Clinical Practice Guideline:
What is the role of reversal agents in the management of ED patients with dabigatran-associated hemorrhage?

Summary Recommendation:
The clinical efficacy of activated PCC, idarucizumab, and rVIIa remains unclear until further research is performed. Activated PCC, idarucizumab, and possibly rVIIa may be considered in patients with serious bleeding from dabigatran, after careful consideration of the possible benefits and risks.

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Introduction
Dabigatran was approved by the Food and Drug Administration (FDA) in 2010 and was the first non-warfarin oral anticoagulant (NOAC) to be introduced to the U.S. market. Dabigatran is a direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. Current indications include prevention and treatment of deep vein thrombosis and pulmonary embolism, non-valvular atrial fibrillation, and postoperative thromboprophylaxis. Dabigatran does not require routine monitoring like warfarin.

Shortly after its approval, patients began to present to emergency departments with bleeding events, some of which included severe gastrointestinal hemorrhage and intracranial hemorrhage. At the time of FDA approval, there was no antidote or known efficacious treatment for dabigatran-induced coagulopathy. In 2015, idarucizumab was approved by the FDA for dabigatran reversal. Idarucizumab is a monoclonal antibody fragment that binds specifically to dabigatran to neutralize the anticoagulant effect. [1] Other treatments, such as prothrombin complex concentrate (PCC), have also been used in an attempt to treat patients with severe dabigatran-associated hemorrhage. The purpose of this clinical practice statement is to evaluate the role of select reversal agents in the management of dabigatran-associated bleeding, understanding that other classes of oral anticoagulants exist and may have targeted reversal agents.

Executive Summary
<u>Factor Replacement</u>
In 2011, Eerenberg and colleagues published the results of a single-center, randomized, placebo-

controlled, crossover study that evaluated the use of PCC to reverse the anticoagulant effect of dabigatran. [2] Twelve healthy male volunteers received 150 mg of dabigatran twice a day for 2.5 days. On the third day, volunteers received an additional dose and then received an infusion of PCC (50 U/kg) or placebo. Activated partial thromboplastin time (aPTT), thrombin time (TT), and ecarin clotting time (ECT) were used to assess dabigatran anticoagulation. The results of this trial demonstrated that PCC did not reverse the prolongation of aPTT, ECT, and TT due to dabigatran. No major or clinically relevant bleeding complications occurred during treatment. Importantly, this trial was limited by its small size.

A 2012 randomized, crossover study evaluated the effect of non-specific reversal agents on the anticoagulant activity of dabigatran in healthy volunteers. [3] Ten healthy, white, male volunteers, ages 18 to 45 years were administered dabigatran 150 mg orally. Blood samples were drawn at 2 hours post-administration to represent peak anticoagulant activity. The three reversal agents tested were recombinant factor VIIa (rFVIIa), activated PCC, and 4-factor PCC, all at various concentrations. Although PCC increased endogenous thrombin potential, only rFVIIa and FEIBA corrected thrombin activity. [3]

Arellano-Rodrigo and colleagues enrolled healthy volunteers to receive dabigatran 150 mg orally every 12 hours for 5 days. [4] rFVIIa, aPCC, and 4-factor PCC were added into blood samples. Dabigatran treatment significantly prolonged both PT and aPTT in blood samples drawn 2 to 3 hours after the last dose taken. While rFVIIa or aPCC partially improved all the parameters, PCC did not modify the prolonged aPTT observed after dabigatran treatment.

Based on these ex vivo studies, only aPCC, and possibly rFVIIa, may be effective in reversing anticoagulation parameter alterations secondary to dabigatran. All three studies enrolled healthy volunteers and tested against therapeutic levels of dabigatran. The studies attempted to use doses of factor similar to what would be used in actual patients, but may not be generalizable from ex vivo extrapolation. Patients with multiple medical conditions and those with dabigatran overdose were not studied. Furthermore, correction of anticoagulation parameters may not translate into cessation of clinical bleeding. In addition, it is difficult to assess the risks of factor replacement in these small sample sizes. Historically, these treatments have been associated with thromboembolic complications.

Idarucizumab

After an initial study to investigate the pharmacokinetics, safety, and tolerability of idarucizumab, [5] Glund and colleagues published the results of a randomized, placebo-controlled, double-blind phase I study to assess the safety, tolerability, and efficacy of idarucizumab on the reversal of dabigatran-induced anticoagulation. [6] Healthy Volunteers aged 18 to 45 years were randomized sequentially into 4 idarucizumab dose groups (1 g, 2 g, 4 g, and 5 g). Patients within each group were randomized in a 3:1 ratio to idarucizumab or placebo. The diluted thrombin time, ECT, TT, aPTT, and endogenous thrombin potential were used to assess the anticoagulant effect of dabigatran. Forty-seven male volunteers completed the study. Immediate and sustained reversal (up to 12 hours) of dabigatran-associated increases in ECT, aPTT, and TT were noted with doses of idarucizumab of 2 g or more. Both studies were conducted in healthy volunteers, not representative of the hemorrhaging patient population who will receive

the antidote.

A prospective, phase 3 trial is currently underway in patients on dabigatran with life-threatening bleeding or requiring urgent surgery. [7] An interim analysis was published in 2015, including 90 patients of the planned enrollment goal of 300. [8] Fifty-one patients had serious bleeding and 39 required an urgent procedure to arrest bleeding. There was no control group. Idarucizumab reversed laboratory markers of anticoagulation from dabigatran rapidly and completely, including diluted TT and ECT. It is important to note that not all institutions have these assays available. The dose that appeared most effective was 5 g IV (two-2.5 g infusions given no more than 15 minutes apart). Median time to cessation of bleeding was 11.4 hours. Twenty-one of the 90 patients had serious adverse effects including 5 thrombotic events, however, direct association with idarucizumab administration is unclear. A key limitation is that only 75% of patients had elevated thrombin times prior to administration of idarucizumab, meaning this cohort may not have needed the drug for reversal in the absence of dabigatran activity.

Conclusion

Only PCC, recombinant factor VIIa, and idarucizumab have been studied in trials meeting the Clinical Practice Committees predefined methodology standards according to the GRADE criteria. [9] All of the studies investigating PCC and recombinant factor VIIa were conducted in healthy volunteers and measured laboratory reversal of anticoagulation parameters. Idarucizumab rapidly reverses laboratory coagulation markers from dabigatran. An interim analysis of the REVERSE-AD trial reported 11.4 hours until clinical cessation of bleeding in patients with life-threatening hemorrhage or requiring reversal for urgent procedures. Each of the idarucizumab studies were supported by the antidote's manufacturer. Some of the studies included only male subjects, and one included only white males.