Vitamin K antagonists, direct oral anticoagulants, and the rationale for reversal agents

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Despite these advantages, clinicians have been concerned over the lack of specific reversal agents for use in the event of a life-threatening bleeding event or when an emergent interventional procedure is required. This concern may limit the use of DOACs, as warfarin can be reversed with the combination of a factor product (fresh frozen plasma or prothrombin complex concentrate) and phytonadione.

Idarucizumab, a dabigatran-specific reversal agent, was approved by the Food and Drug Administration (FDA) in October 2015 for use when reversal of the anticoagulant effects of dabigatran is needed (i.e., for emergency surgery, urgent procedures, or in the event of life-threatening or uncontrolled bleeding). Initial data from a Phase III trial of idarucizumab were published this year. At the time of writing, two more reversal agents—andexanet alfa and ciraparantag—were in clinical development. Both of these reversal agents have been granted accelerated FDA approval pathways. Phase III trials with andexanet alfa and ciraparantag were published this year. At the time of writing, two more reversal agents—andexanet alfa and ciraparantag—were in clinical development. Both of these reversal agents have been granted accelerated FDA approval pathways.

The three reviews in this supplement have been prepared to assist health-system pharmacists in understanding how specific reversal agents may be used to manage bleeding or facilitate invasive procedures in patients taking DOACs.

The pharmacology and mechanism of action of each reversal agent differs. Different dosages or dosing strategies will likely be required for different anticoagulants requiring reversal, and adjustments may be required based on how the patient responds (i.e., some reversal agents may need to be redosed). These agents may also have different indications, as they are being studied in different populations, (e.g., idarucizumab is approved for life-threatening bleeding and urgent surgery, whereas andexanet alfa is being studied only in patients with life-threatening bleeding). Furthermore, the use of agents such as ciraparantag, that can reverse the anticoagulant activity of traditional agents, as well as DOACs, may limit future options for anticoagulation. Pharmacists are perfectly positioned not only to work in ensuring the appropriate use of these agents in direct patient care but also to develop anticoagulation reversal protocols, guidelines, and order sets to help clinicians care for these patients when a pharmacist cannot be at the bedside. Pharmacists can also help promote appropriate patient selection, recommending the use of these agents for DOAC reversal only when a bleeding event is critical or an urgent invasive procedure is required, as well as highlighting the need for other supportive measures that may still be required. Institutional pharmacists, therefore, have a crucial role to play in facilitating the optimal use of reversal agents for DOACs.
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