Reversal Agents for the Direct Oral Anticoagulants

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KEYWORDS

• Anticoagulants • Direct oral anticoagulants • Antidotes • Reversal agents • Bleeding • Hemorrhage • Adverse events • Idarucizumab

KEY POINTS

- The new direct oral anticoagulants have a bleeding risk profile better than the vitamin K antagonists, but are still associated with serious bleeding.
- The new direct oral anticoagulants were developed without specific reversal agents.
- Current recommendations for reversal of the new direct oral anticoagulants when major bleeding occurs include the use of prothrombin complex concentrates.
- There are 3 specific reversal agents in development for the direct oral anticoagulants, with one of them, idarucizumab, recently approved for clinical use.

INTRODUCTION

Oral anticoagulants, because of their intended function to impair coagulation and prevent or retard thrombus development, are associated with an almost obligatory incidence of bleeding ranging from nuisance bleeding to life-threatening and fatal bleeding. This bleeding incidence is well documented with the traditional oral anticoagulant, warfarin, one of the vitamin K antagonists (VKAs).[1] This class of drugs is responsible for the most emergency hospitalizations due to an adverse drug event (bleeding),[2] the most emergency room visits due to an adverse drug event,[3] and the most common cause of death associated with an adverse drug event.[4] Bleeding on warfarin is also an important contributor to the overall costs of anticoagulant therapy.[5] Although most bleeding events occur when patients are therapeutically anticoagulated, VKA therapy is further complicated by poor management that allows patients to be over-anticoagulated and put at a higher risk of anticoagulant-related bleeding.[6] Additional factors, such as poorly controlled hypertension and other comorbidities,

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further enhance the risk of bleeding, and better management of these comorbidities could lessen the incidence of bleeding. Given this serious potential side effect, it is only natural that one would like to be able to reverse anticoagulation when necessary, especially in the setting of life-threatening bleeding. However, having a reversal agent is not so simple. Questions arise as to how effective is the reversal, will reversal of anticoagulation impact overall outcome of the bleeding event, will reversal improve overall patient outcome, does the reversal agent have any deleterious side effects of its own, will reversal of anticoagulation place the patient at an undue risk of a thrombotic event, and will the reversal agent be expensive and possibly not cost-effective. Many of these questions are explored in the following discussion because such agents apply to the new direct oral anticoagulants (DOACs) as well as to warfarin.

WHEN WILL REVERSAL AGENTS BE NEEDED?

The decision to use a reversal agent depends on many factors, including its documented or perceived effectiveness, cost, side-effect profile, and the risk of allowing thrombosis to break through when coagulation is corrected. An effective, inexpensive agent with minimal or no side effects would likely be used more often and for lesser degrees of bleeding than an expensive agent, or one that has potential side effects, or one that has questionable value in improving overall outcome. For reversal of warfarin anticoagulation, vitamin K might fit better in the former category, whereas prothrombin complex concentrates would fit better in the latter category. Given the current complexity and cost structure of reversal agents for the VKAs and the DOACs, it is likely that such agents will be used mostly for patients with major, hemodynamically unstable and life-threatening bleeding or bleeding into a vital organ. They could also be indicated for patients requiring emergent surgery or intervention who are currently on an anticoagulant or patients sustaining severe trauma who might be at great risk of life-threatening bleeding, but without detectable bleeding at the moment. Agents might be used in drug overdose and might even be considered to shorten the interval when an anticoagulant needs to be discontinued for an elective procedure in a patient with a strong underlying thrombotic risk.

ATTRIBUTES OF A USEFUL REVERSAL AGENT

In considering the DOACs and potential reversal agents, one would like an agent that is readily available to clinicians on the front lines, that acts rapidly to reverse anticoagulation and produces sustained normalization of coagulation, that has no significant side effects, does not induce a prothrombotic state, allows re-anticoagulation in the short term if needed, does not induce tolerance, and is relatively inexpensive or cost-effective (**Box 1**). It should also have the potential to improve patient outcomes from the bleeding event, but whether the agent actually halts the bleeding or changes the clinical outcome is as much dependent on the source, size, and location of the bleed as it is on the reversal agent. Demonstrating improved outcomes will be difficult, if not impossible, in a randomized fashion when dealing with life-threatening bleeding.

DO THE VITAMIN K ANTAGONISTS HAVE A REVERSAL AGENT?

The VKAs produce their anticoagulant effect by targeting a key enzyme in the vitamin K pathway, vitamin K oxide reductase complex 1, leading to a decrease in normal functioning vitamin K–dependent coagulation factors (factors II, VII, IX, and X and other vitamin K–dependent proteins).[6] As a result, the prothrombin time (PT), expressed as an international normalized ratio (INR), and the activated partial