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Reversal of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) in the Presence of Major Life-Threatening Bleeding

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Non-vitamin K antagonist oral anticoagulants (NOACs) have gained popularity as alternatives to warfarin for the prophylaxis of stroke and thromboembolic disease as well as treatment for thromboembolic disease. This increased use is being driven by the drugs' benefits including less frequent monitoring, almost no dietary restrictions, and fewer drug-drug interactions than warfarin. However, limitations in reversal of NOACs can complicate management in patients who present with major life-threatening bleeding while taking these drugs.

There are two broad categories of NOACs: direct thrombin inhibitors (DTIs) and factor Xa inhibitors. DTIs, such as dabigatran, prevent the conversion of fibrinogen to fibrin by binding to the active site of thrombin. Factor Xa inhibitors, which include rivaroxaban, apixaban, edoxaban, and betrixaban, bind to free and bound forms of Xa, reducing thrombin production.

For NOACs, bleeding is the most significant adverse effect, ranging from minor ecchymosis to life-threatening hemorrhage. Intracranial bleeding, spinal epidural hematoma, massive gastrointestinal bleeding, and retroperitoneal hemorrhage have all been reported with NOAC use and at times have led to death.

When patients who are taking NOACs present with actual or potential major bleeding, the most important historical factor is time since last dose. In the absence of renal failure, an interval greater than 3 to 5 half-lives since last dose (see Table) would imply little to no drug presence that requires reversal. More recent ingestions require further assessment and possible reversal interventions.

In patients taking NOACs who present with major bleeding, laboratory testing should include baseline and serial hemograms, coagulation studies,

renal function, and a type and cross. Interpreting coagulation studies is not straightforward in these patients because the relationship is not directly proportional to clinical effect and does not necessarily indicate level of anticoagulation. Dabigatran generally increases activated partial thromboplastin time (aPTT) more than prothrombin time/international normalized ratio (PT/INR); however, thrombin time correlates better with drug presence. With rivaroxaban there may be an increase in PT/INR rather than aPTT; however, in general anti-Xa assays calibrated to each individual factor Xa inhibitor correlate better with drug presence. Actual drug levels would be ideal, but it is the rare hospital that can perform such time-dependent testing. Thromboelastography may also provide some measure of anticoagulation effect. In conclusion, do not rely solely on routine coagulation studies to determine the need for reversal of NOACs.

In the presence of suspected drug effect and life-threatening bleeding, consideration should be given for expeditious reversal. To date, poor efficacy has been shown for the use of fresh frozen plasma in reversing these agents. Depending on the NOAC involved, there are a variety of reversal agents that may be potentially useful (Table). The studies that exist use surrogate markers such as reversal of coagulation studies. Unfortunately, there are no randomized clinical trials providing patient-centered outcomes.

Patients with life-threatening bleeding, in the presence of dabigatran, may be given idarucizumab (Praxbind®), an FDA-approved monoclonal antibody fragment (see Table). If this antidote is not available, an activated 4-factor prothrombin complex concentrate (4F-aPCC) such as factor eight inhibitor bypassing activity (FEIBA®) may be useful; however, it is not FDA approved for this indication. Other alternatives include non-activated 4F-PCC (eg, Kcentra®) or recombinant Factor 7a (rVIIa), although there are fewer data to support these. Hemodialysis to enhance removal of dabigatran early after the last dose is unproven and potentially impractical.

In the presence of factor Xa inhibitors, there is currently no FDA-approved antidote. The treatment of choice based on limited animal trials and clinical experience is a non-activated 4F-PCC. The only one currently available in the United States is Kcentra®. If this is not available, 4F-aPCC (FEIBA®) can be considered. If none of these agents is available, rFVIIa or even 3F-PCC with fresh frozen plasma may be administered. At the time of writing of this policy, two specific antidotes are under investigation: (1) andexanet alfa (AndexXa™), a factor Xa decoy protein; and (2) ciraparantag (Aripazine®), a universal reversal agent that binds factor Xa inhibitors and DTIs.

Despite lack of evidence, additional adjunctive measures for severe life-threatening bleeding can be considered such as fresh frozen plasma, packed red blood cells, platelets, tranexamic acid, and desmopressin acetate (DDAVP). Ultimately, when considering the use of reversal agents, the potential for benefit must be weighed against the known risk of thromboembolic complications and their high cost. Institutions should consider the implementation of pathways or guidelines for the care of these complex patients. Because of rapidly evolving therapeutic advances, consider real-time consultation with the hospital pharmacy or local poison center for up-to-date recommendations in treating life-threatening bleeding from NOACs.

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TABLE. Reversal therapies for life-threatening bleeding due to NOACs.

NOAC CLASS	Oral NOACs Generic (Tradename)	Drug Half Lives (with normal renal function)	Suggested Treatment Options
Direct thrombin inhibitor	Dabigatran (Pradaxa®)	12-17 hours	<p>Idarucizumab (Praxbind®) 5g (2 vials 2.5 g each) IV bolus May repeat in severe circumstances</p> <p>Possible alternatives: aPCC (FEIBA®) 50-100 IU/kg 4-factor PCC (Kcentra®) 50 IU/kg rVIIa 90 µg/kg 3-factor PCC (Profilnine®) 50 kg Fresh frozen plasma Hemodialysis</p> <p>Note: Ciraparantag PER977* (Aripazine™) is pending FDA approval for reversal of oral DTIs.</p>
Factor Xa Inhibitor	Rivaroxaban (Xarelto®) Apixaban (Eliquis®) Edoxaban (Lixiana®, Savaysa™) Betrixaban*	5-9 hours 12 hours 10-14 hours 37 hours	<p>No current FDA-approved reversal agents</p> <p>Possible alternatives: 4-factor PCC (Kcentra®) 50 IU/kg aPCC (FEIBA®) 50-100 IU/kg rVIIa 90 µg/kg 3-factor PCC (Profilnine®) 50 IU/kg Fresh frozen plasma</p> <p>Note: Ciraparantag PER977* (Aripazine™) and Andexanet alpha* (AndexXa™) are pending FDA approval for reversal of factor Xa inhibitors.</p>

*Not currently FDA approved or commercially available at the time of writing.