# Reversal of antithrombotic medications in patients with traumatic brain injury: What you need to know

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**ABSTRACT:** Traumatic brain injury (TBI) is a major public health problem and patients with TBI are frequently encountered by trauma surgeons. When TBI occurs in patients who are also taking antithrombotic medications, the risks and complications are increased. Antithrombotic medications can be classified as antiplatelet agents or anticoagulants. Examples of antiplatelet agents include aspirin and clopidogrel. Anticoagulant medications include vitamin K antagonists like warfarin, direct oral anticoagulants, and unfractionated or low-molecular-weight forms of heparin. Each of these agents alter the hemostatic balance through different mechanisms and therefore require distinct reversal strategies. Initial management of TBI in patients receiving antithrombotic agents includes prompt neurological assessment, non-contrast head computed tomography, and laboratory testing to assess coagulation status. Decisions regarding possible reversal of antithrombotic medications must be guided by the severity of injury, bleeding risk, patient co-morbidities, and the specific agents used. This review will discuss what trauma surgeons need to know in terms of managing patients with acute TBI who are taking anticoagulant and antiplatelet medications based on the current literature. (*J Trauma Acute Care Surg.* 2025;99: 828–835. Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.)

**KEY WORDS:** Anticoagulation; antiplatelet agent; traumatic brain injury; intracranial hemorrhage.

Traumatic brain injury (TBI) is a major public health problem, and such patients are frequently encountered by trauma surgeons.[1] A recent review estimated that 2.3% of adults in the United States are taking some form of antithrombotic medication for conditions such as atrial fibrillation, venous thromboembolism, mechanical heart valves, and coronary or intravascular stents.[2] Antithrombotic agents can be subclassified as anticoagulants, agents that primarily inhibit the coagulation cascade and fibrin formation, or antiplatelet agents (APAs), agents that inhibit clot formation by preventing platelet activation and aggregation.[2,3] The increasingly widespread use of antithrombotic medications has led to growing concerns about intracranial bleeding following head trauma because use of oral antithrombotic medications in TBI patients has been shown to be associated with increased mortality.[4,5]

One study of head injury patients at a large tertiary trauma center found that intracranial hemorrhage (ICH) was significantly more common in TBI patients on antithrombotic therapy than for those not on therapy.[6] The radiographic progression of traumatic ICH on routine follow-up head computed tomography (CT) has been shown to range from 17% to 20% in patients without anticoagulation.[7] Patients on antithrombotic therapy who sustain an ICH have increased risk of expansion, resulting in worsened functional outcomes, and up to a 50% higher mortality rate.[8] Patients on antithrombotic therapy who sustain an ICH have up to a 38% higher risk of ICH expansion.[9]

The purpose of this commentary is to discuss what trauma surgeons need to know in terms of managing trauma patients with acute TBI who are taking anticoagulant and antiplatelet medications. This guide will provide comprehensive, but concise, information to assist surgeons if they need to reverse antithrombotic medications in a TBI patient who has been taking antithrombotic medications (Fig. 1). Any decision to reverse such agents will depend on (1) the severity of the brain injury and, more specifically, the magnitude of ICH; (2) the degree of coagulation derangement (e.g., a markedly elevated prothrombin time); (3) the clinical examination (e.g., Glasgow Coma Scale [GCS]); (4) the need for urgent/emergent surgical intervention; and (5) the progression, if any, of ICH over time. If, when, and how to reverse or mitigate the actions of a variety of antithrombotic agents will also be reviewed based on the current literature. Decisions regarding if/when to resume antithrombotic medications subsequently are beyond the scope of this review.

## IDENTIFICATION AND ASSESSMENT OF TBI

Trauma surgeons, along with emergency medicine providers, typically are the first medical personnel that encounter patients with TBI. Initial management follows the Advanced Trauma Life Support (ATLS) primary survey, including rapid assessment of airway, breathing, circulation, and neurological status.[10] The most important aspects of the primary survey are rapid identification of bleeding, airway patency, breathing, and circulation, but neurologic assessment comes next in the ATLS hierarchy. A patient's level of consciousness and alterations in mental status are quantitated with the Glasgow Coma Score (GCS). Information from pre-hospital personnel regarding the presence, and duration, of loss of consciousness is also useful information. Risk of TBI can be accurately recognized clinically, even before imaging studies are available. Table 1 summarizes a clinical classification scheme to stratify acute TBI as mild, moderate, or severe.

During the initial evaluation of trauma patients it is frequently difficult to obtain a complete medical history. At a minimum, an AMPLE (allergies, medications, past illnesses/pregnancy, last meal, and events/environment of the injury) history should be sought from the patient, relatives, or emergency medical system personnel. Knowledge of prior anticoagulant use can be challenging in patients who are obtunded, intoxicated, or have an altered mental state. Evidence of extensive bruising may also alert emergency department personnel to the potential use of anticoagulants. In some instances, the electronic health record can be helpful or accessing medical record information from the lock screen of cellphones.[11] While injured patients may be unable to communicate the antithrombotic agent, dosage, or timing of last administration, it may be beneficial to try to obtain this information because different agents have specific antagonists (see hereinafter), different half-lives, and routes of clearance. A 2017 EAST Multicenter Trial found that, among trauma patients prescribed antithrombotic agents, 50% were

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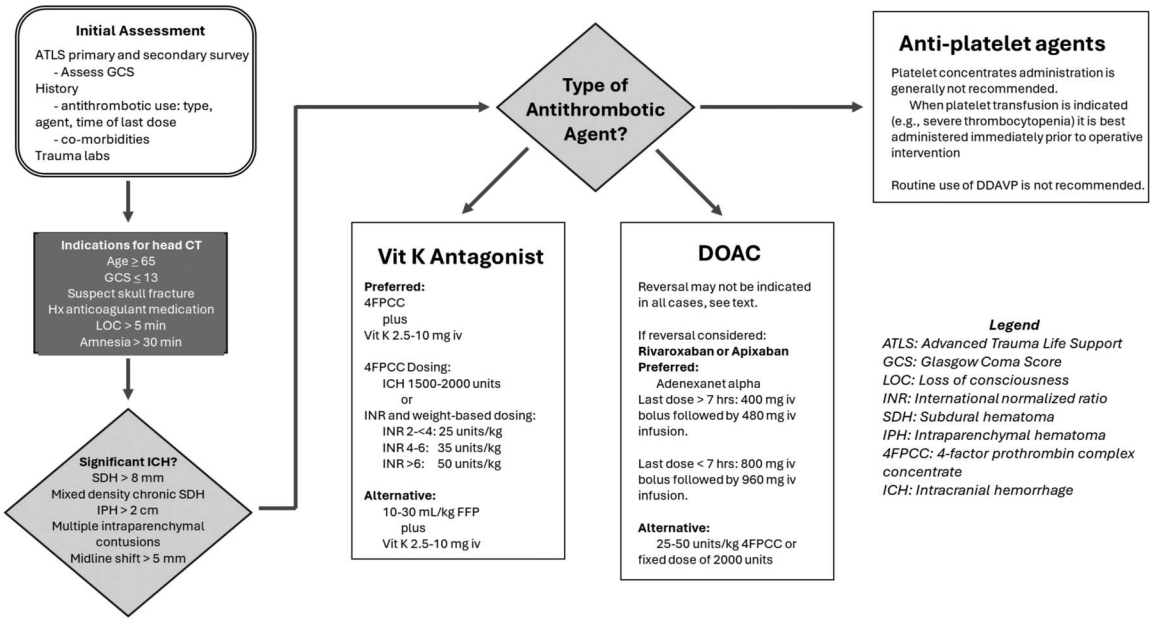


**Figure 1.** Scheme evaluation of patients with TBI along with recommendation for reversal of antithrombotic medications, if indicated. See text for complete discussion.

receiving APAs, 33% were taking warfarin, 10% were on direct oral anticoagulants (DOACs), and 7% had combination therapy.[12] In most cases, the reason for pre-injury antithrombotic use is less important in terms of immediate management of the new injury.

Decisions regarding adjunctive imaging studies (e.g., chest or pelvis radiographs, Focused Abdominal Sonography for Trauma examination, etc.) and routine laboratory testing in the emergency department or trauma bay vary widely based upon local norms, details about the mechanism of injury, and clinical stability. Many emergency departments obtain point-of-care testing, for example, iStat (Abbot, Abbot, IL, USA), which includes, sodium, potassium, chloride, calcium, glucose, venous blood gases, lactate, urea nitrogen, and creatinine. In a setting of significant traumatic injury, routine laboratories include complete blood count (CBC), type and screen, international normalized ratio (INR), blood alcohol level, and other tests depending upon patient factors. In patients with possible TBI who may be taking antithrombotics, the INR and platelet count from the CBC are the most useful and should be obtained prior to CT imaging. The finding of an elevated INR indicates a significant derangement in clotting, whether because of medication or underlying disease (e.g., cirrhosis). The CBC provides information about the platelet count, which is most useful to identify thrombocytopenia, which could be important if major surgery is needed. Thromboelastography is not helpful in patients on anticoagulant medication, as thromboelastography generally simply shows a delayed onset of clotting with decreased amplitude.[13]

## ROLE OF HEAD CT IN TRAUMA PATIENTS

Routine head CT scanning is not mandatory in all trauma patients, even those with possible mild TBI. However, CT scanning should be obtained in all patients who are 65 years or older, in patients with a GCS score of ≤12, if there is clinical suspicion of open or closed skull fracture, and in patients taking anticoagulant medication. Head CT should also be obtained in patients who had a loss of consciousness >5 minutes or those with >30 minutes of retrograde amnesia. Head CT scans may identify a number of specific injuries and findings: epidural hematoma (EDH), subdural hematoma (SDH), intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), skull fractures, and soft tissue injuries.[14] All anticoagulated patients with head trauma should undergo an immediate non-contrast CT scan of the head, regardless of their GCS or presence of symptoms, to rule out intracranial bleeding.[13,14] The European Federation of the Neurological Societies also cites antithrombotic use as a definitive risk factor for intracranial injury after TBI and recommends non-contrast CT scan in all patients.[15] Multiple studies have shown that patients with coagulation disorders, including anticoagulant usage, have increased risk of ICH despite a normal neurological examination. The ACS Trauma Quality Improvement Project Best Practice Guidelines in Imaging also recommends liberal use of imaging in anticoagulated patients with head injury.[16]

## ANTITHROMBOTIC MEDICATIONS

Several antithrombotic agents exist, including vitamin K antagonists (VKAs), platelet inhibitors, DOACs, and intravenous (IV) agents (heparin), each of which require distinct reversal strategies (Table 2). The selection of the appropriate reversal agent depends on the specific antithrombotic used, the severity of the injury, and the patient's clinical status. A recent consensus statement by a

**TABLE 1.** A Classification System for TBI Based on Three Clinically Accessible Parameters

| Classification | Duration of Loss of Consciousness | GCS | Duration of Posttraumatic Amnesia |
|---|---|---|---|
| Mild | <30 min | 13–15 | <24 h |
| Moderate | 30 min to 24 h | 9–12 | 1–7 d |
| Severe | >24 h | 3–8 | >7 d |

**TABLE 2.** Antithrombotic Medications and Reversal Agents

| Agent | Mechanism | Half Life | Reversal Agent | Dosing of Reversal Agent | Reference |
|---|---|---|---|---|---|
| APAs | | | | | |
| Aspirin | Irreversible inhibitor of COX-1 | NA | None | May consider platelet transfusion and desmopressin 0.4 μg/kg IV; if needing neurosurgical operative intervention, administer immediately preop | 1 |
| Clopidogrel, ticagrelor, prasugrel | Blocks ADP receptor P2Y12 on platelets inhibiting aggregation | NA | None | May consider platelet transfusion and desmopressin 0.4 μg/kg IV; if needing neurosurgical operative intervention, administer immediately preop | 1 |
| Anticoagulant medications | | | | | |
| Vitamin K antagonists | | | | | |
| Warfarin | Blocks regeneration of vitamin K epoxide and inhibits synthesis of factors II, VII, IX, and X, and proteins C and S | 5–7 d | 4FPCC Vit K FFP | 4FPCC:<br>Weight based: 25–50 IU/kg<br>INR based:<br>INR 1.5–1.9, 15 IU/kg<br>INR 2.0–3.9, 25 IU/kg<br>INR 4.0–6.0, 35 IU/kg<br>INR >6.0, 50 IU/kg<br>or a fixed dose 1,500 IU or<br>Vit K: 5–10 mg IV<br>FFP: 1–2 U initially | 1,2 |
| **DOAC** | | | | | |
| Apixaban | Direct Xa inhibitor | 6–15 h | AA | AA:<br>Low dose, >8 h or apixaban dose <5 mg: 400 mg bolus, then 480 mg infusion<br>High dose, <8 h since last dose or apixaban dose >5 mg: 800 mg bolus then 960 mg infusion | 1,3 |
| | | | 4FPCC* | 4FPCC: 25–50 IU/kg or fixed dose of 2,000 mg | 4,5 |
| Rivaroxaban | Direct Xa inhibitor | 5–11 h | AA | AA:<br>Low dose, >8 h or rivaroxaban dose <10 mg: 400 mg bolus, then 480 mg infusion<br>High dose, <8 h since last dose or rivaroxaban dose >10 mg: 800 mg bolus then 960 mg infusion | 1,3 |
| | | | 4FPCC* | 4FPCC: 25–50 IU/kg or fixed dose of 2000 mg | 4,5 |
| Dabigatran | Direct thrombin inhibitor | 12–17 h | Idarucizumab | Idarucizumab:<br>2.5 g IV bolus (2 consecutive doses) | 6 |
| | | | 4FPCC* | 4FPCC: 50 IU/kg or fixed dose of 2000 mg | 5 |
| Parenteral anticoagulant | | | | | |
| Heparin infusion | Inactivation of thrombin and Xa | 60–90 min | Protamine | Protamine: 1 mg/100 IU of heparin (no more than 50 mg/dose) | 7 |
| Enoxaparin | Selective inhibition of Xa | 3–6 h | Protamine | Protamine: <8 h from administration, 1 mg protamine per 1 mg of enoxaparin dose<br>>8 h from administration, 0.5 mg protamine per1 mg of enoxaparin dose | 7 |
| | | | AA | AA: 800 mg bolus, then 960 mg infusion | 3 |

*Note: Use of 4FPCC for reversal of DOAC is not an FDA-approved indication and so represents an "Off-label: use of drug."
ADP, Adenosine Diphosphate; COX-1, cyclooxygenase-1; Vit K, vitamin K.

multidisciplinary working group suggested stratifying anticoagulated patients with TBI based on whether they are at low or high risk for ICH, before deciding to use reversal agents.[17] Current guidelines recommend a combination of targeted reversal agents, supportive care, and surgical intervention when necessary.[18]

## REVERSAL OF ANTITHROMBOTIC AGENTS IN THE SETTING OF TBI

Timely and effective reversal of antithrombotic agents may be critical to reducing hematoma expansion and improving patient outcomes in patients receiving active antithrombotic agents.[19] Active treatment with antithrombotic medication can be defined as "treatment with a vitamin K antagonist and an INR >1.5, taking a DOAC within 24 hours, or administration of an APA within the preceding 5 days."[17] No further consideration of antithrombotic reversal is relevant in patients who do not meet this definition of active treatment. Head CT characterization of the acute ICH is also helpful in determining who may be at higher risk for progression of intracranial bleeding and who needs urgent surgery. In general, patients with mild TBI (GCS score, 13–15), no comorbidities, low likelihood of surgical intervention within 12 hours, or acute TBI >72 hours before evaluation are at a low risk for bleeding.[20–23] Conversely, clinical or

radiographic findings that are associated with a significantly higher risk of acute surgical intervention and/or progression of ICH include moderate or severe TBI (GCS score, ≤12),[20,23] SDH ≥8 mm,[24] mixed density chronic SDH,[25] and intraparenchymal hemorrhage ≥2 cm or multiple intraparenchymal contusions.[26] The need for, and timing of, reversal of antithrombotic agents are most relevant to the subset of TBI patients who require acute surgical intervention or are at a high risk for progression of ICH.[12,24,26]

Antiplatelet agents can be administered as a single agent or co-administered during dual antiplatelet therapy regimens. In a comparative study of patients who received single-agent antiplatelet therapy compared with dual-agent antiplatelet therapy, GCS on admission was significantly lower, and the severity of head injuries was significantly higher, in the dual-agent antiplatelet therapy group.[27] However, the rate of deterioration did not differ significantly between the two groups.[27] Overall, patients on clopidogrel are more likely to have progression of an initial ICH and a higher rate of neurosurgical intervention, in comparison with those receivingaspirin.[28] In terms of the need for acute neurosurgical operation, neither preinjury APAs nor anticoagulants were associated with increased operative bleeding complications.[29]

More information is available, and more options exist, with respect to reversal of anticoagulant medications compared to reversal of APAs. For example, a multidisciplinary guideline concluded that reversal of VKA anticoagulation is always recommended in patients with an ICH.[30] This guideline recommended targeting an INR of <1.5 when ICH was identified. In a large retrospective study of elderly patients who sustained ground level falls, preinjury treatment with an anticoagulant was associated with an increased risk of the combined outcome of mortality or discharge to hospice, if patients had been receiving VKA (27.7%) or DOAC (22.9%).[31] In another study that examined risk factors for ICH progression, prior treatment with warfarin was associated with progression, whereas APA and DOAC were not associated with progression.[32]

A multicenter study found no difference in outcomes between a subset of patients with traumatic ICH on oral anticoagulants who were neurologically intact (GCS score, 15) who did or did not undergo anticoagulant reversal.[33] In that study, a total of 693 subjects were taking anticoagulants, and 263 patients were reversed, whereas 391 subjects were not. There was no difference in the in-hospital mortality or discharge to hospice in subjects who were reversed (4.6%) or not (4.9%). There were also no statistically significant differences in the proportion of complications or intensive care unit (ICU) length of stay (LOS).[33] A multidisciplinary consensus statement determined that there were insufficient data in the literature to recommend DOAC reversal in all patients with TBI and insufficient data to determine whether certain patients do not require anticoagulation reversal.[9,30] The Neurocritical Care Society and Society of Critical Care Medicine reported a conditional recommendation for pharmacological reversal of DOAC, but this was guided primarily by the presence of major intracranial bleeding.[4] On the other hand, an EAST multicenter trial that examined the efficacy of anticoagulant reversal did not report a benefit to reversal of DOAC with four-factor prothrombin complex concentrate (4FPCC) in patients with severe TBI.[34]

## Reversal of Specific Anti-platelet Agents

Platelet inhibitors are a diverse group of medications that prevent thrombosis by interfering with platelet activation and aggregation (Table 2). The most widely used platelet inhibitor is aspirin, which irreversibly inhibits the enzyme cyclooxygenase-1. Inhibition of cyclooxygenase-1 prevents the synthesis of thromboxane $A_2$, a potent platelet activator and vasoconstrictor, leading to reduced platelet aggregation. Aspirin's antiplatelet effects last for the lifespan of the platelet (7–10 days).[35] Another major class includes P2Y12 receptor antagonists such as clopidogrel (Plavix, Plavix, Bristol_Myers Squibb, Minneapolis, MN, USA), prasugrel (Effient, Daiichi Sankyo, Inc., Tokyo, Japan), and ticagrelor (Brilinta, Aztra Zeneca Pharmaceutical LP, Cambridge, United Kingdom).[35] These agents block the adenosine diphosphate (ADP) receptor P2Y12 on platelets, thereby impairing ADP-mediated activation of the GPIIb/IIIa receptor complex, which is essential for platelet aggregation. Clopidogrel and prasugrel act irreversibly, while ticagrelor is a reversible inhibitor.

Reversal of APAs is often challenging because most do not have specific reversal agents, particularly those that irreversibly bind to platelet targets. In cases of life-threatening bleeding or need for urgent surgery, the most effective approach may be platelet transfusion, which presumably provides functional platelets to replace those inhibited by irreversible agents like aspirin or clopidogrel. It should be noted that this strategy is less effective for drugs with reversible binding, such as ticagrelor, which can inhibit newly transfused platelets as well.[36] Platelet transfusion is not a benign intervention and is associated with complications including blood group type (ABO) incompatibility reactions, sepsis, arrhythmia, transfusion-related acute lung injury, stroke, and death. In a retrospective study of patients on aspirin alone or aspirin plus clopidogrel, no differences were found in outcomes with regards to progression of ICH or neurosurgical interventions between patients who received platelet transfusions and those who did not.[37] According to the 2022 American Heart Association/American Stroke Association guideline, in the setting of spontaneous ICH, platelet transfusion might be considered to reduce postoperative bleeding and mortality in patients on aspirin who require surgical intervention for ICH.[38] In patients who do not require surgical intervention, platelet transfusions are potentially harmful and should not be administered.[39] In one study of patients receiving platelet transfusion, a worse clinical course, as indicated by greater ICU LOS and higher mortality, was observed in the transfusion recipients.[37] A retrospective study of TBI outcomes in antiplatelet users found that immediate platelet transfusion did not alter the occurrence of ICH extension on follow-up CT, TBI-specific mortality, or need for neurosurgical intervention.[40]

Administration of desmopressin (DDAVP) has also been suggested as a supportive measure, particularly in aspirin-induced bleeding, to enhance platelet adhesion via increased release of von Willebrand factor and factor VIII, although evidence supporting this approach is limited.[4] The effectiveness of DDAVP in reducing the progression of traumatic ICH is unknown, as there is no consistent evidence that DDAVP administration in patients with ICH on platelet inhibitors reduces progression of intracranial hematoma or improves neurologic outcome. Routine use of DDAVP to reverse the effects of antiplatelet medications in mild TBI is not recommended.[30] Platelet transfusion and co-administration of DDAVP have not been associated with a decreased risk of hemorrhage progression or mortality.[41]

## Reversal of Specific Anticoagulants Agents

### Reversal of Heparin

Unfractionated heparin inhibits coagulation by binding to antithrombin, which irreversibly binds to factor II, inhibiting its activity (Table 2). The half-life of heparin is 60 to 90 minutes, but its half-life is dose dependent and increases with the dose. In situations where a patient is on a heparin infusion and ICH occurs or worsens, the infusion should be stopped immediately. The reversal agent is IV protamine sulfate.[42] The suggested dosing of IV protamine is 1 mg for every 100 U of heparin given in the preceding 2 to 3 hours.[4] The total dose of protamine should not exceed 50 mg. If the activated partial thromboplastin time remains elevated after the first administration of protamine, it can be repeated at a dose of 0.5 mg per 100 U of heparin.[4]

### Reversal of Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) activates antithrombin III and then binds to factor Xa, inhibiting it. The half-life of LMWH is about 4 hours after subcutaneous injection and it is not dose dependent. Patients on therapeutic dosing of LMWH who develop, or have worsening of, ICH should have further doses of LMWH held. If the clinical scenario requires reversal of LMWH, IV protamine can be given.[4] Protamine incompletely reverses LMWH Xa inhibition resulting in approximately 60% to 75% reversal of the anticoagulation effect.[43] If enoxaparin had been administered within 8 hours, the dose is 1 mg of protamine per 1 mg of enoxaparin, with the total protamine dose not exceeding 50 mg. If enoxaparin had been administered 8 to 12 hours earlier, the protamine dose is 0.5 mg per 1 mg of enoxaparin. If ≥12 hours have passed, reversal is unlikely to be needed unless the patient has significant renal impairment.[44] Adexanet-alfa may also be effective at reversing the anti-Xa effect of enoxaparin (although this is not a Food and Drug Administration [FDA]–approved indication).[45] The dosing is an 800 mg bolus followed by a 960-mg infusion.

### Reversal of Vitamin K Antagonists

Vitamin K antagonists function by inhibiting the enzyme vitamin K epoxide reductase in the liver. This enzyme is necessary for recycling oxidized vitamin K to its active reduced form. Active vitamin K is essential for the γ-carboxylation of glutamic acid residues on several clotting factors, specifically factors II, VII, IX, and X, as well as proteins C and S.[46] By inhibiting vitamin K epoxide reductase, VKA reduce the activation of these clotting factors, thereby impairing normal clot formation. Since VKA effects the synthesis of clotting factors, there is a delayed onset of action and therapeutic anticoagulation takes several days of treatment.[47]

There are multiple reversal strategies for VKA, but one of the most common is administration of vitamin K (phytonadione) with or without fresh frozen plasma (FFP) depending upon the INR value. Vitamin K can be given orally for non-emergent cases or intravenously for acute bleeding. Vitamin K acts by restoring the liver's ability to synthesize active clotting factors and it typically takes 6 to 12 hours to begin restoring factor levels. A major disadvantage of vitamin K for reversing the anticoagulant effects of VKAs is that reduction of INR to values to less than 1.4 may take up to 24 hours; therefore, it is not recommended alone as the reversal agent for patients with VKA and ICH.[30] An alternative approach to reversal of VKA is through provision of preformed clotting factors, either by infusion of FFP or three-factor prothrombin complex concentrate (PCC) or four-factor PCC (4FPCC), which are concentrated formulations of clotting factors II, VII, IX, and X.[48] A study comparing PCC to FFP infusion for warfarin reversal in geriatric patients with ICH found better INR reversal with 4FPCC.[49] This study also reported a significantly lower rate of neurological deterioration in the 4FPCC group. Four-factor PCC is preferred for rapid reversal, especially in life-threatening bleeding or before emergency procedures,[50] and it is frequently co-administered with IV vitamin K to sustain reversal. Fresh frozen plasma also contains all coagulation factors and can be used when PCCs are not available, but it has a slower onset of action, requires large volumes, and therefore may be less effective in urgent settings.

A study of ICH after falls while on warfarin found that PCC was equivalent to FFP in clinically relevant outcomes, including mortality, radiological progression of ICH, ICU LOS, and hospital LOS.[51,52] The authors noted that PCC achieved INR reversal faster, more reliably, with lower required infusion volumes, and without the risks inherent to blood component therapy. Four-factor PCC is strongly recommended in preference to FFP for treating ICH patients on VKAs.[30] There is strong recommendation for vitamin K co-administration and follow-up INR to ensure durable reversal of INR following VKA-associated ICH, as PCC remains effective for 12 to 24 hours.[4,53] There is no consensus on the dosing of 4FPCC. A recent meta-analysis shows that fixed dosing had faster administration and higher likelihood of clinical hemostasis compared with variable dosing based on weight and presenting INR.[52] Fixed dosing was less likely to achieve an INR of <1.5 compared with variable dosing.[52]

### Reversal of DOACs

Direct oral anticoagulants are being used with increasing frequency in the general population.[54] In contrast to VKA, DOACs have a more rapid onset of effective anticoagulation and they also eliminate the need for patients to monitor their INR.[54] Currently, there are three FDA-approved DOACs in clinical use; apixaban (Eliquis, Eliquis, Bristol-Myers Squibb Co., Minneapolis, MN), rivaroxaban (Xaralto, Xaralto, Janssen Pharmaceuticals, Inc., Division of Johnson & Johnson, Beerse, Belgium.), and edoxaban (Savasya, Savasya, Daiichi, Sankyo, Inc., Tokyo, Japan). Choice of agent may be influenced by patient comorbidities, such as renal or liver impairment, as these agents differ in terms of half-life and route of elimination.[54] As a class, DOACs have also been the focus of a very aggressive advertising campaign to the general public.[55] These agents are classified as factor Xa inhibitors (FXaI) because they act by selectively and reversibly inhibiting factor Xa. Factor Xa catalyzes the conversion of prothrombin (factor II) to thrombin (factor IIa) via the prothrombinase complex.[56] By blocking factor Xa, these agents reduce thrombin generation and thus inhibit both fibrin formation and platelet activation.

The activity of DOAC is highly dependent on the time from last dose. Apixaban has a half-life of 12 hours, and reversal is not indicated at >48 hours from last dose.[57] The half-life of rivaroxaban is 5 to 9 hours, and after more than 36 hours from the last dose, reversal is not indicated. Andexanet-alfa (AA) is an FDA-approved agent for reversal of apixaban and rivaroxaban.[58] Based on the 2019 Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor-4 Trial, AA was conditionally approved by the FDA and the European Medicines Agency in adult patients treated with apixaban or

rivaroxaban for reversal of anticoagulation in the setting of life-threatening or uncontrolled bleeding.[45] Andexanet-alfa is a modified recombinant factor Xa protein that inactivates the FXaI molecules in the plasma. There is a low- and high-dose protocol based on the home dose and the time from last dose. Andexanet-alfa is not approved for reversal of edoxaban.[58]

Dabigatran etexilate (Pradaxa, Boehringer Ingelheim Pharmaceauticals, Inc., Ingelheim am Rhein, Germany) is the only oral direct thrombin inhibitor currently approved. It is a pro-drug that is converted in vivo to dabigatran, which directly inhibits thrombin (factor IIa). By inhibiting thrombin, dabigatran prevents fibrin clot formation, platelet activation, and thrombin-mediated feedback activation of coagulation. Idarucizumab (Praxbind, Boehringer Ingelheim Pharmaceauticals, Inc., Ingelheim am Rhein, Germany) is only approved for reversal of dabigatran.[59] Idarucizumab is a monoclonal antigen-binding fragment antibody to dabigatran with 350 times more affinity to dabigatran than thrombin resulting in rapid reversal of its anticoagulant effect.[59] The recommended dose of idarucizumab is 5 g intravenously, administered in two 2.5 g doses, no more than 15 minutes apart.

Prior to approval of specific reversal agents, PCC had been used for DOAC-associated bleeding and is still used for DOAC without specific reversal agents.[60,61] (Note: Use of 4FPCC for reversal of DOAC is not a FDA-approved indication and therefore represents an "Off-label: use of the drug.") As noted previously, PCC act to reverse the effects of FXaI, but it does not directly inhibit FXaI or effect FXa levels.[56] At the present time, there is ongoing discussion as to whether use of a specific reversal agents or 4FPCC is preferable for reversal of DOAC. In the setting of life-threatening bleeding, including bleeding in critical areas such as ICH subtypes, the American College of Cardiologists recommends treatment with AA for patients on FXaI with 4FPCC being an alternative agent.[18] While several medical professional organizations recommend the use of AA and idarucizumab for reversal agents in ICH, the use of these agents in practice has been limited.[18,60,62] A recent survey of levels 1 and 2 trauma centers in the United States showed that AA and idarucizumab were not available in most trauma centers and 76% of respondents reported financial considerations as the main drawback for use.[63] The median cost of AA for an 80-kg patient was reported as $23,602 in 2022 compared with $6,692 for 4FPCC.[64] Progression of ICH with DOAC seems to generally be less of a problem than progression with VKA. For example, a single-center retrospective study found no significant difference in hemorrhage progression or in-hospital mortality among patients with minor TBI who received PCC to reverse apixaban/rivaroxaban compared with those who did not.[65] Importantly, this study also showed no increase in thromboembolic events with PCC treatment. In another study, of patients on DOAC who sustained mild TBI with ICH, reversal with AA had similar radiographic outcomes to reversal of FXaI with 4FPCC, FFP, or no reversal at all.[65]

## CONCLUSION

Traumatic brain injury presents heightened risks in patients on antithrombotic therapy because of the increased potential for ICH and its progression. Antiplatelet agents and anticoagulants, like VKA and DOAC, all effect coagulation through different mechanisms and therefore require distinct reversal strategies. Initial management of TBI in patients receiving antithrombotic agents includes prompt neurological assessment, non-contrast head CT, and laboratory testing to assess coagulation status. Decisions regarding possible reversal of antithrombotic medications must be guided by the severity of injury, risk of ICH and progression of ICH, patient comorbidities, and the specific agents used.

### AUTHORSHIP

E.P., N.D., and M.A.W. contributed in the literature search, data collection, data interpretation, writing of the article, and critical revision.

### DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/E760).

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