Indications and Methods of Anticoagulation Reversal

Jeremy L. Holzmacher, MD, Babak Sarani, MD*

KEYWORDS

• Anticoagulation reversal • Direct oral anticoagulants • Warfarin
• Prothrombin complex concentrate • Protamine • Idarucizumab • Andexanet alfa
• Aripazine

KEY POINTS

- Understanding the mechanisms of action and pharmacology of anticoagulant drugs is required to maximize the ability to reverse anticoagulation when needed.
- Reversing anticoagulation for invasive procedures should weigh the patient-related risks for thrombosis against the potential for bleeding.
- The approval of idarucizumab for dabigatran reversal and the impending development of specific and non-specific anti-factor Xa reversal agents now comprise a key strategy in the treatment of anticoagulant-associated hemorrhage and perioperative treatment.

INTRODUCTION

The use of anticoagulants within the United States is on the rise with specific direct oral anticoagulant (DOAC) medications gaining Food and Drug Administration (FDA) approval for the prevention of thromboembolic complications, including stroke prevention associated with atrial fibrillation and in the treatment of venous thromboembolism.[1] Normal hemostasis is a tightly controlled and highly regulated process that uses enzyme activation and amplification along with endothelial and platelet interactions to activate thrombin and propagate fibrin formation and cross-linking (**Fig. 1**).[2] Anticoagulant medications disrupt this process directly by inhibiting clotting factor activity, indirectly by depleting vitamin K–dependent clotting factors, or by amplifying native anticoagulant pathways through antithrombin III (ATIII).[2] Historically, the most common anticoagulant prescribed was warfarin, and standard reversal strategy was based on factor repletion using plasma and vitamin K.[2–4] The advent of both oral

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Center for Trauma and Critical Care, Department of Surgery, George Washington University Medical Center, 2150 Pennsylvania Avenue Northwest, Suite 6B, Washington, DC 20037, USA
* Corresponding author. 2150 Pennsylvania Avenue Northwest, Suite 6B, Washington, DC 20037.
E-mail address: bsarani@mfa.gwu.edu

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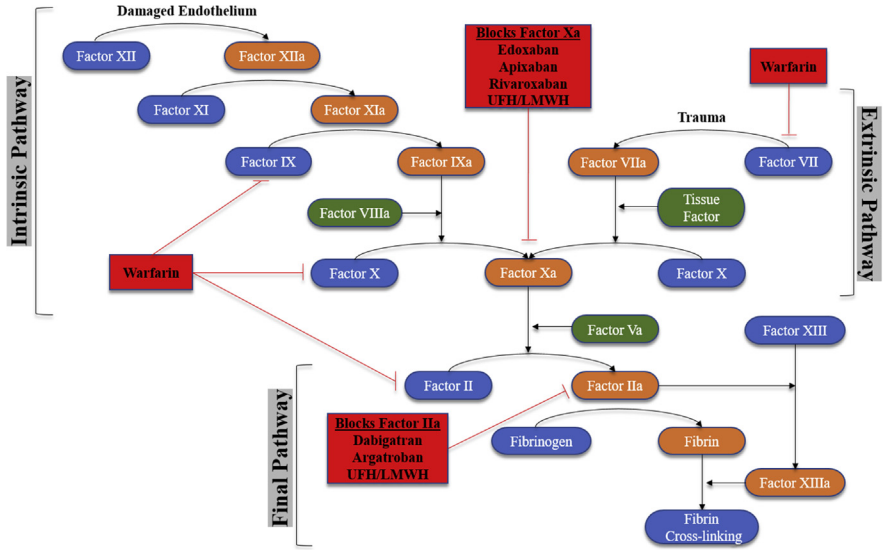

Fig. 1. Coagulation cascade and targets of oral and parenteral anticoagulant agents. (*Data from* Ferreira JL, Wipf JE. Pharmacologic therapies in anticoagulation. Med Clin North Am 2016;100(4):695–718.)

and parenteral direct anti–factor Xa and thrombin (factor IIa) inhibitors, however, has required the development of alternative reversal methods.

In 2010, the FDA approved dabigatran, a direct thrombin inhibitor, for the prevention of stroke in patients with nonvalvular atrial fibrillation. Shortly thereafter, 3 additional DOACs—rivaroxaban, apixaban, and edoxaban—were approved for similar indications.[2] The benefits of DOAC drugs were the immediacy of full anticoagulation without the need for routine blood monitoring and better overall bleeding profiles; however, DOAC-specific antidotes have been slow to development, have limited availability, and are expensive.[5] As such, reversal strategies for these newer medications are either newly formed or still forming.

Considering the evolving nature of anticoagulation and need for cogent and evidenced based reversal strategies, this article reviews the mechanisms of action of the commonly used anticoagulants as well as the indications for and current methodologies of anticoagulation reversal. Although many patients on full anticoagulation may also be taking antiplatelet medications, the methods for mitigating their effects on hemostasis are beyond the scope of this article. Similarly, postprocedural resumption of anticoagulation and periprocedural bridging are not discussed.

REVERSAL STRATEGIES FOR ALL ANTICOAGULANTS

Underlying any decision to reverse a patient's anticoagulation status is the risk-benefit analysis weighing possible thrombosis against potential bleeding (Fig. 2). With this understanding, anticoagulation reversal can be divided into 3 categories depending on the urgency needed to restore hemostasis: (1) emergent or urgent requiring reversal in less than an hour, (2) semiurgent requiring reversal within hours, or (3) nonurgent reversal that can typically happen over a matter of days. Regardless of the urgency, reversing any anticoagulant starts by withholding the offending agent. In emergent and semiurgent circumstances, considerations should be given toward administering