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REVIEW ARTICLE

Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage

A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine

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Abstract

Background The use of antithrombotic agents, including anticoagulants, antiplatelet agents, and thrombolytics has increased over the last decade and is expected to continue to rise. Although antithrombotic-associated intracranial hemorrhage can be devastating, rapid reversal of coagulopathy may help limit hematoma expansion and improve outcomes.

Methods The Neurocritical Care Society, in conjunction with the Society of Critical Care Medicine, organized an international, multi-institutional committee with expertise in neurocritical care, neurology, neurosurgery, stroke, hematology, hemato-pathology, emergency medicine, pharmacy, nursing, and guideline development to evaluate the literature and develop an evidence-based practice guideline. Formalized literature searches were conducted, and studies meeting the criteria established by the committee were evaluated.

Results Utilizing the GRADE methodology, the committee developed recommendations for reversal of vitamin K antagonists, direct factor Xa antagonists, direct thrombin inhibitors, unfractionated heparin, low-molecular weight heparin, heparinoids, pentasaccharides, thrombolytics, and antiplatelet agents in the setting of intracranial hemorrhage.

Conclusions This guideline provides timely, evidence-based reversal strategies to assist practitioners in the care of

The Neurocritical Care Society and Society of Critical Care Medicine affirm the value of this guideline as an educational tool for clinicians.

Jennifer A. Frontera and John J. Lewin III are guideline co-chairs.

Jennifer A. Frontera and John J. Lewin III have contributed equally to the manuscript.

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patients with antithrombotic-associated intracranial hemorrhage.

Keywords Anticoagulant · Antiplatelet · Antithrombotic · Intracranial hemorrhage · Intracerebral hemorrhage · Intraparenchymal hemorrhage · ICH · Subarachnoid hemorrhage · SAH · Subdural hematoma · SDH · Reversal · Antidote · Vitamin K antagonist · VKA · Warfarin · Coumadin · Direct thrombin inhibitor · DTI · Dabigatran · Factor Xa inhibitor · Apixaban · Rivaroxaban · Edoxaban · Low-molecular weight heparin · Heparin · Heparinoid · Pentasaccharide · Fondaparinux · TPA · rtPA · Alteplase · Thrombolytic · Plasminogen activator · Aspirin · Clopidogrel · Prothrombin complex concentrates · PCC · aPCC · FEIBA · Activated prothrombin complex concentrates · FFP · Fresh frozen plasma · Recombinant factor VIIa · rFVIIa · Protamine · Platelets · DDAVP · Desmopressin · Cryoprecipitate · Guideline · GRADE criteria

Introduction

Antithrombotics, including anticoagulants, antiplatelet agents, and thrombolytics are used to treat or decrease the risk of thrombotic or embolic events in a wide variety of medical conditions. With the introduction of new antithrombotics to the market, an aging patient population, and the increasing prevalence of atrial fibrillation, the use of antithrombotics is expected to continue to rise in future years [1, 2]. As compared to patients experiencing spontaneous intracranial hemorrhage without anticoagulation, those on antithrombotics have a higher likelihood of secondary hematoma expansion, and an increased risk of death, or poor functional outcome [3–5].

Because of the controversial literature regarding the optimal antithrombotic reversal strategies in patients with intracranial hemorrhage, the Neurocritical Care Society/Society of Critical Care Medicine Antithrombotic Reversal in Intracranial Hemorrhage Guideline Writing Committee was established in October 2012. Its aim was to develop evidence-based guidelines for counteracting the effects of commonly available antithrombotic agents in the setting of intracranial hemorrhage.

Methodology

The Neurocritical Care Society along with the Society of Critical Care Medicine assembled a 13-person, international, multi-institutional committee with expertise in neurocritical care, neurology, neurosurgery, stroke, hematology, emergency medicine, pharmacy, nursing, hematopathology, and guideline development. The target population was adult patients with intracranial hemorrhage including subarachnoid hemorrhage (traumatic or spontaneous), intraparenchymal hemorrhage (traumatic or spontaneous), intraventricular hemorrhage, subdural hematoma, epidural hematoma, or traumatic contusion. Committee members were assigned one or more of the following sub-topic areas: vitamin K antagonists, direct factor Xa antagonists, direct thrombin inhibitors, unfractionated heparin, low-molecular weight heparin, pentasaccharides, thrombolytics, and antiplatelet agents. The group did not address reversal of intrinsic coagulopathies such as those due to inherited hemophilia, liver, or renal disease.

The committee developed a comprehensive list of key search words including the generic and commercial names of the aforementioned antithrombotic agents, intracranial hemorrhage, subarachnoid hemorrhage, intracerebral hemorrhage, intraparenchymal hemorrhage, subdural hematoma, subdural hemorrhage, intraventricular hemorrhage, epidural hemorrhage, epidural hematoma, and traumatic brain injury. A professional librarian organized this list of key words, developed medical subject heading (MeSH) terms, searched relevant clinical databases (including PubMed/Medline, Library of Science, the Cochrane database, EMBASE, and CINAHL), and created a database using Endnote™ software. The original search included articles published through January 2013, and was limited to articles describing human subjects that were published in the English language. As guideline development progressed, committee members were responsible for updating the search intermittently to identify the more recent literature for inclusion (through November 2015). Clinical trials, meta-analyses, case series, preclinical studies and practice guidelines were all eligible for inclusion. Results were supplemented with the literature recommended by the committee or identified from reference lists.

The writing committee reviewed articles selected from this database for inclusion in the treatment recommendations. The quality of evidence was analyzed, and treatment recommendations were drafted based on the Grading of

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Recommendations Assessment, Development, and Evaluation (GRADE) system [6]. The system allows for two grades of recommendations: "strong" and "conditional" (weak). Definitions for the quality of evidence are as shown in Table 1.

In certain circumstances, a strong recommendation can be made using low- or very low-quality evidence such as in the following five paradigms [7]:

1. A life-threatening clinical situation in which the intervention may reduce mortality and the adverse effects are not prohibitive.
2. There is uncertain benefit to an intervention, but substantial established harm.
3. There is potential equivalence between treatment options, but one is clearly less costly or less risky.
4. There is high confidence in equivalence between treatment options, but one option is possibly more costly or risky.
5. The utility of the intervention is unknown, there is the possibility of harm and a high value is placed on avoiding potentially increased harm, which could be catastrophic.

The GRADE criteria also allow for the assignment of "Good Practice" statements. These statements imply high confidence in the estimates of the effect of the intervention, but are garnered from indirect evidence that would be challenging to subject to a formalized GRADE evaluation [8–10]. Good practice statements should be actionable, necessary, have a large or unequivocal benefit, be based on data that are difficult to collect (or cannot be collected due to ethical or logistical reasons) and be based on a clear rationale [9].

All committee members were in consensus with the recommendations presented in this guideline.

Anticoagulant Agents

Vitamin K Antagonists

Vitamin K antagonists (VKA) include warfarin, acenocoumarol, phenprocoumon, dicoumarol, tecarfarin, and fluindione (Table 2). Their use more than doubles the risk of spontaneous intraparenchymal hemorrhage [11] and is associated with 12–14 % of all intraparenchymal hemorrhages [1, 12]. Overall, intraparenchymal hemorrhage occurs in 0.3–1.1 % of patients on VKA therapy (compared to a 0.15 %/year baseline risk) and accounts for approximately 3500 intraparenchymal hemorrhages per year in the United States [11, 13–19]. With an aging population and an increasing prevalence of atrial fibrillation, VKA use has increased four-fold over the last decade, and is expected to increase further [1]. The risk of hemorrhage also increases with increasing International Normalizing Ratio (INR), although most VKA-related intraparenchymal hemorrhages occur within the recommended therapeutic range [11, 20–25].

Outcomes following VKA-associated intracranial hemorrhage can be devastating. Intraparenchymal hemorrhage accounts for 90 % of all VKA-associated deaths [26], and both mortality rates and functional outcomes are worse for those with VKA-associated intraparenchymal hemorrhage compared to non-coagulopathic intraparenchymal hemorrhage [27–29]. The increased morbidity and mortality are likely due to larger hemorrhage volumes [3, 30], increased risk of hematoma expansion [5], and increased number of comorbidities among anticoagulated patients [28].

VKA Reversal Agents Prompt reversal of anticoagulation is the mainstay of treatment in VKA-related intracranial hemorrhage, irrespective of the hematoma size, location, or

Table 1 GRADE criteria for quality of evidence [6, 422]

Quality of evidence	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain
Strength of recommendation	**Description**
Strong	Most patients should receive the intervention
Conditional	Most patients would benefit from the intervention, though some may not. The pros and cons of the intervention should be assessed taking into account the available evidence and the values and preferences of the patient
Good practice	There is a high confidence in the estimates of the effect of the intervention, but there is only indirect evidence that would be challenging to subject to a formalized GRADE evaluation

Table 2 Pharmacokinetic parameters for selected anticoagulants and antiplatelet agents [161, 423]

Medication	Mechanism of action	Elimination	Half-life	Impairment affects excretion		Dialyzable
				Renal	Hepatic	
Vitamin K antagonists						
Warfarin	Inhibits vitamin K-dependent γ-carboxylation of coagulation factors II, VII, IX, and X, reducing activity of clotting factors	Hepatic metabolism; 92 % renal elimination	20–60 h	Yes	Yes	No
Direct factor Xa inhibitors						
Rivaroxaban	Prevents factor Xa-mediated conversion of prothrombin to thrombin	66 % renal; 28 % fecal	5 h	Yes	Yes	No
Apixaban	Prevents factor Xa-mediated conversion of prothrombin to thrombin	majority fecal; 27 % renal	12 h	Yes	Yes	Minimal, area under the curve decreased by 14 % over 4 h
Edoxaban	Prevents factor Xa-mediated conversion of prothrombin to thrombin	50 % renal	10–14 h	Yes	Yes	No
Direct thrombin inhibitors						
Dabigatran	Competitive direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	>80 % renal	12–17 h 16.6 h in mild, 18.7 h in moderate, 27.5 h in severe renal failure, 34.1 h in patients on hemodialysis	Yes	No	Yes ~57 % over 4 h
Argatroban	Reversible direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	0 % renal	39–51 min	No	Yes	Yes ~20 % over 4 h
Bivalirudin	Reversible direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	20 % renal	25 min; GFR 30-59 34 min GFR 10–29, 57 min	Yes	No	Yes ~25 % over 4 h
Desirudin	Irreversible direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	40–50 % renal	2 h; With renal impairment 12 h	Yes	No	Yes
Lepirudin	Irreversible direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	90 % renal	1.3 h; With renal impairment 2 days	Yes	Yes	Yes
Unfractionated Heparin, LMWHs, and Heparinoids						
Heparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa). By inactivating thrombin, heparin prevents fibrin formation.	Renal	60–90 min	No	No	No
Enoxaparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	40 % Renal	4.5 h	Yes	No	No
Dalteparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	Renal	2.5 h; 3.7–7.7 h with renal insufficiency	Yes	No	No
Nadroparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	Renal	3.5 h	Yes	No	No
Tinzaparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	Renal	3.4 h	Yes	No	No

Table 2 continued

Medication	Mechanism of action	Elimination	Half-life	Impairment affects excretion		Dialyzable
				Renal	Hepatic	
Danaparoid	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	40 % Renal	25 h; 29–35 h with renal insufficiency	Yes	No	No
Pentasaccharides						
Fondaparinux	Binds with antithrombin and potentiates inhibition of free factor Xa, preventing formation of the prothrombinase complex	50–77 % Renal	17–21 h; prolonged in elderly and in renal insufficiency	Yes	No	Yes, clearance increased by 20 %
Thrombolytics						
Alteplase	Catalyzes conversion of fibrin-bound plasminogen to plasmin. Plasmin exerts additional proteolytic effects, including cleavage of platelet GPIIIa and GP1B causing inhibition of platelet function	Hepatic	Plasma: 3–6 min; Terminal: 26–77 min	No	Yes	Unknown, unlikely
Reteplase	Catalyzes conversion of fibrin-bound plasminogen to plasmin. Plasmin exerts additional proteolytic effects including cleavage of platelet GPIIIa and GP1B causing inhibition of platelet function	Renal	Plasma: 13–16 min; Terminal: not reported	Yes	No	Unknown, unlikely
Tenecteplase	Catalyzes conversion of fibrin-bound plasminogen to plasmin. Plasmin exerts additional proteolytic effects including cleavage of platelet GPIIIa and GP1B causing inhibition of platelet function	Hepatic	Plasma: 11–24 min; Terminal: 90–138 min	No	Yes	Unknown, unlikely
Antiplatelets						
Aspirin	Irreversible cyclooxygenase-1 and 2 (COX-1 and 2) enzyme Inhibitor (inhibits thromboxane A2)	5.6–35.6 % renal	20 min	Yes	Yes	Yes
Ibuprofen	Reversible COX-1 and 2 enzyme Inhibitor	80 % renal	2–4 h	Yes	Yes	No
Naproxen	Reversible COX-1 and 2 enzyme Inhibitor	95 % renal, 3 % fecal	12 h	Yes	Yes	No
Dipyridamole	Reversible adenosine reuptake inhibitor	Fecal	10 h	No	Yes	No
Clopidogrel	Irreversible inhibition of P2Y12 ADP receptor	50 % renal, 46 % fecal	6–8 h	Yes	Yes	No
Prasugrel	Irreversible inhibition of P2Y12 ADP receptor	68 % renal, 27 % fecal	2–15 h	Yes	Yes	No
Ticagrelor	Reversible inhibition of P2Y12 ADP receptor	26 % renal, 58 % fecal	7 h Metabolite = 9 h	No	Yes	No
Ticlopidine	Irreversible inhibition of P2Y12 ADP receptor	60 % renal, 23 % fecal	12 h (increases with renal failure 4–5 days after repeated doses)	Yes	Yes	No
Cilostazol	Reversible phosphodiesterase (PDE) III inhibitor, increases cAMP, inhibits ADP induced platelet aggregation, and causes vasodilation	74 % renal, 20 % fecal	10 h	Yes	Yes	No
Anagrelide	Reversible PDE inhibitor, inhibits megakaryocyte formation	70 % renal, 18 % fecal	3 days	Yes	Yes	No

Table 2 continued

Medication	Mechanism of action	Elimination	Half-life	Impairment affects excretion		Dialyzable
				Renal	Hepatic	
Abciximab	Irreversible Glycoprotein IIB/IIIA antagonist	Unknown, likely proteolytic degradation	Free drug = 30 min; Receptor bound drug = 24–48 h	No	No	Unknown, unlikely
Eptifibatide	Reversible Glycoprotein IIB/IIIA antagonist	71.4 % renal, 1.5 % fecal	20–40 min	Yes	No	Yes Approximately 73–83 % after 1 h
Tirofiban	Reversible Glycoprotein IIB/IIIA antagonist	65 % renal, 25 % fecal	20–45 min	Yes	No	Yes
Vorapaxar	Reversible protease-activated receptor-1 (PAR-1) thrombin receptor antagonist (effectively irreversible due to long half-life)	25 % renal, 58 % fecal	3–4 days, terminal half-life 8 days	No	No	Unknown, unlikely

the indication for anticoagulation. Reversal may improve outcomes [31, 32], reduce mortality [32], and limit hemorrhage expansion [33–36]. Urgent reversal is warranted, since hematoma expansion may continue for up to 72 h after ictus in the context of VKA use [30, 36, 37]. For some patients who are neurologically intact with small radiographic hematomas and very mild elevation in INR (e.g., INR < 2), conservative management may be reasonable, though the risks and benefits of VKA reversal should be discussed. Patients with cerebral venous thrombosis with concomitant intraparenchymal hemorrhage should not receive reversal agents due to the increased risk of hematoma expansion related to venous hypertension. In fact, anticoagulation therapy is recommended in patients with cerebral sinus thrombosis, even in the context of intraparenchymal hemorrhage [38–40]. Additionally, caution should be exercised before using reversal agents in patients with concomitant life-threatening ischemia, thrombosis, or severe disseminated intravascular coagulopathy (DIC) because of the possibility of provoking thrombosis and ischemia.

Reversal of VKAs can be achieved by several treatment approaches including Vitamin K (oral or parenteral), fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), and recombinant Factor VIIa (rFVIIa). While all of these options reduce the INR, their efficacy, timeliness, and safety vary.

Vitamin K (phytonadione) Vitamin K antagonists act by inhibiting vitamin K-dependent γ-carboxylation of coagulation factors II, VII, IX, and X [41, 42]. Vitamin K normalizes the INR by providing the necessary substrate to synthesize these coagulation factors. There are no high-quality studies evaluating the efficacy of Vitamin K monotherapy for improving mortality rates or functional outcomes after VKA-related intracranial hemorrhage. However, in other populations, several small randomized, controlled, and prospective cohort trials demonstrate the utility of Vitamin K in correcting the INR [43–49]. The majority of these studies included patients with supratherapeutic INRs, without clinical bleeding, who were treated with Vitamin K or placebo.

The major limitation of vitamin K is that reduction of the INR to values less than 1.4 may take up to 24 h [49, 50]. Because most intraparenchymal hemorrhage expansion occurs in the first hours after ictus [51], vitamin K monotherapy is not adequate for preventing hemorrhage growth [43, 44, 49, 50, 52–56]. Indeed, a small, retrospective study found that administration of Vitamin K alone was associated with a 50 % incidence of intraparenchymal hemorrhage growth, compared to a 33 % or 19 % incidence when combined with FFP or PCC, respectively [33]. Another retrospective study of 55 VKA-related intraparenchymal hemorrhage patients who were treated with different reversal strategies reported that 5 of 6 patients treated with Vitamin K monotherapy experienced hematoma expansion [33].

Despite the delayed onset of action, Vitamin K results in a sustained and durable reversal of anticoagulant activity and is therefore recommended in conjunction with other reversal agents [54, 57]. Small case-controlled studies suggest that protocol-driven administration of Vitamin K along with FFP or PCC may improve functional outcomes and mortality rates [31, 52, 58, 59].

The route of administration and dose of Vitamin K significantly affects its ability to reverse VKA. Intravenous administration of Vitamin K is more effective at INR reversal than the same dose of Vitamin K administered subcutaneously [48, 54, 60, 61]. Although oral administration of Vitamin K results in a similar percentage of

patients with effective INR reversal at 24–72 h, reversal is expedited with the intravenous route [54, 61]. Overall, the decreased bioavailability and prolonged onset of action diminish the utility of subcutaneous and oral routes [43, 48, 60, 62, 63]. Similarly, high doses of Vitamin K more effectively reverse the INR over a shorter period of time than low doses [52, 54, 60, 64]. Therefore, administration of Vitamin K as a single, large dose (10 mg IV) is preferred over divided dosing [65].

The risks of Vitamin K are low. Anaphylactoid reactions are more common with intravenous administration; however, the incidence is only 3 per 10,000 doses [62, 63, 66]. Reducing the infusion rate may reduce the risk, although this is controversial [66].

Fresh Frozen Plasma FFP contains all of the coagulation factors and proteins present in whole blood and reverses the anticoagulant effects of VKAs by replacing clotting factors. Benefits of FFP include its widespread availability and lower cost (approximately US $200–400 per dose) compared to PCC and rFVIIa [67]. However, the data supporting its use in VKA-related intracranial hemorrhage are derived primarily from small cohort studies and there are little data demonstrating improved functional outcomes. One study did show a decrease in mortality rates from 48 % (historical controls) to 10 % with a formalized FFP-based reversal protocol in patients with intraparenchymal hemorrhage [35]. Another large, multi-center, retrospective registry study of 1547 patients with VKA-associated intraparenchymal hemorrhage found the highest adjusted mortality rates for no reversal (62 %), followed by FFP (46 %), PCC (37 %), and PCC + FFP (28 %). Although the mortality rate for PCC was lower than FFP, this difference was not statistically significant after adjusting for baseline factors. This study was limited by its inability to adjust for withdrawal of life-sustaining therapy and practice variations at different centers [68]. Compared to PCC, the use of FFP in warfarin-associated intracranial hemorrhage has been associated with a higher risk of major hemorrhage (52 vs. 6 %, $P = 0.005$) and an increased risk of death or severe disability at three months (84 vs. 56 %, $P = 0.030$) in a small retrospective study [59].

Several studies have demonstrated the ability of FFP to normalize the INR after VKA-related intracranial hemorrhage [34, 35, 69–73]. The degree of normalization depends on the initial INR and the dose of FFP administered [74]. Although typical doses range from 5 to 20 mL/kg, a dose of 30 mL/kg produces more complete correction of coagulation factor levels [75–81]. The amount of FFP required to adequately correct INR may vary on an individual basis due to the non-linear, exponential relationship between clotting factor levels and coagulation test results [82–84].

Despite its ability to correct INR, the time to correction and volume of product required limits the utility of FFP for use in VKA-related intracranial hemorrhage [34, 70, 72, 73, 85]. Several studies have found that INR correction using FFP may take more than 30 h [69, 72, 73, 86]. In a study of 41 patients requiring urgent anticoagulant reversal, no patient who received 4 units (800 ml) of FFP had an INR < 2 fifteen minutes post-infusion [74]. In a large cohort study of 414 patients with warfarin-associated bleeding (38 % of whom had intracranial hemorrhage), FFP failed to correct the INR to $\leq$1.3 in 67 % of patients up to 24 h after administration and was unsuccessful at decreasing the INR to $\leq$1.5 in nearly 40 % [87]. Two large, randomized, controlled trials of warfarin reversal comparing 4-factor PCC to FFP found that no patient in the FFP group had an INR ≤ 1.3 within one hour of initiation of reversal agent administration compared to 54–63 % of those in the PCC group [85, 88]. In a study of 63 patients comparing FFP-based therapy (FFP in combination with Vitamin K) to both rFVIIa- and PCC-based approaches, the time to target INR (< 1.3) was twice as long in the FFP group (1933 $\pm$ 905 vs. 784 $\pm$ 926 and 980 $\pm$ 1021 min, respectively) [69]. In fact, INR correction with FFP and Vitamin K may be as much as 4–5 times slower than with PCC [34]. The need for blood type matching, the thawing process, and administration time may, in part, explain the slower correction of INR with FFP. Unfortunately, every 30 min of delay in initiation of FFP infusion decreases the odds of INR reversal within 24 h by 20 % [70].

Failure to correct the INR within 2 h was found to be an independent predictor of death or severe disability in one retrospective cohort study of intracranial hemorrhage patients, and others have found worse outcomes with delays in treatment [33, 71, 86]. In a cohort of patients with VKA-associated intraparenchymal hemorrhage who received FFP, the median time to INR normalization was 30 h and hematoma expansion occurred in 12 of 45 patients (27 %). Eight of the 12 patients were diagnosed with expansion during FFP infusion and four had already completed the infusion when expansion occurred [72]. In a large retrospective study of 853 patients with VKA-associated intraparenchymal hemorrhage, the risk of hematoma enlargement more than doubled with failure to correct INR to <1.3 within 4 h of admission (41.5 vs. 19.8 %, $P < 0.001$) [36].

In addition to the delayed treatment effect, FFP administration carries many potential complications. The required volume of FFP per body weight may cause pulmonary edema and intravascular volume overload, as well as transfusion-related reactions such as transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) [69, 75, 89]. There is also a low risk of infection from products derived from pooled human plasma. Large randomized trials have found similar thrombosis rates (3–8 %) for 4-factor PCC and FFP [85, 88]. A retrospective cohort study found a significantly

higher adverse event rate of 19.5 % for FFP compared to 9.7 % for 4-factor PCC, even after adjusting for baseline history and reason for treatment [90].

In summary, although FFP-based strategies may be effective in reversing the INR, the prolonged time to INR reversal limits the utility of FFP compared to other reversal strategies. Benefits of FFP include its lower cost and widespread availability. FFP may be considered when PCC is not available or in those with a history of allergy or adverse reaction to PCC or its components. Because redosing of some 4-factor PCCs (i.e., Kcentra) is not recommended by the manufacturer, FFP may be considered in patients who have already received a full dose of PCC but do not have adequate INR correction.

Prothrombin Complex Concentrates (PCC) and activated PCC (aPCC) PCCs contain variable amounts of factors II, VII, IX, X; proteins C, S, and Z; and heparin. They are dosed based on their factor IX component (Table 3). Four-factor PCCs (e.g., Kcentra, Octaplex, Cofact, and Kaskadil) are distinguished from 3-factor products by the inclusion of appreciable amounts of Factor VII. Benefits of PCC include its fast preparation and reconstitution time, rapid INR reversal, small volume, and lower risk of infection as compared to FFP [91, 92]. Weight-based dosing of PCC is more effective than standard dose administration. Similarly, an INR-guided PCC dosing algorithm is superior to standard dosing regimens [52, 85]. Several studies suggest that PCC use in VKA-associated intracranial hemorrhage leads to faster INR reversal, less hematoma expansion [33, 34, 52, 59, 69, 85, 93], and similar or better mortality rates and functional outcomes compared to FFP [32, 59, 94].

A prospective, multi-center, randomized, controlled phase 3b trial of 202 patients comparing FFP and 4-factor PCC (Beriplex/Kcentra) for warfarin-associated hemorrhage demonstrated non-inferiority of PCC for achieving hemostasis within 24 h and superiority for rapid correction of INR to $\leq$1.3 within 30 min of reversal agent administration [85]. Only 12 % of patients in this study had intracranial bleeding. Rapid INR correction was achieved in 62.2 % of the PCC group compared to only 9.6 % in the FFP group ($P < 0.0001$). Hemostatic efficacy was comparable between the two groups, with excellent or good hemostasis occurring in 72.4 % of the PCC group and 65.4 % of the FFP group. There were no significant differences in adverse events. Thromboembolic adverse events occurred in both groups (3.9 % PCC vs. 2.8 % FFP), but fluid overload was more common with FFP (4.9 % PCC vs. 12.8 % FFP). A second prospective, multi-center, randomized, controlled, phase 3b trial of 181 patients comparing FFP and 4-factor PCC (Beriplex/Kcentra) for rapid VKA reversal in patients requiring urgent surgical or invasive interventions found that PCC was superior to FFP both for hemostasis and rapid correction of the INR to $\leq$1.3 [88]. Only two patients had cranial neurosurgery. Thromboembolic adverse events were similar and occurred in 7 % of the PCC group and 8 % of the FFP group. Again, there was more fluid overload in the FFP group (13 vs. 3 %).

The aforementioned randomized trials may have limited generalizability to neurocritical care patients, since few patients with intracranial hemorrhage or cranial neurosurgery were included. Two prospective studies of patients with VKA-associated intracranial hemorrhage suggest an outcome benefit with PCC. The first is a multi-center registry which includes 141 patients with VKA-associated intracranial hemorrhage (66 intraparenchymal hemorrhage, 59 subdural hematoma, 15 subarachnoid hemorrhage, and 1 epidural hematoma) [93]. All patients received PCC (Octaplex), 85 % also received Vitamin K, and 22 % also received FFP. INR reversal occurred within 1 h in 71 % of patients receiving PCC. The thrombosis rate was 2 % within 7 days in the PCC

Table 3 Composition of common prothrombin complex concentrates (IU per 100 IU of Factor IX)

Trade name	Factor II	Factor VII	Factor IX	Factor X	Protein C	Protein S	Protein Z	Antithrombin III	Heparin
3-factor products									
Bebulin[a]	100	<5	100	100	–	–	–	–	<0.15[b]
Preconativ	83.3	–	100	83.3	–	–	–	–	–
Proplex-T	50	400	100	50	–	–	–	–	<1.5
Prothrombinex-HT	100	Low	100	100	–	–	–	5	40
Profilnine SD[a]	150	35	100	100	–	–	–	–	–
4-factor products									
Beriplex (Kcentra[a])	106.9	55.1	100	141.4	120.7	86.2	124.1	2.1	1.7
Cofact	56–140	28–80	100	56–140	–	–	–	<0.6	–
Kaskadil	148	40	100	160	–	–	–	–	20
Octaplex	50–129	50–129	100	50–129	50–129	50–129	–	–	20–48

[a] Indicates FDA approval in US

[b] indicates IU per 1 unit factor IX

group. The second study was a prospective observational study of 64 patients with warfarin-associated intracranial hemorrhage (6 subarachnoid, 26 subdural, and 32 intraparenchymal hemorrhage patients). This study compared rates of major bleeding, adverse events, and 3-month functional outcomes (modified Rankin score) among patients who received either FFP alone, 3-factor PCC alone (Bebulin 50 IU/kg IV), or the combination of PCC and FFP [59]. All patients received one dose of Vitamin K 10 mg IV. There were no differences in the time to or degree of INR correction, though patients who received FFP alone had more subsequent major hemorrhage (including intracranial hemorrhage expansion, new intracranial hemorrhage, anemia requiring transfusion, or gastrointestinal bleeding) compared to those who received PCC (52 vs. 6 %, $P = 0.005$). PCC followed by FFP was not associated with reduced major hemorrhage compared to PCC alone (26 vs. 6 %, $P = 0.169$). After adjusting for age, admission Glasgow Coma Score, initial INR, and bleed type, the use of PCC was associated with a lower risk of death or severe disability at 3 months compared to FFP alone (84 vs. 56 %; adjusted OR 0.02, 95 % CI 0.001–0.8; $P = 0.039$) [59]. Reversal agent complications (pulmonary embolus, deep vein thrombosis, myocardial infarction, or pulmonary edema) were similar across groups (19 % in PCC group, 28 % in FFP group, and 17 % in PCC plus FFP group; $P = 0.670$). The recently completed randomized, controlled trial of PCC compared to FFP (INCH Trial: INR Normalization in Coumadin Associated Intracerebral Haemorrhage) will provide more definitive data in an intraparenchymal hemorrhage population [95].

Although prospective studies have been promising, several retrospective studies have yielded conflicting data on functional outcomes in patients with VKA-associated intracranial hemorrhage reversed with PCC. A retrospective cohort study of 104 warfarin-associated intraparenchymal hemorrhage patients found that PCC (Prothrombinex-HT 25–50 IU/kg) plus Vitamin K 5–10 mg IV was associated with significantly improved survival compared to FFP alone after adjusting for intraparenchymal hemorrhage severity [32]. Additionally, patients who received 3-factor PCC were noted to have greater rates of functional independence at discharge than those who did not ($P = 0.049$). A study of 50 VKA-associated intraparenchymal hemorrhage patients found that PCC conferred significantly improved modified Rankin scores at 30 days and lower in-hospital mortality (both $P < 0.05$) compared to a control group (56 % received Vitamin K and only 17 % received FFP) [94]. Conversely, five other retrospective cohort studies did not demonstrate a difference in functional outcomes in patients with VKA-associated intracranial hemorrhage reversed with FFP versus PCC, despite demonstrating more rapid INR reversal with PCC [33, 58, 68, 96, 97]. In one retrospective study, intraparenchymal hemorrhage patients treated with FFP (primarily enrolled in Canada) were compared to those treated with 4-factor PCC (enrolled in Europe). Although PCC appeared to significantly reduce all-cause 30-day mortality in unadjusted analysis, after adjusting for hematoma volume, location, and age, the protective effect of PCC became non-significant [97]. However, this study may be underpowered to detect an effect after adjustment for several covariates. Additionally, differences in treatment and withdrawal of life-sustaining therapy in different countries were not accounted for.

Though 4-factor PCC has theoretical hemostatic advantages over 3-factor PCC due to higher concentrations of factor VII, 3- and 4- factor PCC have not been directly compared. A large, multi-centered retrospective registry study of 1547 patients with VKA-associated intraparenchymal hemorrhage observed that 4-factor PCC was associated with a higher 30-day case fatality rate than 3-factor PCC in patients with VKA-associated intraparenchymal hemorrhage [68]. However, 4-factor PCC was defined as either 4-factor PCC (of any formulation) or the combination of 3-factor PCC plus rFVIIa. The authors did not specify which brands of PCC were used nor the number of patients who received rFVIIa. Since the combination of PCC and rFVIIa may lead to an elevated risk of thrombotic complications and DIC, side effects may explain the higher mortality rates observed. Furthermore, the choice of 3- or 4-factor PCC varied by center as did the rate of concomitant vitamin K administration (neither of which were accounted for). A systematic review of 18 studies found that the INR was corrected to $\leq$1.5 within one hour in 6 of 9 warfarin reversal studies using 3-factor PCC and 12 of 13 studies evaluating 4-factor PCC. The authors concluded that more reliable correction occurs with 4-factor PCC [118]. Other small studies have shown rapid INR reversal with 3-factor PCC. In a study of 3-factor PCC, a weight-based and INR-guided PCC reversal algorithm resulted in normalization of the INR in 12 intracranial hemorrhage patients [98]. Time to an INR $<$ 1.5 in the PCC group was substantially faster than with FFP alone (152 $\pm$ 84 vs. 485 $\pm$ 321 min). A similar retrospective cohort of patients with various types of VKA-associated intracranial bleeding exhibited consistent reduction in INR after 3-factor PCC administration (INR 2.3–1.4, $P < 0.001$) [99]. Still, given the differences in composition of the PCCs, the theoretical hemostatic benefits of factor VII, and stronger quality and quantity of evidence supporting the use of 4-factor PCC for rapid INR reversal and hemostasis in mixed populations, we suggest using 4-factor PCC over 3-factor PCC.

Some have advocated for combining FFP with 3-factor PCC in order to supplement factor VII levels [99]. A retrospective, multi-centered study of 1547 patients with VKA-associated intraparenchymal hemorrhage observed that the combination of FFP and PCC (97 % of patients in

the combination group received 3-factor PCC) may be associated with lower 30-day case fatality as compared to FFP alone or PCC alone [68]. Limitations of this study include the fact that the authors could not adjust for withdrawal of life-sustaining therapy (which may have differed between groups) or institutional variability in treatment, there were lower rates of vitamin K use in the PCC alone group (82 %) compared to the combination group (95 %), and the combination group had higher rates of surgical intervention, which could have improved outcome or be a surrogate marker for more aggressive treatment. Furthermore, 119/131 (92 %) of the patients in the combination group came from two centers in Australia where patient demographics and treatment variation may account for the observed effect. The authors also conducted a propensity-matched sensitivity analysis, wherein the rates of vitamin K use and surgical intervention were still significantly lower in the propensity-matched PCC alone cohort compared to the propensity-matched combination cohort. In this analysis, PCC alone was not significantly associated with increased mortality compared to the combination. The propensity analysis was limited, however, by not adjusting for enrollment center. Additionally, complications related to each reversal agent were not reported. Finally, functional outcomes are a more meaningful endpoint than mortality, since many patients may have survived in a severely disabled state. Notably, in one small, prospective, observational study of VKA-associated intracranial hemorrhage patients, INR reversal, rates of major hemorrhage, and 3-month functional outcomes (modified Rankin score) were similar among patients who received 3-factor PCC alone compared to those who received FFP plus 3-factor PCC [59]. In another study of 70 patients with intracranial hemorrhage, the addition of FFP to 3-factor PCC did not increase the likelihood of INR reversal [100]. Overall, the addition of FFP to PCC has not been definitively shown to improve outcomes and may place patients at higher risk of thrombosis, DIC, and other transfusion-related complications and is therefore not empirically recommended. However, in patients who do not have adequate INR reversal following PCC administration, FFP may be considered.

Activated PCC has also been compared to FFP in a retrospective study of 72 patients with warfarin-associated life-threatening bleeding. Activated PCC corrected INR faster and more completely when compared to FFP, though 7 % of patients had aPCC-associated adverse events [101]. Another observational study of 16 patients (12 with subdural hematoma or subarachnoid hemorrhage) with warfarin-associated bleeding found that aPCC (dosed at 500–1000 units) led to clinical hemostasis in 93 % of patients with no thrombotic events [102]. PCC and aPCC for warfarin reversal have not been directly compared.

As with all reversal agents, PCC or aPCC use is associated with a risk of complications. A wide range of thrombosis rates have been reported in patients receiving PCC products, although in controlled studies where patients with risk factors for thrombosis are excluded, the rates appear to be low (3.9–7 %) [59, 85, 99]. PCCs should be used with caution in patients who have evidence of acute arterial thrombus, DIC, or other coagulopathic states. Because of the rapid reversal action of PCC, a follow-up INR can be checked within 15–60 min of administration [33, 34, 59, 69, 85]. While PCC products have a rapid onset of action, the pharmacologic effects begin to wane after approximately 12–24 h [52]. This is likely because Vitamin K-dependent clotting factors provided by PCC decrease in the plasma 12–24 h after dosing [52]. Little information exists regarding the risks and benefits of repeated doses of PCC and multiple doses are not recommended by the published prescribing information [103, 104]. Since aPCC contains activated clotting factors, it is presumed to be more thrombogenic than PCC, although reported rates of thrombotic events are low (4–8 events per 100,000 infusions) [105]. However, adverse event rates for aPCC were largely generated in a population of young hemophiliacs, who may not have the same thrombotic risk factors as an intracranial hemorrhage population. Therefore, the thrombotic risks may be higher than reported.

Recombinant Factor VIIa rFVIIa results in rapid INR reversal similar to that of PCC [69, 106]. Although several small, retrospective studies suggest that rFVIIa rapidly reverses INR compared to FFP, there is very limited data to support improved hemostasis, mortality, or functional outcomes in patients treated with rFVIIa compared to other reversal strategies [71, 104, 106–108]. One small, retrospective, cohort study suggested that patients with traumatic brain injury and concomitant VKA therapy had reduced mortality after rFVIIa and FFP administration compared to FFP alone (0 vs. 39 %, $P = 0.03$) and had more effective reversal of INR (1 vs. 3, $P = 0.02$). However, the dose of FFP (1 unit) was lower than the recommended dose for VKA-associated coagulopathy, and the study was underpowered to show meaningful differences in outcome [109].

Recombinant Factor VIIa has been associated with a relatively high-thrombosis rate (12.8–24 %), likely due to the pro-coagulant state and thrombin burst associated with higher doses, though this is somewhat controversial [86, 110–112]. Patients with a concomitant hypercoagulable state or vascular injury are at higher risk of thrombotic complications, particularly arterial thrombosis. In a study of non-coagulopathic intraparenchymal hemorrhage patients who received rFVIIa, there was a 5 % excess risk of arterial thrombosis compared to controls [113]. Recombinant Factor

VIIa can lower the INR quickly at a rate comparable to PCC [69, 71]. However, the INR is particularly sensitive to factor VII levels and INR correction may occur despite inadequate levels of factors II, IX, and X that are required for hemostasis. In addition, rFVIIa is expensive compared to other reversal strategies [71, 86, 104, 106–108, 110–112]. Taking all these factors into account, we recommend against rFVIIa use for VKA reversal in patients with intracranial hemorrhage. However, in circumstances in which the patient or their surrogate will not accept blood products (e.g., Jehovah's witness), rFVIIa can be considered, though there is a paucity of data to suggest efficacy.

In summary, vitamin K should be administered immediately to patients with VKA-associated intracranial hemorrhage. Additionally, several studies suggest that PCC leads to more rapid INR correction than FFP [85, 88] and may be associated with improved hemostasis and outcomes [32, 59, 94]. Other benefits of PCC include its rapid reconstitution, lower volume and lower risk of infection, pulmonary edema, TRALI, and TACO compared to FFP [114]. The higher unit cost of PCC compared to FFP may lead some to believe that FFP may be more cost effective. However, the literature suggests the contrary. In a decision analysis comparing FFP to 4-factor PCC for the treatment of warfarin-associated life-threatening bleeding, the total cost of reversal was $\leq$15 % of the hospitalization cost and PCC was found to be more cost-effective than FFP [115]. The cost of intracranial hemorrhage expansion, longer length of stay, disability, lost productivity, and post-hemorrhage rehabilitation care that could occur with failure to rapidly correct the INR, may outstrip the cost of the reversal agent. Furthermore, the increased cost associated with management of FFP-associated fluid overload has been found to defray the upfront cost of 4-factor PCC in the treatment of VKA-associated bleeding [116].

We recommend an INR target $<$1.4 since this was the target INR in two high-quality studies [85, 88]. Certain PCC formulations (i.e., Kcentra) were only studied in patients with an INR $\geq$ 2.0 [85, 88]. When the INR is between 1.4 and 1.9, we suggest using the lowest marketed dose of the PCC product (i.e., 25 IU/kg for Kcentra), though lower doses such as 10 IU/kg may be reasonable [98, 117]. Although 3- and 4-factor PCCs have not been directly compared, we suggest 4-factor PCC based on the theoretical benefits of inclusion of Factor VII, it's more rapid reversal of INR in a systematic review, and the fact that it has been compared to FFP in two high-quality randomized, controlled trials [85, 88, 118]. Although the combination of FFP and PCC was shown to be associated with lower mortality in one retrospective study [68], the aforementioned limitations of this study and the possible thrombotic complications associated with FFP plus PCC preclude recommendation of this combination.

Recommendations for VKA Reversal

(1) We recommend discontinuing vitamin K antagonists when intracranial hemorrhage is present or suspected. (Good Practice statement)

(2) We recommend urgent reversal of vitamin K antagonists in patients with intracranial hemorrhage (Strong recommendation, moderate quality evidence) with the following considerations:

   (a) We suggest against VKA reversal in patients where there is a high suspicion of intracranial hemorrhage due to cerebral venous thrombosis. (Conditional recommendation, very low-quality evidence)
   (b) We recommend assessing risks and benefits when considering VKA reversal in intracranial hemorrhage patients with concurrent symptomatic or life-threatening thrombosis, ischemia, heparin-induced thrombocytopenia, or DIC. (Good Practice statement)

(3) We recommend administration of Vitamin K to ensure durable reversal of INR following VKA-associated intracranial hemorrhage. Vitamin K should be dosed as soon as possible or concomitantly with other reversal agents. (Strong recommendation, moderate quality evidence)

   (a) We suggest one dose of Vitamin K 10 mg IV. Subsequent treatment should be guided by follow-up INR. (Good Practice statement)
   (b) If repeat INR is still elevated $\geq$1.4 within the first 24–48 h after reversal agent administration, we suggest redosing with vitamin K 10 mg IV. (Good Practice statement)

(4) We recommend administering 3-factor or 4-factor PCC rather than FFP to patients with VKA-associated intracranial hemorrhage and INR $\geq$ 1.4. (Strong recommendation, moderate quality evidence)

   (a) We suggest the use of 4-factor PCC over 3-factor PCC. (Conditional recommendation, low-quality evidence)
   (b) We suggest initial reversal with PCC alone (either 3- or 4- factor) rather than combined with FFP or rFVIIa. (Conditional recommendation, low-quality evidence)
   (c) We recommend that PCC dosing should be weight-based and vary according to admission INR and type of PCC used. (Strong recommendation, moderate quality evidence)

(d) We recommend repeating INR testing soon after PCC administration (15–60 min), and serially every 6–8 h for the next 24–48 h. Subsequent treatment should be guided by follow-up INR, with consideration given to the fact that repeat PCC dosing may lead to increased thrombotic complications and risk of DIC. (Good Practice statement)

(e) If the repeat INR is still elevated $\geq$1.4 within the first 24–48 h after initial PCC dosing, we suggest further correction with FFP. (Conditional recommendation, low-quality evidence)

(5) We recommend against administration of rFVIIa for the reversal of VKA. (Strong recommendation, low-quality evidence)

(6) If PCCs are not available or contraindicated, alternative treatment is recommended over no treatment. (Strong recommendation, moderate quality evidence) Treatment choice may be guided by available therapies and patient-specific factors. (Good Practice statement)

(a) Treatment with FFP and Vitamin K is recommended over no treatment. (Strong recommendation, moderate quality evidence)

(b) We suggest dosing FFP at 10–15 ml/kg IV along with one dose of vitamin K 10 mg IV. (Conditional recommendation, low-quality evidence)

Direct Factor Xa Inhibitors

Three oral direct Factor Xa inhibitors are currently available for clinical use: rivaroxaban, apixaban, and edoxaban (Table 2). They exert their anticoagulant effect by preventing factor Xa-dependent conversion of prothrombin to thrombin. Current indications include primary stroke prevention in patients with non-valvular atrial fibrillation (rivaroxaban, apixaban, and edoxaban), treatment of deep vein thrombosis and pulmonary embolus (rivaroxaban, apixaban, and edoxaban), and secondary prevention of deep venous thrombosis or pulmonary embolism (rivaroxaban and apixaban only) [119–128].

As with all anticoagulants, oral factor Xa inhibitors are associated with a risk of intracranial hemorrhage. However, in large trials of oral direct factor Xa inhibitors for primary stroke prevention in patients with non-valvular atrial fibrillation, the risk of intracranial hemorrhage was significantly lower for rivaroxaban 20 mg daily (HR 0.67, 95 % CI 0.47–0.93), apixaban 5 mg twice daily (HR 0.42, 95 % CI 0.30–0.58), and edoxaban 60 mg daily (HR 0.54, 95 % CI 0.38–0.77) compared to warfarin [123, 124, 128].

Because of their relatively short half-life, discontinuation of direct factor Xa inhibitors may be sufficient in cases of minor, non-life-threatening hemorrhage [129], but may not be prudent in patients with intracranial hemorrhage because of the high risk of hematoma expansion and neurological deterioration. Information on reversing anticoagulation from oral direct factor Xa inhibitors is predominantly limited to ex vivo and in vivo studies on healthy volunteers and animal models of bleeding.

Factor Xa Inhibitor Reversal Agents

Activated Charcoal Administration of 50 g of activated charcoal 2 h after a single dose of 20 mg of apixaban reduced exposure to the drug by 50 % in healthy volunteers. The effect was less pronounced when activated charcoal was given 6 h after the dose of apixaban [130]. Activated charcoal may also reduce the concentration of rivaroxaban when administered very shortly after ingestion; however, its utility may be limited by the rapid gastric absorption of rivaroxaban [131, 132]. Administration of activated charcoal may be difficult and pose an aspiration risk in non-intubated patients with altered mental status. Therefore, it should be considered primarily in intubated patients with enteral access and in alert patients with minimal aspiration risk.

Hemodialysis Hemodialysis does not reverse the effect of oral direct factor Xa inhibitors because these drugs are highly protein bound.

Prothrombin Complex Concentrates, Activated PCC, and rFVIIa Four-factor PCC and aPCC have been tested in several studies of healthy humans and in animal models of hemorrhagic injury. In a murine model of intraparenchymal hemorrhage following rivaroxaban exposure, the administration of 4-factor PCC, FFP, or rFVIIa within 30 min of ictus prevented hematoma expansion in a dose-dependent fashion and restored factors II and X activity [133]. However, none of the three agents completely corrected the PT. In two animal models of systemic hemorrhage after exposure to high-dose rivaroxaban, 4-factor PCC, aPCC, and rFVIIa significantly reduced the bleeding time and partially corrected the PT [134]. Studies on healthy volunteers have shown partial or complete reversal of rivaroxaban-induced coagulation abnormalities with 4-factor PCC (50 U/kg) [135–139], aPCC (25 and 80 U/kg) [136, 138, 139], and rFVIIa [136, 138]. The extent of reversal appears to depend on the coagulation parameter assessed [137, 139]. In vitro studies support the finding that although some coagulation parameters can be improved following administration of procoagulants such as PCC, aPCC and rFVIIa, baseline levels are not restored [140]. In a prospective study of

Table 4 Specific antidotes for novel oral anticoagulants in development

Name	Type of drug	Target	Evidence
Aripazine (PER977)	Synthetic small molecule	Oral factor Xa (apixaban, edoxaban, rivaroxaban) Direct thrombin inhibitors (dabigatran) Unfractionated Heparin LMWH	Not FDA approved. 80 healthy volunteers on edoxaban had improved whole-blood clotting time after aripazine [424]. Animal studies demonstrate reversal of bleeding following exposure to rivaroxaban, apixaban, edoxaban or dabigatran [425–427]
Andexanet (PRT064445)	Recombinant modified factor Xa protein	Oral factor Xa (apixaban, edoxaban, rivaroxaban) LMWH Pentasaccharides	Not FDA approved. Ex vivo, animal studies and phase 2 healthy volunteer studies demonstrate that andexanet reverses inhibition of factor Xa, corrects clotting times, restores hemostasis and reduces blood loss [174, 428–433]
Idarucizumab or Praxbind®	Humanized antibody fragment against dabigatran	Dabigatran	FDA approved October 2015. Phase I safety studies and interim analysis of RE-VERSE AD study published [170, 171, 173, 434] Idarucizumab immediately and safely reversed dabigatran and normal hemostasis was achieved in 90 % of patients who underwent procedures following reversal

intraparenchymal hemorrhage patients at a single institution from 2013 to 2015, 5 of 127 enrolled patients (4 %) had an oral factor Xa inhibitor associated hemorrhage and received aPCC for coagulopathy reversal. No patient had a thrombotic complication or hemorrhage expansion in this small series [141]. Two clinical case reports describe the use of aPCC in patients with rivaroxaban-associated subdural hematoma and iliac artery aneurysm rupture who underwent surgical intervention with adequate hemostasis and clinical exam improvement [142, 143]. While some studies found aPCC and rFVIIa to be more effective than PCC [136, 138, 144], others found less convincing evidence for rFVIIa (120 mcg/kg) [138, 139]. Since none of these studies directly assessed hemostasis, it is difficult to determine which laboratory parameters are most meaningful and, in turn, which reversal agent is most efficacious for rivaroxaban reversal.

In vitro studies of apixaban-exposed blood have demonstrated that PCC, aPCC, and rFVIIa all improve thrombin generation and aPCC and rFVIIa additionally improve clotting time and clot formation time [145]. However, other animal experiments using rivaroxaban and apixaban showed no decrease in blood loss after the administration of PCC or rFVIIa, despite partial improvement in coagulation parameters [146, 147].

Reported effects of PCC, aPCC, and rFVIIa on abnormal coagulation tests induced by edoxaban have been mixed [148, 149], but 4-factor PCC (10, 25, and 50 U/kg) has been shown to decrease bleeding in an edoxaban-treated animal model of acute hemorrhage [150], and after punch biopsies in healthy volunteers [151].

Overall, the available data are not sufficient to support the efficacy of available hemostatic agents for the reversal of anticoagulation induced by oral factor Xa inhibitors. Nevertheless, administration of agents to correct anti-factor Xa-associated coagulopathy is advisable. Because of better correction of coagulation parameters and lower risk of thromboembolism, it seems reasonable to favor 4-factor PCC or aPCC over rFVIIa.

Fresh Frozen Plasma There is very scant information on the value of FFP for reversal of Xa inhibitors, as most studies used PCC instead. In one murine hematoma model, FFP, PCC, and rFVIIa prevented excess hematoma expansion induced by rivaroxaban, but none fully corrected hemostasis [133]. There are no data on the value of combining FFP and PCC for reversal of Xa inhibitors.

Investigational reversal agents Other agents under development (Table 4) to reverse factor Xa inhibitors, such as andexanet alfa and aripazine, are discussed in Online Appendix 2.

Recommendations for Oral Direct Factor Xa Inhibitors Reversal

(1) We recommend discontinuing factor Xa inhibitors when intracranial hemorrhage is present or suspected. (Good Practice statement)
(2) We recommend obtaining information on the time elapsed since the last dose of direct factor Xa inhibitor and possible medication interactions to

assist in estimating the degree of anticoagulation exposure. (Good Practice statement)

(3) We suggest that pharmacological reversal of oral factor Xa inhibitors should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing. (Conditional recommendation, low-quality evidence)

(4) We suggest administration of activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of ingestion of an oral direct factor Xa inhibitor. (Conditional recommendation, very low-quality evidence)

(5) We suggest administering a 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure or in the context of liver failure. (Conditional recommendation, low-quality evidence)

(6) We suggest administering 4-factor PCC or activated PCC over rFVIIa because of the lower risk of adverse thrombotic events. (Conditional recommendation, low-quality evidence)

Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTI) are used for primary stroke prevention in patients with non-valvular atrial fibrillation [152], for treatment of deep venous thrombosis and pulmonary embolus [153, 154], and in the management of heparin-induced thrombocytopenia [155]. Available DTIs include dabigatran (oral), bivalirudin (intravenous only), desirudin (subcutaneous), argatroban (intravenous only), and lepirudin (intravenous only, see Table 2).

Reports of the incidence and outcomes of DTI-related intracranial hemorrhage are sparse. In a subgroup analysis of the RE-LY trial, the intracranial hemorrhage rate was 0.2–0.3 % per year with dabigatran doses of 220 mg or 300 mg per day, respectively. The distribution of intracranial hemorrhages was 46 % intraparenchymal hemorrhage, 45 % subdural hematoma, and 8 % subarachnoid hemorrhage [156]. There were significantly lower intracranial hemorrhage rates with both doses as compared to warfarin, though major hemorrhage was only reduced with the 110 mg twice daily dose. In the phase 2 RE-ALIGN trial of dabigatran versus warfarin in patients with mechanical heart valves, ischemic or "unspecified" stroke occurred in 5 % of patients receiving dabigatran 300 mg daily over 12 weeks, though it is unclear what percentage, if any, of the "unspecified" strokes were hemorrhagic. Major hemorrhages were recorded in 4 %, but all occurred in the pericardial space [157]. Among experimental rodent models of intraparenchymal hemorrhage expansion, dabigatran led to dose-dependent hemorrhage expansion in one model [158], but not in two other models [159, 160]. Data on functional outcome following direct thrombin inhibitor-related intracranial hemorrhage are presently not available; however, registry data are currently being collected.

Reversal Agents

DTI Discontinuation All DTIs should be discontinued if intracranial hemorrhage is suspected or diagnosed. If a DTI was last administered more than 3–5 half-lives before presentation, there is no role for reversal agents since a negligible anticoagulation effect exists after this time frame. For patients exposed to a DTI with a short half-life, simple discontinuation of the medication may be sufficient. However, patients with renal insufficiency metabolize certain DTIs (e.g., dabigatran) at a much slower rate and may be exposed to the anticoagulant effect for a longer time (Table 2). Similarly, patients taking concomitant P-glycoprotein inhibitors (e.g., cyclosporine, dronedarone, and ketoconazole), which may enhance the absorption of dabigatran, may also be expected to have a more pronounced or sustained exposure to dabigatran, especially in the context of renal insufficiency [161]. One study reported on eight patients with dabigatran-associated intracranial hemorrhage. In these patients, dabigatran was simply discontinued without any further interventions. No patient experienced hematoma growth, and functional outcomes were acceptable, though the authors do not report the time from the last dabigatran dose to hemorrhage onset and there was no control group [162].

Oral-Activated Charcoal Oral-activated charcoal can be used to remove the unabsorbed dabigatran pro-drug from the gastrointestinal tract if administered within two hours of dabigatran dosing [163]. As with oral factor Xa inhibitors, consideration should be given to the risk of aspiration in patients with altered mental status who are not intubated.

Idarucizumab (Praxbind®) Idarucizumab is a specific, neutralizing, monoclonal antibody fragment, which adheres to the thrombin-binding site of dabigatran (Table 4). It became FDA approved for use in the United States in October 2015 for the reversal of dabigatran-induced coagulopathy in patients with life-threatening or uncontrolled bleeding and in patients requiring emergent/urgent procedures [164, 165]. Because it has a much higher affinity for dabigatran than thrombin, it renders dabigatran inactive. The idarucizumab-dabigatran complex is then cleared by the kidneys. Idarucizumab completely reversed the dabigatran-induced prolongation of aPTT and thrombin time within 1 min after a single injection in an ex vivo study [166]. In two trauma models of dabigatran-fed pigs,

the addition of idarucizumab restored all dabigatran-prolonged coagulation parameters (PT, aPTT, clotting time, and clot formation time) to baseline. In an in vivo study of the effects of idarucizumab to reverse dabigatran-associated forearm bleeding in healthy volunteers, there was a dose-dependent return of fibrin formation [167–169].

In a phase I, randomized double-blind, placebo-controlled safety and dose escalation trial in 110 healthy male dabigatran-naïve volunteers, administration of increasing doses of idarucizumab (up to 8 grams IV) was safe and well tolerated. Adverse events were mild (headaches and erythema at the infusion site) and similar in frequency to the placebo group. Coagulation parameters such as dilute thrombin time, thrombin time, ecarin clotting time, aPTT, endogenous thrombin potential (ETP), and activated clotting time were not affected by idarucizumab infusions (i.e., idarucizumab was not pro-thrombotic). Idarucizumab concentrations rapidly declined to 4 % 4 h after the end of infusion and the half-life of idarucizumab was estimated at 45 min (terminal half-life 10.3 h) [170]. In another phase I, prospective, randomized trial enrolling 47 healthy volunteers taking dabigatran 220 mg twice a day for 3 days, idarucizumab infusions resulted in a dose-dependent complete and sustained reversal of coagulation parameters (ecarin clotting time, dilute thrombin time, aPTT, thrombin time, and ACT) for more than 72 h with minimal, mild adverse events (infusion site erythema, hot flashes, epistaxis, hematuria, and infusion site hematoma) [171]. In another double-blind randomized, placebo-controlled trial, 46 middle aged and elderly volunteers with impaired renal function exposed to dabigatran 150 or 220 mg BID were treated with idarucizumab (up to 5 g IV) or placebo. No major adverse events occurred. Idarucizumab reversed the anticoagulant effect (measured by dilute thrombin time, ecarin clotting time, and aPTT) of dabigatran immediately by the end of the 5 min infusion [172]. In two of the aforementioned studies, a partial return of the anticoagulant effects 2–4 h after the idarucizumab infusion was shown with lower idarucizumab doses (1 gram) [170, 171].

An interim analysis of 90 patients included in the prospective cohort study of dabigatran reversal in patients with uncontrolled or life-threatening bleeding or requirement for emergency procedures (RE-VERSE AD [NCT02104947]) found that idarucizumab (5 g in two 2.5 g infusions within 15 min) demonstrated complete reversal of the anticoagulant effect of dabigatran (75–150 mg BID) within 4 h as measured by ecarin clotting time and dilute thrombin time. Furthermore, idarucizumab normalized the test results in 88–98 % of patients who had abnormal coagulation profiles at baseline (often within minutes). Unbound dabigatran levels were $<$20 ng/mL in 93 % of patients at 12 h and in 79 % at 24 h. In this study, 64 % of patients were taking dabigatran 110 mg twice daily, and the median time from last ingestion was 15.4 h. Normal hemostasis was achieved in 92 % (33/36) of patients requiring surgery or other procedures. Among the 35 patients with bleeding who could be assessed, hemostasis was restored in a median of 11.4 h. The time to hemostasis was a secondary outcome assessed by clinicians at 10, 30 min, 1, 2, 4, 12, and 24 h after idarucizumab administration. Although a formalized bleeding severity scale was used, given the small number of patients, the large intervals between assessments, and the difficulty in assessing those with intracranial or retroperitoneal hemorrhage, it is unclear if 11.4 h represents an accurate time to hemostasis. Adverse events included 18 deaths (due to vascular causes in 10) and 5 thrombotic events off anticoagulation [173]. Twenty-two patients had increased dabigatran concentrations along with increased ecarin clotting times 24 h after idarucizumab administration. The authors conjecture that this may reflect redistribution of dabigatran from the extravascular to intravascular space, though it is unclear if these patients would benefit from idarucizumab redosing. A major limitation of this study is the lack of a control group.

Though dabigatran levels appear to correlate with dilute thrombin time and ecarin clotting time, these tests are not widely available in a timely fashion, and the manufacturer makes no recommendations currently regarding laboratory monitoring. Because the sensitivity and specificity of these laboratory assays for predicting hemostasis and outcome following idarucizumab reversal are largely unknown, we do not currently recommend monitoring or redosing reversal agents based on laboratory parameters. Rather, redosing of idarucizumab should be based on evidence of clinically significant ongoing bleeding.

Idarucizumab is the most specific and fastest reversal agent for dabigatran, and its administration appears to be safe. Because it is a Fab (fragment antigen binding), it does not have endogenous targets or bind to Fc receptors. Additionally, renal impairment does not alter the efficacy of idarucizumab, and no dosing adjustments are required. Potential shortfalls of idarucizumab include possible rebound anticoagulation due to redistribution of dabigatran from the extravascular to intravascular space and the formation of antibodies against idarucizumab, which may limit recurrent use. However, the reversal effects of idarucizumab seem to be sustained, because as dabigatran redistributes from the extravascular to intravascular space it is immediately neutralized by idarucizumab, maintaining a high-diffusion gradient out of the extravascular space. Since the dissociation rate of idarucizumab from dabigatran is $>$260 h, the neutralization effect is long-lasting

[174]. However, re-anticoagulation with dabigatran is possible within a short time frame. In healthy volunteers, therapeutic anticoagulation with dabigatran was achieved 24 h after idarucizumab administration. Additionally, when these dabigatran-exposed volunteers were given a repeat dose of idarucizumab 2 months after initial administration, the same dose effectively neutralized dabigatran, suggesting minimal immunogenicity to the drug [172].

Prothrombin Complex Concentrates (PCC) The best available evidence for the efficacy of PCC in reversing the anticoagulation effect of DTIs includes animal studies [158, 175–177], trials with healthy volunteers [135, 138, 178], and in vivo investigations [168, 169, 179]. Several preclinical models have shown that 4-factor PCC (Beriplex/Kcentra) can reduce hematoma growth, and improve bleeding time, hemostasis, and mortality in dabigatran-exposed animals [158, 175, 177, 179]. Only one study failed to show improved hemostasis using PCC or aPCC. In this study, administration of 4-factor PCC (Octaplex) or aPCC to dabigatran-fed mice did not reduce the amount of blood volume loss after tail transection [176]. However, overall, preclinical investigations support a reduction of hemorrhage in dabigatran-exposed animals treated with higher PCC doses [158, 175, 177].

There are several animal and healthy volunteer studies suggesting that PCC can correct dabigatran-induced laboratory parameters of coagulopathy [135, 138]. In a small prospective, randomized cross-over study of healthy human volunteers, 4-factor PCC (Kanokad) corrected dabigatran-induced prolongation of endogenous thrombin potential in a concentration-dependent fashion [138]. In a porcine polytrauma model using dabigatran, PCC (Beriplex/Kcentra, Cofact, Prothromplex NF, Octaplex, Bebulin, and Profilnine) significantly reduced dabigatran-induced prolongation of the PT, thromboelastography clotting time, and clot formation time by 80–90 %. However, without prior fibrinogen supplementation, PCC had no effect on the aPTT [168, 169]. In a rabbit kidney injury model, PCC (Beriplex/Kcentra) increased peak thrombin generation and shortened the PT in a dose-dependent fashion, whereas it had no effect on the aPTT [177].

However, other studies have failed to show that PCC can correct dabigatran-induced laboratory abnormalities. Tail bleeding time, thrombin time, and the aPTT were significantly reduced by PCC (Octaplex) in combination with rFVIIa in a mouse model; however, administration of PCC alone had no effect on these coagulation parameters [176]. In an in vitro study of dabigatran, 4-factor PCC (Cofact) had no effect on abnormalities in clotting time [180]. In the only human prospective cross-over in vivo study, 4-factor PCC (Cofact; 50 IU/kg) did not correct dabigatran-induced abnormalities in thrombin time, endogenous thrombin potential, ecarin clotting time, or aPTT [135].

Overall, PCC seems to reverse dabigatran-induced prolongation of thrombin generation, clot formation, and clotting time in animal models, but the effect is dose-dependent and variable, and little data exist to support its efficacy in humans [166, 168, 169, 176–179].

Activated Prothrombin Complex Concentrates Because of the variable effect of PCC on dabigatran-induced laboratory abnormalities, interest has increased in aPCC (i.e., FEIBA or factor eight inhibitory bypassing activity) as a reversal agent. In one study, while 4-factor PCC and rFVIIa had minimal effect on dabigatran-induced abnormalities in clotting time in an in vitro model, aPCC (1.8 IU/ml) normalized the clotting time by one-third [180]. Other studies have demonstrated that aPCC corrects endogenous thrombin potential lag time, thrombin generation, thromboelastography clotting time, and clot formation time in a dose-dependent manner [138, 166, 168, 176, 178]. One case report noted restoration of hemostasis after aPCC dosing for dabigatran-associated pericardial hemorrhage [181]. Two case reports described the use of aPCC to reverse dabigatran prior to emergency surgery (hernia repair and gallbladder drainage) and found minimal intraoperative blood loss [182, 183]. Another case series ($n = 4$) and a case report of patients with life-threatening dabigatran-associated bleeding (including two with subdural hematoma and one with intraparenchymal hemorrhage) describe adequate hemostasis following aPCC administration [143, 184]. Each of these anecdotal cases used different measures of clinical or laboratory hemostasis and the time from dabigatran administration to hemorrhage onset was highly variable. Doses of aPCC in the aforementioned case reports ranged from 26 to 100 units/kg [181–184]. However, the patient that received only 26 units/kg required an additional 16 units/kg due to the concern for ongoing bleeding [181]. The European Heart Rhythm Association and others have suggested a dose of 50 units/kg of aPCC for dabigatran-associated bleeding [185, 186]. Because the risk of thrombotic events and DIC increases with higher doses, 50 units/kg of aPCC is likely a reasonable dose, although further studies are required. There are no studies directly comparing the efficacy of PCC to aPCC for improving hemostasis or reducing hematoma growth in dabigatran-exposed animals or humans.

PCC and aPCC administration may be associated with serious side effects such as arterial and venous thrombosis in 0.7–10 % of patients, immediate allergic reactions, and heparin-induced thrombocytopenia (depending on the heparin content of the PCC). Because of a higher prothrombin and thrombin content, and the presence of

activated clotting factors in aPCC, the risk of thrombosis is expected to be higher with aPCC than with PCC [85, 93, 99, 104, 187–194].

Fresh Frozen Plasma FFP administered to dabigatran-fed mice after induction of intraparenchymal hemorrhage did not have any effect on 24 h mortality. It prevented hematoma expansion at the lower dabigatran dose (4.5 mg/kg), but had no effect at higher doses (9 mg/kg) [158]. In two case series, emergency treatment with FFP was part of a complex reversal strategy in dabigatran-associated intracranial hemorrhage. In both of these studies, patients received a variety of reversal products, including rFVIIa and hemodialysis, making it difficult to discern if FFP had any appreciable effect [195, 196].

Recombinant Factor VIIa Only one study (in an in vitro dabigatran mouse model) has demonstrated improved hemostasis and increased thrombin generation after rFVIIa administration [179]. Other studies have not supported the use of rFVIIa as a reversal agent. Recombinant Factor VIIa failed to reduce intraparenchymal hematoma growth and mortality in a dabigatran-fed mouse model [158]. In another mouse model, dabigatran-induced blood loss and bleeding time were not affected by rFVIIa, though there was a reduction in aPTT [176]. In a healthy volunteer study, rFVIIa added to dabigatran-containing plasma decreased lag time of thrombin formation and time to peak thrombin formation, but did not increase the thrombin peak above baseline [138].

Hemodialysis Due to its low-protein binding (35 %) and high rate of renal excretion, dabigatran can be removed by hemodialysis [197]. Evidence of the efficacy of hemodialysis in dabigatran reversal is limited to small single-center trials without any data on intracranial hemorrhage patients or their long-term outcome. One study investigated dabigatran clearance in seven clinically stable patients with end stage renal disease requiring hemodialysis. After 4 h of hemodialysis, plasma clearance of dabigatran was 48.8 % at a blood flow rate of 200 ml/min, 57–58.5 % at 300 ml/min, and 59.3 % at 400 ml/min. Four to 8 h after discontinuation of hemodialysis, an increase of dabigatran plasma concentration (7.2–15.5 %) was noted. The aPTT and thrombin time were markedly reduced [198]. In another single-center study, 35 patients with mild, moderate, severe, or end stage renal impairment received a single dose of 150 mg dabigatran. Renal excretion of dabigatran was dependent on the degree of renal failure. About 62–68 % of dabigatran was eliminated after 4 h of hemodialysis [197]. In two case series reporting 5 and 7 patients, respectively, hemodialysis was included as part of the management of dabigatran-associated hemorrhage. Hemodialysis was executed in 2–4 h intermittent, sessions or as continuous venovenous hemodiafiltration (CVVHDF) resulting in a reduction of dabigatran levels by 45–77 % after 4 h. Initiation of CVVHDF after intermittent hemodialysis attenuated the rebound effect in one patient and contributed to a reduction in dabigatran concentrations by 81 % over 30 h. In each series, two patients died [195, 196]. Others have noted that the large volume of distribution in the terminal phase of dabigatran elimination may necessitate continuous hemodialysis to prevent rebound coagulopathy [199].

Overall, hemodialysis and CVVHDF appear to be effective strategies for emergency dabigatran removal at high blood flow rates of 200–400 ml/min, and dialysate flow rates of 700 ml/min for at least 4 h, followed by continuous renal replacement therapy. Monitoring for the rebound effect of dabigatran within four to 8 h after hemodialysis is recommended.

Certain risks should be considered when using hemodialysis in patients with intracranial hemorrhage. First, there is the potential for exacerbation of cerebral edema by increasing brain water content through rapid urea reduction in the serum, which can lead to elevated intracranial pressure. Second, there is a risk of reduction of cerebral perfusion due to systemic hypotension. Even small fluctuations in blood pressure or electrolyte shifts may not be tolerated in an injured brain that does not auto-regulate appropriately [200]. One way to counter these risks is to use continuous renal replacement therapy and reduce blood and dialysate flow rates. Unfortunately, high flow rates are needed to effectively eliminate dabigatran. In patients with intracranial hemorrhage associated with midline shift, mass effect, or edema, dialysis may not be well tolerated [201–204].

Investigational reversal agents Other agents under development (Table 4) to reverse the direct thrombin inhibitors, such as Aripazine, and modified thrombin molecules are discussed in Online Appendix 2.

Idarucizumab should be the first-line agent for dabigatran reversal in the context of intracranial hemorrhage. When not available, 4-factor PCC and aPCC may be used based on data that suggest these agents can improve hemostasis and correct dabigatran-induced laboratory abnormalities in animal models and healthy volunteers. Because of the risks of dialysis disequilibrium, cerebral edema, and elevated intracranial pressure, hemodialysis should be considered primarily in patients with continued clinically significant bleeding after idarucizumab administration if the patient can tolerate high flow hemodialysis. Redosing idarucizumab for ongoing clinically significant bleeding may also be an option. There is not enough evidence for the efficacy of FFP or rFVIIa to support their use in DTI reversal.

Recommendations for Direct Thrombin Inhibitor Reversal

(1) We recommend discontinuing direct thrombin inhibitors when intracranial hemorrhage is present or suspected. (Good Practice statement)
(2) We recommend assessing the time and amount of the last ingested dose, renal function, and possible medication interactions to assist in estimating the degree of anticoagulation exposure. (Good Practice statement)
(3) We suggest that pharmacological reversal of direct thrombin inhibitors should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing. (Conditional recommendation, low-quality evidence)
(4) We suggest administering activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of ingestion of an oral direct thrombin inhibitor. (Conditional recommendation, very low-quality evidence)
(5) We recommend administering idarucizumab (5 g IV in two divided doses) to patients with intracranial hemorrhage associated with dabigatran if:
    (a) the dabigatran was administered within a period of 3–5 half-lives and there is no evidence of renal failure (Strong recommendation, moderate quality of evidence) or
    (b) there is renal insufficiency leading to continued drug exposure beyond the normal 3–5 half-lives (Strong recommendation, moderate quality of evidence)
(6) We suggest administering aPCC (50 units/kg) or 4-factor PCC (50 units/kg) to patients with intracranial hemorrhage associated with direct thrombin inhibitors if idarucizumab is not available or if the hemorrhage is associated with a DTI other than dabigatran if:
    (a) the direct thrombin inhibitor was administered within a period of 3–5 half-lives and there is no evidence of renal failure (Conditional recommendation, low-quality evidence) or
    (b) there is renal insufficiency leading to continued drug exposure beyond the normal 3–5 half-lives. (Conditional recommendation, low-quality evidence)
(7) In patients with dabigatran-associated intracranial hemorrhage and renal insufficiency or dabigatran overdose, we suggest hemodialysis if idarucizumab is not available. (Conditional recommendation, low-quality data)
(8) In patients with dabigatran-associated intracranial hemorrhage who have already been treated with idarucizumab, PCC, or aPCC, with ongoing evidence of clinically significant bleeding, we suggest consideration of redosing idarucizumab and/or hemodialysis. (Conditional recommendation, low-quality evidence)
(9) We recommend against administration of rFVIIa or FFP in direct thrombin inhibitor-related intracranial hemorrhage. (Strong recommendation, low-quality evidence)

Unfractionated Heparin

Unfractionated heparin (UFH) is a parenteral anticoagulant that indirectly inhibits Factor Xa and Factor IIa via antithrombin. Heparin-associated intracranial bleeding occurs in 0–0.1 % of patients on intravenous heparin therapy for non-neurological indications [205–208]. Although there are many studies evaluating the pharmacological neutralization of heparin, few specifically address the reversal of heparin after intracranial hemorrhage.

Unfractionated Heparin Reversal Agents

Protamine Protamine sulfate is a basic protein derived from fish sperm. It binds heparin and forms a stable salt. There are no prospective studies assessing the utility of protamine sulfate in reversing the anticoagulant effects of UFH in intracranial hemorrhage. However, several animal studies demonstrate that protamine completely neutralizes heparin activity (aPTT, anti-factor Xa, and thromboelastography R levels) and decreases heparin-induced blood loss [209–217]. Additionally, considerable data exist on heparin reversal with protamine in vitro [218–220] and in other patient populations [215, 221–223]. In a randomized, double-blind, cross-over study of 15 healthy volunteers, protamine (1 mg per 100 IU UFH) led to near complete reversal of aPTT, thrombin time, and anti-Xa levels [224]. In a trial of 201 patients undergoing cardiac catheterization with heparin, 92 % demonstrated effective reversal of the aPTT with protamine (1 mg per 100 IU UFH) [221]. Additionally, in a small randomized trial of patients undergoing off-pump coronary bypass surgery, protamine (1 mg per 100 IU UFH) was associated with a significant reduction in post-operative bleeding, transfusion requirement, and pericardial effusion compared to no protamine [225]. In another randomized, double-blind study of saline versus protamine for heparin reversal in 120 peripheral vascular surgery patients, plasma heparin concentration, aPTT, and activated clotting time were significantly lower

in those receiving protamine compared to saline. However, the total surgical blood loss did not differ significantly between groups [226].

There are little data to support the reversal of prophylactic doses of heparin. In a randomized, controlled trial of 115 patients with acute deep vein thrombosis treated with equal doses of UFH via IV or SQ route, intermittent subcutaneous administration of heparin failed to maintain the aPTT in the therapeutic range [227]. Therefore, reversal of intermittent low-dose subcutaneous heparin, as it is employed for venous thromboembolism pharmacoprophylaxis, is not recommended. However, if subcutaneous administration prolongs the aPTT, reversal may be reasonable.

In general, 1 mg of protamine neutralizes 80–120 units of UFH [228, 229]. The half-life of protamine is approximately 7 min [230], whereas the half-life of UFH is 60–90 min [231]. Therefore, the dosing of protamine should account for the amount of UFH infused over the preceding 2–3 h [218, 232]. For simplicity and expediency, a dose of 1 mg of protamine per 100 units UFH administered over the last 2–3 h is the preferred dosing [233]. Subsequent administration is generally guided by the aPTT [234, 235]. Protamine should not be administered at a rate greater than 20 mg/min and no more than 50 mg should be given over any 10-min period [236, 237]. Repeat dosing of protamine may be necessary to fully reverse the anticoagulant effects of UFH (due to its short half-life and rapid clearance); however, excessive protamine administration may exacerbate bleeding, since protamine itself is a weak anticoagulant.

Adverse reactions (anaphylaxis, hypotension, bradycardia, and bronchoconstriction) are dose-dependent but can be attenuated by slowing the infusion [218, 238–240]. Patients who have previously received certain formulations of insulin (e.g., neutral protamine Hagedorn, or NPH), have undergone vasectomy, or have a known allergy to fish may be at increased risk of adverse reactions, as prior exposure can lead to antibodies against protamine sulfate. Patients considered at risk for allergy may be pre-treated with corticosteroids and histamines, although this has not been shown to definitively decrease the risk of adverse effects and should not delay reversal [241].

Other Reversal Agents Recombinant Factor VIIa has demonstrated efficacy in reversing UFH in animal studies and case reports, although it remains unknown if there are any benefits over the use of protamine [242–245].

Recommendations for Unfractionated Heparin Reversal

(1) We recommend discontinuing heparin infusions when intracranial hemorrhage is present or suspected. (Good Practice statement)

(2) We recommend urgently reversing anticoagulation in patients who develop intracranial hemorrhage during full dose heparin infusion. (Good Practice statement)

(3) We do not recommend routinely reversing prophylactic subcutaneous heparin. (Good Practice statement)

   (a) We suggest considering reversal of prophylactic subcutaneous heparin if the aPTT is significantly prolonged. (Good Practice statement)

(4) We recommend administering intravenous protamine sulfate to reverse heparin in the context of intracranial hemorrhage. (Strong recommendation, moderate quality evidence)

   (a) We recommend dosing protamine according to the dose of heparin infused over the preceding 2–3 h. (Strong recommendation, high-quality evidence)
   (b) We recommend dosing protamine sulfate at 1 mg for every 100 units of heparin given in the previous 2–3 h with a maximum single dose of 50 mg. (Strong recommendation, moderate quality evidence)
   (c) If the aPTT remains elevated, we suggest repeat administration of protamine at a dose of 0.5 mg protamine per 100 units of UFH. (Conditional recommendation, low quality of evidence)

Low-Molecular Weight Heparin (LMWH)

LMWHs bind and activate antithrombin, which inhibits coagulation factors Xa and IIa. LMWHs have more predictable pharmacokinetics and bioavailability than UFH [246]. Enoxaparin and dalteparin are FDA approved and available in the United States, while nadroparin and tinzaparin are only available outside the U.S. Danaparoid is a heparinoid with a similar mode of action to the LMWHs (Table 2).

LMWHs are indicated for the prophylaxis and treatment of deep vein thrombosis, acute pulmonary embolism, and unstable angina/non-ST segment elevation myocardial infarction (NSTEMI) [246]. Meta-analyses of randomized controlled trials examining differences in recurrent embolic events, major bleeding, and all-cause mortality between UFH and LWMH for the treatment of venous thromboembolism in the general population do not identify clear differences in recurrence rates or major bleeding. However, these studies did find that treatment with a LMWH is associated with significantly reduced mortality rates (RR

0.76, 95 % CI 0.59–0.98) when compared to UFH for venous thromboembolism treatment [247, 248]. Additionally, several multi-center randomized trials support the use of LWMH for venous thromboembolism prophylaxis in neurologically injured and critically ill patients [249–253].

The formulation and dosing of LMWH may affect bleeding risk. A Cochrane review of 19 studies compared subcutaneous LMWHs to intravenous infusions of UFH for the treatment of venous thromboembolism. The overall risk of bleeding was lower with the LMWHs among the total pooled cohort of 7124 patients (OR 0.57, 95 % CI 0.39–0.83), but only the studies evaluating tinzaparin demonstrated a significant reduction in major bleeding (OR 0.30, 95 % CI 0.12–0.73) [248]. Conversely, enoxaparin increased the risk of major bleeding (OR 1.14, 95 % CI 0.5–2.61), as did reviparin (OR 1.26, 95 % CI 0.49–3.19), though these results did not reach statistical significance. When given in prophylactic doses, there are little data to suggest LMWH impacts bleeding risk [254, 255].

Due to the reduced frequency of dosing, lower risk of heparin-induced thrombocytopenia, and overall safety profile of these agents, LMWHs are used routinely for venous thromboembolism treatment and prophylaxis in certain populations. However, given the lack of specific inhibitors for complete reversal of the LMWHs, it remains controversial whether LMWHs are preferable to UFH for therapeutic anticoagulation or even venous thromboembolism prevention in patients with critical neurologic illnesses, where the risk of intracranial hemorrhage is higher than in other populations.

Low-Molecular Weight Heparin Reversal Agents

Protamine Currently, there is no reversal agent specific to LWMHs. Protamine is widely utilized; however, its ability to reverse LMWH varies significantly, based primarily on the molecular weight and the sulfate charge density of the specific formulation of LMWH. For example, protamine is more effective at reversing highly sulfated tinzaparin as compared to dalteparin or enoxaparin [256, 257]. Moreover, although it can successfully neutralize the anti-IIa activity of LMWH, it is only partially effective at reversing anti-Xa activity. In an in vitro study of pooled plasma from subjects with normal coagulation profiles exposed to tinzaparin, protamine reversed 99 % of the anti-IIa effect and 40 % of the anti-Xa effect. In enoxaparin-exposed plasma, only 64 % of the anti-IIa effect and 35 % of the anti-Xa effect was reversed [256]. Other studies have found similar neutralization of tinzaparin-induced anti-Xa and anti-IIa activity with protamine [258]. One study found that protamine improves factor Xa activity in enoxaparin-exposed plasma, but only to approximately 40 % of normal levels [259]. Danaparoid and fondaparinux are not effectively reversed with protamine given their increased relative anti-Xa activity [256].

Despite its limited ability to reverse anti-Xa activity, protamine can improve hemostasis. This may be partly because protamine decreases the tissue factor pathway inhibition caused by LMWH [260, 261]. Indeed, some clinical studies have failed to detect a correlation between bleeding tendency and anti-Xa activity [262]. In a randomized, double-blind trial of 194 patients with acute venous thromboembolism, there was no relationship between those patients with the highest anti-Xa levels and bleeding complications [263]. In animal models, protamine has been shown to reduce LWMH-induced bleeding, despite having limited effects on the correction of the anti-Xa and anti-IIa activities [264, 265]. In a small case series including 14 patients with active bleeding on therapeutic doses of enoxaparin, protamine stopped hemorrhage expansion in 64 % of patients, despite little effect on anti-Xa levels [266]. In this study, 36 % (5/14) of patients continued to bleed despite protamine, although it was frequently under-dosed [266]. However, another case report describes continued enoxaparin-related intracranial bleeding associated with elevated anti-Xa levels, despite multiple doses of protamine, underscoring its potentially incomplete efficacy at reversing the effect of LMWHs [267].

The typical dose of protamine is 1 mg per 1 mg of enoxaparin administered within the previous 8 h, with a maximum single dose of 50 mg [237]. If greater than 8 h have elapsed since enoxaparin administration, a dose of 0.5 mg of protamine per 1 mg of enoxaparin is suggested [262, 265, 266, 268]. For tinzaparin and dalteparin, 1 mg of protamine should be administered for every 100 anti-Xa units of LMWH [224, 269, 270]. For ongoing bleeding, an additional dose of 0.5 mg per every 100 anti-Xa units can be considered [224, 258].

Recombinant Factor VIIa rFVIIa may have some efficacy in reversing LMWH. One clinical study found that factor VIIa levels are reduced by 65 % within an hour of enoxaparin administration [271]. Ex vivo studies using thromboelastography suggest that rFVIIa may reverse the effects of enoxaparin [272]. Bleeding time and blood loss were also reduced in tinzaparin-treated rats who received rFVIIa [243]. Conversely, rFVIIa failed to demonstrate an improvement in bleeding time in a LMWH-treated rabbit model [273]. Several case reports have described rFVIIa use in LMWH-related hemorrhage and suggest potential utility in patients with either obesity or renal insufficiency [274–281]. Due to the high risk of both venous and arterial thrombosis, rFVIIa should be reserved for patients with a contraindication to protamine or LMWH-related bleeding refractory to protamine.

Other Reversal Agents FFP, PCC, and aPCC have not been shown to improve anti-Xa or anti-IIa activity in plasma exposed to either enoxaparin or tinzaparin and are therefore not recommended for the reversal of LWMH [256] (see Table 4 and Online Appendix 2 for further information on investigational reversal agents).

Hemodialysis The LMWHs have increased bioaccumulation in the setting of renal insufficiency [282, 283] and several case studies have indicated a possible increased risk of bleeding in this population [282–287]. However, a meta-analysis of randomized controlled trials of LWMH (given predominantly in prophylactic doses) in hemodialysis patients did not find a significant difference in bleeding or thrombosis compared to UFH [288].

Insofar as whether hemodialysis can be used to reverse the effects of LMWH, one study found neither accumulation nor removal of LMWH (nadroparin) during continuous venovenous hemofiltration, suggesting that hemodialysis may not be an effective acute reversal strategy [289]. However, in a pharmacokinetic study, dalteparin exhibited a zero-order elimination process over 240 min of dialysis [290]. The clearance of various LMWHs via hemodialysis likely depends on their molecular size and other drug-specific factors, and more data are required before renal replacement therapy can be recommended as a routine reversal strategy for LMWH.

Heparinoids Danaparoid: Danaparoid is a combination of glycosaminoglycans (84 % heparan sulfate, 12 % dermatan sulfate, and 4 % chondroitin sulfate) that is derived from the same substance in porcine intestinal mucosa as unfractionated and low-molecular weight heparins. It is not available in the US, but remains available in other countries. It inhibits factors Xa and IIa in a ratio much higher than UFH (22–28:1) by an antithrombin-mediated mechanism [291, 292]. The anti-Xa activity of danaparoid on a milligram basis is approximately tenfold less than that of LMWH [293].

Major bleeding occurs in 2.5–3.1 % of danaparoid-treated patients [294–296]. In ex vivo studies, danaparoid was not reversed by protamine, PCC, FFP, or aPCC. However, rFVIIa improved endogenous thrombin potential by 40 % and decreased anti-Xa activity by 16 % [256]. Plasmapheresis has also been used for emergent reversal of danaparoid, though its efficacy is not established [297]. As no other reversal options exist, rFVIIa may be considered for danaparoid-related intracranial hemorrhage. New emerging reversal agents may have a role in the future (see Table 4 and Online Appendix 2) [174].

Recommendations for Low-Molecular Weight Heparin Reversal

(1) We recommend discontinuing LMWH when intracranial hemorrhage is present or suspected. (Good Practice statement)
(2) We recommend reversing LMWH in patients with intracranial hemorrhage receiving therapeutic doses of LMWH. (Strong recommendation, moderate evidence)
(3) We recommend protamine administration by slow intravenous injection over a period of about 10 min according to the following dosing:
    (a) For enoxaparin: If enoxaparin was given within 8 h, protamine sulfate should be administered at a dose of 1 mg per 1 mg of enoxaparin administered (up to a maximum single dose of 50 mg). If enoxaparin was given within 8–12 h, a dose of 0.5 mg of protamine per 1 mg of enoxaparin should be administered. After 3–5 half-lives have elapsed, protamine is probably not needed. (Strong recommendation, moderate quality evidence)
    (b) For dalteparin, nadroparin, and tinzaparin: Dose protamine at 1 mg per 100 anti-Xa units of LMWH administered in the past 3–5 half-lives of the drug, up to a maximum single dose of 50 mg. (Strong recommendation, moderate quality evidence)
    (c) If life-threatening bleeding persists, or the patient has renal insufficiency, we suggest redosing protamine (0.5 mg of protamine per 100 anti-Xa units or per 1 mg of enoxaparin). (Conditional recommendation, very low-quality evidence)
(4) We suggest considering recombinant Factor VIIa (90 mcg/kg IV) if protamine is contraindicated. (Conditional recommendation, very low-quality evidence)
(5) We recommend against the reversal of LMWH in patients with intracranial hemorrhage receiving prophylactic dosing of LMWH. (Good Practice statement).
(6) We suggest against reversing danaparoid with protamine. (Conditional recommendation, low-quality evidence)
(7) We suggest reversing danaparoid with recombinant Factor VIIa (90 mcg/kg IV once) in the context of intracranial hemorrhage. (Conditional recommendation, very low-quality evidence)

(8) We suggest against using FFP, PCC, or aPCC to reverse LMWH. (Conditional recommendation, low-quality evidence)

Pentasaccharides

Pentasaccharides, including fondaparinux, idraparinux, and idrabiotaparinux, have been studied for the treatment of venous thromboembolism, superficial leg vein thrombosis [298], and acute coronary syndrome [299]. They have also been investigated for the prevention of venous thromboembolism in moderate to high risk populations, including patients undergoing major gynecologic, urologic, or orthopedic surgeries [299–301]. Fondaparinux is the only pentasaccharide available in the United States. It binds antithrombin and potentiates its inhibition of free factor Xa, preventing formation of the prothrombinase complex [302, 303]. Unlike heparin, fondaparinux is associated with a minimal risk of heparin-induced thrombocytopenia (HIT). The incidence of major bleeding in patients receiving full anticoagulant doses of fondaparinux is 1.3 % [304].

Pentasaccharide Reversal Agents

Prothrombin Complex Concentrates As with other antithrombotics, pentasaccharides should be held in the context of intracranial hemorrhage. Unlike for LMWH and heparin, protamine sulfate does not reverse pentasaccharides [305, 306]. Although there are no direct reversal agents for fondaparinux, small studies suggest that aPCC may normalize thrombin-generation time, which is prolonged in the context of fondaparinux. In an in vitro study of recombinant rFVIIa, PCCs, and aPCCs in healthy volunteers exposed to fondaparinux, PCCs demonstrated some normalization of thrombin-generation time in a dose-dependent fashion, while rFVIIa showed no efficacy at any of the dosing levels. Activated PCC at a dose of 20 IU/kg effectively normalized thrombin-generation time [307]. In a study of rats exposed to fondaparinux, aPCC was found to reduce bleeding times and hemorrhage volume, while rFVIIa normalized laboratory coagulation studies but had no effect on bleeding time or hemorrhage volume [308].

Animal studies suggest that PCC may also be efficacious in fondaparinux reversal. In a rabbit model, PCC reduced fondaparinux-related blood loss and normalized thromboelastography parameters of coagulopathy [309].

Recombinant Factor VIIa Recombinant factor VIIa reverses some laboratory markers of coagulopathy after fondaparinux administration [310–312]. Several studies of fondaparinux or idraparinux-exposed healthy volunteers have demonstrated that rFVIIa corrects thrombin-generation time [310, 311, 313], clotting time [312, 314], aPTT, PT [311], and thromboelastography measures of coagulopathy [272]. However, it only partially reverses fibrinolysis [312, 314], may not reduce the lag time in thrombin activation induced by higher doses of fondaparinux [313], and has no effect on factor Xa assays [272]. One study found that rFVIIa incompletely reversed the inhibitory effects of fondaparinux on thrombin generation [313].

None of the aforementioned studies examined hemostasis or the clinical efficacy of rFVIIa in pentasaccharide-exposed subjects. One retrospective study examined patients with acute coronary syndrome or venous thromboembolism, who were treated with fondaparinux and had a 10 % decrease in hematocrit, intracranial bleeding, or cardiovascular collapse. Interventions were multiple and not standardized and included PCC administration, platelet transfusion, direct hemostatic control, and administration of rFVIIa (90 mcg/kg). Laboratory markers for clinical efficacy included measurements of the PT, aPTT, anti-Xa activity, and thrombin-generation time. Hemostasis was attributed to rFVIIa in 50 % ($n = 8$) of the patients [315].

Based on limited data in healthy subjects and retrospective case series, it appears that both aPCC and rFVIIa may be able to normalize some laboratory measures of coagulopathy attributed to pentasaccharides. Because two studies found aPCC led to superior normalization of laboratory values and improved bleeding time compared to rFVIIa, we recommend aPCC over rFVIIa for the reversal of pentasaccharides [307, 308].

Recommendations for Pentasaccharide Reversal

(1) We recommend discontinuing pentasaccharides when intracranial hemorrhage is present or suspected. (Good Practice statement)
(2) We suggest reversing pentasaccharides in patients with intracranial hemorrhage receiving full therapeutic doses. (Good Practice statement)
    (a) We suggest administration of aPCC (20 IU/kg) for reversal of pentasaccharides. (Conditional recommendation, low-quality evidence)
    (b) If aPCC is contraindicated or not available, we suggest administration of rFVIIa (90 mcg/kg). (Conditional recommendation, low-quality evidence)
    (c) We recommend against protamine for reversal of pentasaccharides. (Strong recommendation, low-quality evidence)

(3) In intracranial hemorrhage patients receiving pentasaccharides for venous thromboembolism prophylaxis, we suggest against reversal unless there is evidence of bioaccumulation or impaired clearance. (Good Practice statement)

Thrombolytics (Plasminogen Activators)

Plasminogen activators convert plasminogen to plasmin, which can degrade fibrinogen and fibrin and cause thrombolysis. They are categorized as fibrin-non-selective and fibrin-selective. Fibrin-non-selective plasminogen activators degrade both fibrinogen and fibrin, producing an anticoagulant state that, in addition to thrombolysis, can promote hemorrhage. Non-selective agents include urokinase plasminogen activator and streptokinase. Fibrin-selective agents lead to primarily fibrin degradation because the plasminogen activators convert plasminogen to plasmin more effectively in the presence of fibrin than fibrinogen. Selective agents include recombinant tissue plasminogen activator (rtPA), and the related molecules reteplase and tenecteplase (Table 2).

Depending on the dose, plasminogen activators can produce breakdown of fibrinogen accompanied by low-serum fibrinogen levels and elevated fibrin degradation products [316–318]. Following administration of 100 mg of alteplase, there is a 16–36 % decrease in circulating fibrinogen [319, 320]. Severe decreases in fibrinogen after alteplase occur in approximately 5 % of stroke cases [321]. In a controlled trial, 8 of 73 (11 %) patients receiving 1.25 mg/kg alteplase over 3 h experienced a decrease in fibrinogen to below 100 mg/dL [320]. Hypofibrinogenemia slowly corrects over 24 h in many patients [317, 322], but in some cases can be decreased by 87 % from baseline at 24 h [321]. Fibrinogen degradation has been shown to be a strong predictor of parenchymal hemorrhage following rtPA administration for ischemic stroke. In one prospective study of 157 ischemic stroke patients who received rtPA, decreased fibrinogen and increased fibrin degradation products were significantly associated with an increased risk of a parenchymal hematoma [317, 322].

Thrombolytic agents can also produce an antiplatelet effect by plasmin-mediated cleavage of fibrinogen, and cleavage of platelet GPIIIa and GP1b causing inhibition of platelet function [323, 324]. Plasminogen activators have been shown to reduce platelet aggregates and fibrinogen binding to GPIIb/IIIa; however, platelet parameters can normalize 12 h after exposure [316].

Indications for thrombolytics include acute ischemic stroke [325–327], massive pulmonary embolus [328], and ST-elevation myocardial infarction [329], though other off-label uses exist [330–335]. Third generation thrombolytic agents (reteplase, tenecteplase) are engineered to have longer half-lives, which has therapeutic advantages in myocardial infarction [336–341]. However, third generation thrombolytics have not been proven safe or efficacious for use in acute ischemic stroke [342].

Symptomatic intraparenchymal hemorrhage with mass effect occurs in approximately 2–7 % of patients with ischemic stroke who receive intravenous alteplase [325, 343–346]. Rates of intracranial hemorrhage are much lower (0.4–0.9 %) when thrombolytics are used for indications other than ischemic stroke [347]. Symptomatic intraparenchymal hemorrhage remains a devastating complication of thrombolytic therapy with hematoma expansion occurring in up to 40 % of patients and mortality rates ranging from 9 to 61 % at 3 months [325, 348–350].

Thrombolytic Reversal Agents

Thrombolytic infusions should be stopped immediately in any patient with acute clinical changes suggestive of intracranial hemorrhage, and hemorrhage should then be confirmed by non-contrast head CT. Because fibrinogen levels slowly correct over days, and in some cases can still be very low at 24 h [321, 349], and because the longer *terminal* half-lives of alteplase and tenecteplase (as compared to their *plasma* half-lives) means that effects may be present for several hours after administration [321], it is reasonable to administer reversal agents during the first 24 h after thrombolytic exposure. While reversal is indicated in patients with symptomatic deterioration related to intracranial hemorrhage and/or in those with large intraparenchymal hemorrhages with mass effect, patients with small, asymptomatic hemorrhagic conversion of an ischemic stroke may be conservatively managed on a case by case basis after weighing the risks and benefits of reversal agent administration.

Cryoprecipitate In a multi-centered, retrospective study of 128 patients with symptomatic intracranial hemorrhage following treatment with alteplase for ischemic stroke, a fibrinogen level <150 mg/dL was the only significant factor associated with hematoma expansion [350]. Additionally, considering the observed association of low-fibrinogen levels and increased risk of parenchymal hematoma following alteplase administration for ischemic stroke, it is reasonable to replace fibrinogen in thrombolytic-associated intracranial hemorrhage [317]. Cryoprecipitate contains fibrinogen (200 mg/unit), Factor VIII, fibronectin, factor XIII, and von Willebrand Factor. Ten units of cryoprecipitate will raise fibrinogen levels by roughly 70 mg/dL in a 70 kg patient [351, 352]. In the past fibrinogen level targets >100 mg/dL have been used, [353] though some guidelines now recommend a higher

target of 150 mg/dL [354, 355]. Additionally, one multi-centered study found that thrombolytic-associated intracranial hemorrhage expansion was significantly more likely with fibrinogen levels <150 mg/dL. Therefore, a target ≥ 150 mg/dL is reasonable [350]. In general, use of fibrinogen as a marker for continued administration of cryoprecipitate may be useful, although there are no case series or clinical trial data to guide this practice [352].

Despite the association of low-fibrinogen levels with intraparenchymal hemorrhage following thrombolytic administration, there are little outcome data supporting the utility of cryoprecipitate transfusion. A retrospective review of the "Get With the Guidelines—Stroke" database identified 20 patients (of 2362 total patients) with alteplase-associated symptomatic intraparenchymal hemorrhages. Of these, 11 received agents that could affect coagulation (7 FFP, 5 cryoprecipitate, 4 vitamin K, 3 platelets, and 1 aminocaproic acid). None of these products affected outcomes and continued bleeding occurred in 4 of 10 patients who had follow-up brain imaging [349]. A retrospective study of 45 patients with rtPA-associated symptomatic intracranial hemorrhage compared 19 patients who received clotting factors (18 received FFP and 7 received cryoprecipitate) to 26 who were conservatively managed. There were no differences in mortality, modified Rankin scores, or hematoma expansion [356]. Another retrospective study of 128 patients with symptomatic intracranial hemorrhage following IV thrombolysis for ischemic stroke found no significant association between cryoprecipitate, FFP, PCC or aminocaproic acid administration and hematoma expansion or outcome [350]. However, all of these studies were small and underpowered, observational, subject to prescriber bias, and examined heterogeneous reversal strategies [349, 350, 356].

Along with cryoprecipitate, FFP also contains fibrinogen (cryoprecipitate is derived from FFP that is thawed at 4 °C). However, a larger volume of FFP must be transfused due to lower concentrations of fibrinogen. Therefore, cryoprecipitate is suggested over FFP.

Antifibrinolytics Antifibrinolytics, such as ε-aminocaproic acid and tranexamic acid, competitively bind to plasminogen and block its conversion to plasmin, thereby inhibiting fibrin degradation. While antifibrinolytics have a theoretical advantage over cryoprecipitate in regards to lower cost (particularly for the intravenous route), lower infection risk, and shorter administration time (since cryoprecipitates must be thawed [357]), there is very little data to support their efficacy in thrombolytic-associated intraparenchymal hemorrhage. A single case report of tranexamic acid (1.675 g) given within 3 h of alteplase infusion in a Jehovah's Witness patient found no hemorrhage expansion [358]. A retrospective review of 19 patients described one patient with alteplase-associated intraparenchymal hemorrhage who received ε-aminocaproic acid along with FFP, cryoprecipitate, and platelets. Hematoma expansion could not be assessed because a follow-up head CT was not performed and the patient later died [349]. A retrospective study of 128 patients with symptomatic intracranial hemorrhage following intravenous rtPA for ischemic stroke identified only two patients that received aminocaproic acid [350]. Both survived to hospital discharge and neither had hematoma expansion.

Platelet Transfusion Platelet transfusion for rtPA-associated intraparenchymal hemorrhage has been advocated by the American Heart Association/American Stroke Association, since platelet aggregation may be altered by plasminogen activators [352]. However, there is a dearth of data supporting the benefit of platelet transfusion in this context and it is unclear if the risks outweigh the benefits. One multi-centered, retrospective study of patients with symptomatic intracranial hemorrhage following intravenous rtPA found an association of platelet transfusion and increased rate of hematoma expansion. However, given the retrospective nature of this study, it is impossible to know if hematoma expansion led to platelet transfusion or if transfusion actually had a negative effect [350].

Hemodialysis Reteplase is the only thrombolytic agent that is metabolized by the kidney. There are no reported cases of reteplase-associated symptomatic intracranial hemorrhage managed with dialysis. Given its short plasma half-life (13–16 min), there appears to be no role for dialysis in the reversal of reteplase.

Recommendations for Thrombolytic Reversal

(1) We recommend discontinuing thrombolytic agents when intracranial hemorrhage is present or suspected. (Good Practice statement)
(2) We suggest using cryoprecipitate (10 units initial dose) in patients with thrombolytic agent-related symptomatic intracranial hemorrhage who have received a thrombolytic agent in the previous 24 h. (Conditional recommendation, low-quality evidence)
(3) In cases where cryoprecipitate is contraindicated or not available in a timely manner, we suggest using an antifibrinolytic agent (tranexamic acid 10–15 mg/kg IV over 20 min or ε-aminocaproic acid 4–5 g IV) as an alternative to cryoprecipitate. (Conditional recommendation, very low-quality evidence)
(4) We suggest checking fibrinogen levels after administration of reversal agents. If the fibrinogen is less than 150 mg/dL, we suggest administration of

additional cryoprecipitate. (Conditional recommendation, very low-quality evidence)

(5) It is unclear if platelet transfusion is useful and we cannot offer a recommendation at this time.

Antiplatelet Agents

Several classes of FDA-approved antiplatelet agents exist including cyclo-oxygenase inhibitors (COX-inhibitors), adenosine diphosphate (ADP) receptor inhibitors, phosphodiesterase inhibitors, glycoprotein IIB/IIIA (GP IIB/IIIA) antagonists, thromboxane receptor antagonists, and protease-activated receptor-1 antagonists (PAR-1). Commonly used agents are listed in Table 2. In general, ADP receptor inhibitors provide more potent antiplatelet effect than COX-inhibitors such as aspirin.

It remains controversial whether antiplatelet agents influence intracranial hemorrhage expansion or neurologic outcome. Several studies with various designs, sizes, and exclusion criteria have produced conflicting results. Some have reported that a pre-hospital antiplatelet regimen may be associated with hematoma expansion, an increased mortality rate, and poor functional outcome in spontaneous as well as traumatic intracranial hemorrhage [359–363], while other studies have failed to detect differences in outcome or hematoma growth [364–368]. Additionally, a pooled analysis of 14 randomized trials including approximately 28,000 patients found no difference in the rates of intracranial hemorrhage with GP IIb/IIIa inhibitors plus heparin compared to heparin alone [369]. Since it is unclear if antiplatelet use increases the incidence, morbidity, or mortality of intracranial hemorrhage, the utility of reversal agents is also unknown [370].

For reversible platelet inhibitors (see Table 2), once 3–5 half-lives of the antiplatelet agent have passed, normal platelet function is restored. For irreversible platelet inhibitors (see Table 2), after withdrawal of the agent, normal platelet function occurs only when new platelets are synthesized and enter the blood stream. Irreversible platelet inhibitors can also affect megakaryocytes and newly generated platelets. The average life span of a platelet is 8–20 days [371, 372]. Thus, the effects of irreversible platelet inhibitors can be long-lasting. Transfused platelets have a somewhat shorter half-life of approximately 58 h, depending on the length of time they have been stored [371].

Antiplatelet Reversal Agents

Platelet Transfusion Only one randomized trial of platelet transfusion in patients with intracranial hemorrhage was identified [373]. This prospective, double-blind, parallel, randomized, controlled trial enrolled 780 patients with acute hypertensive basal ganglia hemorrhages undergoing craniotomy and hematoma evacuation. Of these patients, those who had taken aspirin and were aspirin-sensitive (based on a platelet aggregation test), were randomized to receive no transfusion, 6 units of platelets before surgery, or 12 units of platelets (6 units before surgery and 6 units 24 h later). In those who received platelets, there was less intraparenchymal hemorrhage recurrence (14 vs. 35 %, $P = 0.02$) and lower post-operative hematoma volume (35 ± 20 cm [3] in treated groups versus 57 ± 20 cm [3] in the untreated group, $P = 0.001$). Additionally, those who received platelets had a significant reduction in mortality compared to those who did not (15.5 vs. 34.2 %, $P = 0.02$). Activities of daily living assessed at 6 months were improved by 15 % in the platelet transfusion group. The number of platelet transfusions (one or two) did not affect any outcomes. Patients who were aspirin-resistant at baseline and did not receive transfusion had similar outcomes to aspirin-naïve patients and better outcomes than aspirin-sensitive patients who did not receive a platelet transfusion.

Despite its positive results, this study has several limitations. First, the large number of subgroups leads to small numbers of patients in each group, and increases the risk of a type I error due to multiple comparisons. Second, the results may not be applicable to diverse populations, since all patients enrolled were Chinese and genetic differences may affect the risk of hemorrhage expansion and response to transfusion. In addition, routine craniotomy for small, deep, intraparenchymal hemorrhage (without shift or mass effect) has not been shown to change outcome in two large randomized, controlled trials and is therefore not the standard of care in North America and many other countries [374, 375].

A single-center prospective, observational study, examined patients with intraparenchymal hemorrhage and abnormal platelet function (as assessed by Verify Now®) and found that platelet transfusion within 12 h of spontaneous intraparenchymal hemorrhage (as compared to >12 h) was associated with smaller follow-up hemorrhage size (8.4 vs. 13.8 mL, $P = 0.04$). Platelet transfusion also increased the odds of independence (mRS < 4) at 3 months (55 vs. 0 %, $P = 0.01$) [376]. Platelet activity was significantly increased in all patients receiving transfusion. However, this study did not have a control group, the population included both aspirin and clopidogrel users, and a range of transfusion doses were given. Additionally, 16 % of patients had adverse events related to transfusion.

Several retrospective studies of both spontaneous intraparenchymal hemorrhage and traumatic brain injury patients exposed to a variety of different antiplatelet agents

(sometimes in combination) failed to show an impact of platelet transfusion on mortality, functional outcome, or intracranial hemorrhage growth [377–379]. In a systematic review of seven retrospective studies of antiplatelet-associated intracranial hemorrhage (in which more than half of the studies examined traumatic intracranial hemorrhage), the pooled in-hospital mortality for platelet transfusion in traumatic intracranial hemorrhage patients was 1.77 (95 % CI 1.00–3.13), whereas the pooled in-hospital mortality for platelet transfusion in primary intraparenchymal hemorrhage was 0.49 (95 % CI 0.24–0.98) [380]. The authors concede that the methodological limitations of the reviewed studies preclude any conclusions regarding the utility of transfusion. Further, the studies analyzed did not control for confounding variables between cohorts. Even with attempts to adjust for differences in baseline prognostic variables, it is probable that significant bias existed in the decision to transfuse platelets or not. Another retrospective study of 408 patients with traumatic intracranial hemorrhage (126 of whom received platelet transfusion with DDAVP and 282 who did not) found no difference in the risk of hematoma expansion or mortality between those who underwent transfusion plus DDAVP versus those who did not [381]. This study is limited by the fact that only 30 % of patients who received platelets and DDAVP had prior exposure to an antiplatelet agent. Furthermore, the transfusion group was significantly older, more hypertensive, and had significantly larger ICH volume. Because this was a retrospective study, transfusion may have occurred *after* hemorrhage expansion and results may be confounded both by indication and provider bias.

Studies addressing the ability of platelet transfusion to improve laboratory metrics of platelet function have yielded mixed results. Some studies have shown that platelet transfusion following aspirin-associated intraparenchymal hemorrhage increases platelet activity in vivo (using the Verify Now® platelet function assay with a cutoff of greater than 550 aspirin reaction units) [382–384]. Others have found that transfusion of one single-donor apheresis unit of platelets did not improve platelet function (also measured by the Verify Now® device) in 81 % of patients taking aspirin (325 mg daily) prior to traumatic intracranial hemorrhage [378]. Similarly, in vitro studies testing platelet aggregation after clopidogrel use reveal that approximately 40–60 % of platelets remain dysfunctional at steady state after platelet transfusion [385]. A major limitation of the aforementioned studies is that the accuracy of these laboratory metrics remains unclear. There are currently no studies utilizing the gold standard of light transmission platelet aggregation (optical aggregometry) to assess platelet function after transfusion for antiplatelet-associated intracranial hemorrhage. Furthermore, the correlations among hemostasis, functional outcomes, and platelet function assay measures remain largely understudied, particularly in the context of intracranial hemorrhage. The strengths and limitations of various platelet assays are provided in Online Appendix Table 1.

Platelet transfusion is associated with serious risks including transfusion-related acute lung injury, thrombosis, disseminated intravascular coagulopathy, hemolytic transfusion reactions, and transfusion-associated sepsis, among others [386]. In studies of patients with intraparenchymal hemorrhage, platelet transfusions were associated with a 14–16 % increase in adverse events such as hypotension, fever, cardiac and respiratory events, and decline in neurological status [377, 379, 387, 388]. Only one study found no increase in side effects associated with platelet transfusion [373]. Worldwide shortages of blood products, including platelets, may necessitate their allocation to patients with more established indications for transfusion.

Based on the limited evidence that antiplatelet use prior to intracranial hemorrhage actually has any impact on hemorrhage expansion or outcome, the lack of substantive data to suggest that platelet transfusion improves outcome, and the risks associated with platelet transfusion, the risk to benefit ratio does not appear to favor platelet transfusion in patients with antiplatelet associated intracranial hemorrhage who *will not* undergo a neurosurgical procedure.

Based on a single-randomized trial, platelet transfusion may be efficacious in patients with documented aspirin-related platelet dysfunction undergoing neurosurgery [373]. However, based on this trial, there does not appear to be a benefit of platelet transfusion for patients with aspirin resistance or normal platelet function undergoing a neurosurgical procedure. If platelet function tests are not available, it may be reasonable to transfuse platelets prior to neurosurgical procedures in intracranial hemorrhage patients exposed to aspirin, though there are little data to support this.

Because most NSAIDS have a short half-life, reversible effect, and low risk of hemorrhage, platelet transfusion has little role in NSAID-related intracranial hemorrhage. In the case of GP IIb/IIIa inhibitors eptifibatide and tirofiban, each drug overwhelmingly inhibits the GP IIb/IIIa receptors by several orders of magnitude, rendering platelet transfusion ineffective [389]. Although some have anecdotally advocated for platelet transfusion in abciximab-related hemorrhage, there is a dearth of data to support this practice. Because the half-lives of available GP IIb/IIIa inhibitors are short, simply stopping these drugs in the context of intracranial hemorrhage may be sufficient. The only available PAR-1 inhibitor (vorapaxar) is contraindicated in patients with a history of stroke, TIA, or intracranial hemorrhage [390, 391]. Due to its long terminal half-life (8 days) any transfused platelets would be inhibited.

If a platelet transfusion is given, it should ideally be administered after 3–5 terminal half-lives of the antiplatelet agent to avoid pharmacologic inhibition of the transfused platelets. The presence of active metabolites (as with clopidogrel) could lead to even longer platelet inhibition. We suggest an infusion of one single-donor apheresis unit (equivalent to 6 pooled units or one random donor unit per 10 kg of body weight) based on one randomized trial that demonstrated efficacy with this amount and no difference between one and two apheresis units [373].

The PATCH trial is a multi-center, randomized, controlled trial comparing platelet transfusion within 6 h of ictus to standard care in patients with spontaneous intraparenchymal hemorrhage exposed to aspirin, dipyridamole, and/or clopidogrel [392]. Results of this study should provide more definitive evidence regarding the utility of platelet transfusion in antiplatelet-associated intracranial hemorrhage.

DDAVP Desmopressin (DDAVP) is an analog of vasopressin with very little vasopressor activity. It increases the endothelial release of large factor VIII: von Willebrand factor multimers and may also increase platelet membrane glycoprotein expression, thereby promoting platelet adhesion to the endothelium [393–395]. DDAVP has been shown to reduce bleeding time and normalize hemostasis in patients with uremic platelets undergoing surgery [396]. Additionally, uremic patients exposed to aspirin have also been found to have improved platelet function (as measured by collagen/epinephrine-closure time) following DDAVP administration [397]. Within healthy populations on aspirin/COX-1 inhibitors or ADP receptor inhibitors, DDAVP demonstrated an improvement in several tests of platelet function (bleeding time, ADP-activated PFA-100, thromboelastography-based ADP-dependent platelet activity, collagen/ADP-Closure time, and collagen/epinephrine-closure time) compared to those who received no reversal agents [398–410]. DDAVP has also been shown to significantly reduce blood loss and improve thrombus formation in cardiac surgery patients exposed to aspirin pre-operatively [403, 411–413]. Conversely, two randomized, double-blind trials of DDAVP in patients undergoing cardiopulmonary bypass or aortic surgery failed to identify a benefit [414, 415]. However, these studies did not explicitly examine patients exposed to an antiplatelet. DDAVP for antiplatelet reversal has been reported in two studies of intraparenchymal hemorrhage patients. One study examined a mixed cohort of 14 patients with intraparenchymal hemorrhage with either reduced platelet activity on point-of-care testing (PFA-100), and/or known aspirin use [400]. All patients received DDAVP 0.4 μg/kg IV. Von Willebrand Factor antigen and closure times (PFA-100 with epinephrine) were measured before and 1 h after DDAVP administration. Platelet function improved, von Willebrand factor antigen increased, and only 2 of 14 patients had hematoma growth. However, this study was small and had no control group. Another study evaluated 13 patients with different types of intracranial hemorrhage (subdural hematoma, intraparenchymal hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke) [416]. Ten patients had a history of aspirin use with abnormal platelet function (as measured by PFA-100). Platelet function was restored within 30 min of DDAVP administration (0.4 μg/kg IV), though the effect was short-lived and PFA-100 abnormalities returned to baseline values within 3 h. No complications related to electrolyte abnormalities or volume status were noted. The authors concluded that DDAVP can stabilize platelet function, but the duration of effect is influenced by the amount and frequency of antiplatelet dosing. It is conceivable that repeat dosing may be required in some patients.

Reported side effects of DDAVP include facial flushing, peripheral edema, hypervolemia, decreased urine output, and hyponatremia [417]. There are rare reports of cerebrovascular or cardiac thrombosis (<1 %) with DDAVP use; therefore, caution should be applied in patients with recent ischemic stroke or acute myocardial infarction [418].

Because of the low risk of serious side effects, the relatively low cost, and the suggestion of benefit in the aforementioned studies, we suggest consideration of a single dose of DDAVP (0.4 mcg/kg) in intracranial hemorrhage patients exposed to antiplatelet agents. In patients deemed appropriate (e.g., those undergoing a neurosurgical procedure), DDAVP can be used in addition to platelet transfusion.

Recombinant Factor VIIa Recombinant factor VIIa has been used to improve hemostasis in patients with Glanzmann thrombasthenia who suffer from a severe deficiency of GP IIb/IIIa. Recombinant factor VIIa may act to increase thrombin generation on the platelet surface, and may be a reversal option for patients with GP IIb/IIIa-associated intracranial hemorrhage [419, 420]. However, data are insufficient at this time to recommend its use.

Fibrinogen Supplementation GP IIb/IIIa inhibitors prevent platelet aggregation via fibrinogen-platelet crosslinking. In an in vitro study of platelets exposed to either tirofiban or eptifibatide, fibrinogen supplementation using either cryoprecipitate or fresh frozen plasma resulted in improved platelet aggregation in a dose-dependent manner [421]. The use of cryoprecipitate in GP IIb/IIIa-related intracranial hemorrhage may be considered, though there is little literature to support its use.

Recommendations for Antiplatelet Agent Reversal

(1) We recommend discontinuing antiplatelet agents when intracranial hemorrhage is present or suspected. (Good Practice statement)
(2) We suggest *against* platelet transfusion for patients with antiplatelet-associated intracranial hemorrhage who will *not* undergo a neurosurgical procedure, regardless of the type of platelet inhibitor, platelet function testing, hemorrhage volume, or neurological exam. (Conditional recommendation, low-quality evidence)
(3) We suggest platelet transfusion for patients with aspirin- or ADP inhibitor- associated intracranial hemorrhage who will undergo a neurosurgical procedure. (Conditional recommendation, moderate quality of evidence)
    (a) We recommend platelet function testing prior to platelet transfusion if possible. (Strong recommendation, moderate quality evidence)
    (b) When platelet function testing is not readily available, empiric platelet transfusion may be reasonable. (Conditional recommendation, low-quality evidence)
    (c) We recommend against platelet transfusion for patients with laboratory documented platelet function within normal limits or documented antiplatelet resistance. (Strong recommendation, moderate quality evidence)
(4) We suggest against platelet transfusion in NSAID or GP IIb/IIIa inhibitor-related intracranial hemorrhage, even in the context of neurosurgical intervention.

Table 5 Summary of recommendations for reversal of antithrombotic agents in patients with intracranial hemorrhage

Antithrombotic	Reversal agent
Vitamin K antagonists	If INR $\geq$ 1.4:
	Vitamin K 10 mg IV, plus
	3 or 4 factor PCC IV
	(dosing based on weight, INR and PCC type) OR FFP 10–15 ml/kg IV if PCC not available
Direct factor Xa inhibitors	Activated charcoal (50 g) within 2 h of ingestion,
	Activated PCC (FEIBA) 50 units/kg IV OR 4 factor PCC 50 units/kg IV
Direct thrombin inhibitors	For dabigatran reversal:
	Activated charcoal (50 g) within 2 h of ingestion, AND
	Idarucizumab 5 g IV (in two 2.5 g/50 mL vials)
	Consider hemodialysis or idarucizumab redosing for refractory bleeding after initial administration
	For other DTIs:
	Activated PCC (FEIBA) 50 units/kg IV OR
	4 factor PCC 50 units/kg IV
Unfractionated heparin	Protamine 1 mg IV for every 100 units of heparin administered in the previous 2–3 h
	(up to 50 mg in a single dose)
Low-molecular weight heparins	Enoxaparin:
	Dosed within 8 h: Protamine 1 mg IV per 1 mg enoxaparin (up to 50 mg in a single dose)
	Dosed within 8–12 h: Protamine 0.5 mg IV per 1 mg enoxaparin (up to 50 mg in a single dose)
	Minimal utility in reversal $>$12 h from dosing
	Dalteparin, Nadroparin and Tinzaparin:
	Dosed within 3–5 half-lives of LMWH: Protamine 1 mg IV per 100 anti-Xa units of LMWH (up to 50 mg in a single dose)
	OR
	rFVIIa 90 mcg/kg IV if protamine is contraindicated
Danaparoid	rFVIIa 90 mcg/kg IV
Pentasaccharides	Activated PCC (FEIBA) 20 units/kg IV or rFVIIa 90 mcg/kg IV
Thrombolytic agents	Cryoprecipitate 10 units IV OR
(plasminogen activators)	Antifibrinolytics (tranexamic acid 10–15 mg/kg IV over 20 min or ε-aminocaproic acid 4–5 g IV) if cryoprecipitate is contraindicated
Antiplatelet agents	DDAVP 0.4 mcg/kg IV $\times$ 1
	If neurosurgical intervention: Platelet transfusion (one apheresis unit)

PCC prothrombin complex concentrates, *LWMH* low-molecular weight heparin, *rFVIIa* recombinant factor VIIa, *DDAVP* desmopressin

(Conditional recommendation, very low-quality evidence)

(5) In candidates for platelet transfusion, we suggest an initial dose of one single-donor apheresis unit of platelets. Platelet testing is suggested prior to repeat platelet transfusion, if available and repeat transfusion should be used only for those with persistently abnormal platelet function tests and/or ongoing bleeding. (Conditional recommendation, moderate quality evidence)

(6) We suggest consideration of a single dose of desmopressin (DDAVP) in intracranial hemorrhage (0.4 mcg/kg IV) associated with aspirin/COX-1 inhibitors or ADP receptor inhibitors. In patients deemed appropriate (e.g., those undergoing a neurosurgical procedure), DDAVP can be used in addition to platelet transfusion. (Conditional recommendation, low-quality evidence)

Limitations

This guideline addresses commonly encountered antithrombotic-associated intracranial hemorrhage scenarios for which data and experience have been reported. Management of patients with complex situations (e.g., intracerebral hemorrhage with intrinsic coagulopathy, thrombocytopenia, DIC, polytrauma, and/or concomitant ischemia or thrombophilia) will require prioritizing interventions and risk–benefit analyses. For these situations the information here should serve as a first guide, with reliance upon local and outside experts in a multidisciplinary team to help formulate treatment plans where necessary. This guideline did not specifically address antithrombotic reversal in a pediatric population.

Future Directions

The recommendations of this guideline are summarized in Table 5. With new antithrombotics and new reversal agents under development, the state of the art in treatment of antithrombotic-associated intracranial hemorrhage is rapidly evolving (see Table 4 and Online Appendix 2). As new therapeutic options for reversal become available, these guidelines will be amended and updated accordingly. As a corollary to this work, the Committee will address resumption of antithrombotics following intracranial hemorrhage in a future guideline.

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Compliance with Ethical Standards

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