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Review

Introduction to direct oral anticoagulants and rationale for specific reversal agents ^{☆☆☆}



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In late 2010 a new class of oral anticoagulants, now known as the direct oral anticoagulants (DOACs), was introduced in the United States, as an alternative to vitamin K antagonists (VKAs), for the prevention of thromboembolic events in patients with nonvalvular atrial fibrillation. Subsequently these drugs were also shown to be safe and effective in the prevention and treatment of venous thromboembolism. [1–4]. The direct thrombin inhibitor dabigatran etexilate was the first agent to be approved, followed by the factor Xa (FXa) inhibitors rivaroxaban, apixaban, and edoxaban. These DOAC agents have demonstrated similar or superior efficacy to that of VKAs such as warfarin for the prevention of stroke in patients with nonvalvular atrial fibrillation, and similar efficacy for the treatment of venous thromboembolism in clinical trials [5]. The DOACs also offer clear advantages over warfarin, such as fixed dosing, fewer drug–drug interactions, and administration without the need for routine monitoring via coagulation tests [6]. With all anticoagulant therapies, bleeding risks are an ongoing safety concern, but overall risks of major bleeding with DOACs seem to be similar to or better than that of warfarin [5,7,8]. Furthermore, the risk of intracranial hemorrhage is significantly reduced, and there may be a slightly increased risk of gastrointestinal bleeding [5,7,8].

Fortunately, because of the short half-lives of the DOACs, the majority of DOAC-associated bleeding complications can be managed simply by withholding the agent and providing supportive care for the patient. [6]. Similarly, the short half-lives of the DOACs facilitate the timing of elective surgery after the withdrawal of the agent [1–4]. However, urgent reversal of the anticoagulant effect of a DOAC is required in rare clinical situations, such as uncontrolled or life-threatening bleeding or when an emergency invasive procedure is required.

Until recently, management of such situations was complicated by the lack of specific reversal agents. This has changed, however, with the introduction of DOAC-specific reversal agents. The dabigatran-specific reversal agent idarucizumab was approved by the U.S. Food

and Drug Administration in October 2015 and by the European Medicines Agency in November 2015, for use in the rare instances when the reversal of the anticoagulant effects of dabigatran is needed (ie, for emergency surgery and urgent procedures, or if there is life-threatening or uncontrolled bleeding) [9,10]. Two other specific reversal agents, andexanet alfa (r-Antidote, PRT064445; Portola Pharmaceuticals, South San Francisco, Calif) and ciraparantag (aripazine, PER-977; Perosphere, Danbury, Conn) are currently in development. Andexanet alfa is an FXa decoy molecule with no intrinsic coagulation activity that has been shown to reverse the effects of direct and indirect FXa inhibitors in studies involving nonbleeding volunteers [11–13]. Ciraparantag is a potential antidote for direct and indirect FXa inhibitors and direct thrombin inhibitors, as well as unfractionated heparin and low-molecular-weight heparins such as enoxaparin, and thus is being developed as a “universal agent” [14]. It is hoped that these agents will streamline the management of patients who require urgent reversal of the anticoagulant effects of DOACs in the emergency settings of life-threatening bleeds, or as in the case of idarucizumab, both emergency surgery or life-threatening bleeds.

This special issue of *The American Journal of Medicine* provides information and clinical guidance on the rationale for specific reversal agents and their appropriate use. Clinical data on DOAC-associated bleeding from phase 3 clinical trials and postmarketing trials are reviewed, as are current strategies for the management and assessment of bleeding events, perioperative management in the setting of DOAC therapy, and reinitiation of DOAC therapy after a bleeding event. Current data relating to the mode of action, efficacy, and safety of each of the agents are also provided, alongside a review of the potential place for these agents in guidelines and hospital protocols.

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