding (apixaban, rivaroxaban, edoxaban; if andexanet alfa is not available): 50 units/kg
- Direct thrombin inhibitor-mediated bleeding (argatroban, dabigatran [if idarucizumab is not available], hirudin, rb-hirudin, bivalirudin, desirudin]): 50 units/kg
- Pentasaccharide-mediated (fondaparinux – full therapeutic dose only): 20 units/kg

aPCC seems to reverse the anticoagulant effect of Xa inhibitors more effectively than rFVIIa and 3F or 4F-PCC by evaluation with thromboelastometry [28].

(d) Warnings and Precautions

Activated prothrombin complex concentrate administration can lead to increased risk of thromboembolic events. Patients should be monitored for thrombotic sequelae following administration of aPCC.

Recombinant Activated Factor VII (rFVIIa)

Low-dose rFVIIa was initially tested with success as a rapid reversal modality for major bleeding events in the presence of warfarin and an elevated INR in a dose range of 11–25 mcg/kg (1.2 mg) in ICU patients [29]. It was also shown to reverse the anticoagulant effects of argatroban, bivalirudin, fondaparinux, enoxaparin, and heparin as assessed ex vivo by thromboelastography [30].

Due to its cost and its potential thrombotic properties and the availability of more suitable options, its use in the context of anticoagulation reversal is currently limited.

Idarucizumab (Praxbind) [31]

(a) Mechanism of Action

Idarucizumab is a humanized monoclonal antibody fragment that binds to dabigatran, thereby inhibiting the activity of dabigatran as an anticoagulant. Idarucizumab binds to dabigatran and its metabolites with very high affinity, approximately 300-fold more potent than the binding affinity of dabigatran for thrombin.

(b) Indication

Idarucizumab is indicated for adult patients treated with dabigatran when rapid specific reversal of the anticoagulant effect is required for life-threatening bleeding and/or emergent procedures.

(c) Dose and Administration

The recommended dose of idarucizumab is 5 grams (administered as two separate 2.5 g doses no more than 15 minutes apart) [32].

If a second emergency surgery/urgent procedure is required and patient has elevated coagulation parameters (aPTT), consider administration of an additional 5 g, although data to support this approach is limited.

In patients with dabigatran-associated intracranial hemorrhage, if refractory bleeding occurs after the initial idarucizumab dose, consider re-dosing and/or hemodialysis [26].

(d) Warnings and Precautions

Anaphylactic reactions and possible hypersensitivity adverse events including bronchospasm, rash, pyrexia, pruritus, and hyperventilation have been reported in clinical trials [31].

Andexanet Alfa (Andexxa) [33]

(a) Mechanism of Action

Andexanet alfa is a modified recombinant inactive form of human factor Xa developed for reversal of factor Xa inhibitors [33].

(b) Indication

Andexanet alfa is indicated in patients with acute major bleeding associated with the use of a factor Xa inhibitor [33]. Administration in this setting led to effective hemostasis occurring in approximately 80% of patients [34, 35].

(c) Dose and Administration

Dosing is based on the severity of bleeding and the dose of anti-Xa anticoagulant used. Two dosing approaches were suggested based on the timing and strength of the anticoagulant used (please refer to Fig. 13.1).

- Low dose: 400 mg IV bolus administered at a rate of ~30 mg/minute, followed 2 minutes later by 4 mg/minute IV infusion for up to 120 minutes
- High dose: 800 mg IV bolus administered at a rate of ~30 mg/minute, followed 2 minutes later by 8 mg/minute IV infusion for up to 120 minutes

(d) Warnings and Precautions

Arterial and venous thromboembolic events, ischemic events, and cardiac events, including sudden death, have occurred during treatment with andexanet alfa.

Ciraparantag (Aripazine)

Ciraparantag (aripazine) is a drug under investigation, which consists of two L-arginine units connected with a piperazine containing linker chain, as an antidote for a number of anticoagulant drugs, including factor Xa inhibitors (rivaroxaban, apixaban and edoxaban), dabigatran, LMWH, and UH by binding directly to anticoagulants via hydrogen bonds from or guanidine and amide parts of the molecule [36, 37]. At a dose of 300 mg, it reverses the whole blood clotting time induced by enoxaparin in a dose-related manner and produces no procoagulant signal or deleterious adverse events [38].

In a double-blind controlled fashion, escalating, single IV doses (100–300 mg) of ciraparantag were administered alone and following a 60 mg oral dose of edoxaban to healthy volunteers. Fibrin diameter within clots was restored to normal 30 minutes after a single dose of 100–300 mg ciraparantag as determined by scanning electron microscopy and change in fibrin diameter quantified by automated image analysis [39, 40].

Conclusion

When immediate hemostasis is needed in patients receiving therapeutic anticoagulation, reversal of anticoagulation may be achieved with multiple modalities. Protamine sulfate helps reverting the action of heparin and partly reverts the action of LMWHs, whereas vitamin K and plasma-derived products are used to counteract the action of warfarin. Recombinant FVIIa emerged with a limited role in reversal. Idarucizumab binds dabigatran reversing its action, whereas andexanet alfa, a modified recombinant inactive form of human factor Xa, was developed for the reversal of factor Xa inhibitors. A complete palette of reversal agents is therefore now available.

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