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Review

# Reversal agents for direct oral anticoagulants: A focused review

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ABSTRACT

For several decades the vitamin K antagonist oral anticoagulants were the only outpatient therapy that existed to reduce the risk of stroke and thromboembolism. When the new direct oral anticoagulants were approved for use and addressed many of the issues associated with oral vitamin K antagonists, a new concern arose—the lack of rapid ability to reverse these agents. Physicians and patients were concerned that in cases of life-threatening bleeding or need for emergent surgery, an antidote to reverse the anticoagulation effect of these agents did not exist. Contemporary research has aimed to produce reversal agents that can be administered to safely neutralize the anticoagulant effect. In this focused review we describe the clinical development as well as mechanisms of action of three agents (idarucizumab, andexanet alpha, and ciraparantag). We review the pharmacokinetics, animal and human study data of these reversal agents and outline the evidence supporting their use. Although questions of safety and appropriate use remain, these reversal agents offer a significant step forward in the widespread use of direct oral anticoagulants and overall management of the anticoagulant effect.



## 1. Introduction

For nearly 50 years oral vitamin K antagonists (VKA) were the only anticoagulants available. While these agents decrease the risk of stroke and systemic thromboembolism in patients with atrial fibrillation (AF) by nearly 70% [1] and improve morbidity and mortality from deep vein thrombosis (DVT) and pulmonary embolism (PE) by over 90% [2], the clinical management of patients taking warfarin is difficult due to multiple drug–drug interactions, dietary interactions, and routine monitoring required to attain a therapeutic window of effect. This has translated into poor patient adherence and significant underuse of VKAs [3]. Starting in 2009, a new class of anticoagulants, direct oral anticoagulants (DOACs) were approved for the prevention of embolic stroke in patients with nonvalvular AF and treatment of DVT/PE. Currently this class includes dabigatran, rivaroxaban, apixaban, and edoxaban. Advantages of these agents include rapid onset of action, absence of an effect of dietary vitamin K intake on their activity, and fewer drug interactions. A meta-analysis of the pivotal phase 3 clinical trials in patients with AF showed that DOACs had a favorable risk–benefit profile, with significant reductions in stroke (19% compared to warfarin), intracranial hemorrhage (51% compared to warfarin) and mortality (10% compared with warfarin) [4]. Global and national data on "real-world" patients has shown that these agents continue to be underprescribed in AF patients [5,6]. A major concern regarding DOACs has been the lack of an antidote to reverse their anticoagulation effect in case of life-threatening bleeding or need for emergent surgery. For this reason, intense effort has been focused on developing specific reversal agents that can quickly neutralize the anticoagulant effects of DOACs. The goal of this review is to describe the bleeding risks in patients on oral anticoagulants and DOAC-specific reversal agents that are in different stages of clinical development.

## 2. Bleeding risk with direct oral anticoagulants

Bleeding is the main adverse outcome of anticoagulant therapy. Risk factors for major bleeding with oral VKA prescription include age, previous stroke, and time within therapeutic range [7]. Pharmacological properties of DOACs were promising in addressing some of these risks and adoption of these agents has been dependent on their safety profile. The hazard of bleeding in patients treated with DOACs was initially assessed in four landmark Phase III trials (RE-LY [8], ROCKET-AF [9], ARISTOTLE [10], ENGAGE AF-TIMI 48 [11]). The risk of major bleeding was significantly reduced with dabigatran 110 mg b.i.d., apixaban and edoxaban while the bleeding rates for dabigatran 150 mg b.i.d. and rivaroxaban were similar to those with warfarin [4].

Gastrointestinal (GI) bleeding accounts for 90% of extracranial bleeding in patients with AF receiving VKAs [12]. In the initial clinical trials, patients who received dabigatran at a dose of 150 mg b.i.d., rivaroxaban, and edoxaban at a dose of 60 mg experienced significantly higher rates of GI bleeding compared with patients who were randomized to warfarin. Patients on apixaban had similar rates of GI bleeding, while patients who took edoxaban 30 mg had significantly lower rates of GI bleeding compared with warfarin.

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Intracranial hemorrhage (ICH) is the most feared bleeding event in terms of location and severity, due to its increased morbidity and mortality [13]. While ICH is often cited as the most catastrophic scenario in a patient taking a DOAC due to bleed within a closed space that cannot be reversed, the DOACs consistently outperform VKAs in this type of bleeding event. In a meta-analysis of RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials, Ruff et al. showed that DOACs had a significant reduction in ICH compared to warfarin (0.49, 0.38–0.64; $P < 0.0001$) [4]. Each DOAC has been associated with a reduced risk of ICH when used for stroke prevention in AF and there are several mechanisms that have been proposed [14].

In many clinical circumstances, bleeding can be controlled with cessation of anticoagulation or standard supportive care. However, in cases of life-threatening bleeding or emergent surgery, the need for a specific and rapid reversal agent arises. Intracranial hemorrhage, has the highest likelihood of significant morbidity and fatal outcome, and is one of the primary aims for reversal agents. While real-world studies appear to corroborate the safety profile of the DOACs seen in clinical trials [14], development of specific reversal agents is necessary to provide patients the broadest protection.

## 3. Specific reversal agents

Several novel drugs that act as specific reversal agents to DOACs have undergone clinical development. These agents include idarucizumab, a reversal agent for dabigatran, andexanet alfa, a reversal agent for Factor Xa (FXa) inhibitors, and ciraparantag, a universal reversal agent active against all DOACs, as well as fondaparinux and heparin.

### 3.1. Idarucizumab

#### 3.1.1. Development and pharmacokinetics of idarucizumab

The first step in the development of idarucizumab was to immunize mice with dabigatran-derived haptens to produce antibodies against dabigatran [15]. The antigen-binding fragment (Fab) of antibodies with the highest affinity for dabigatran were then isolated. Murine protein sequences were replaced with human sequences and expressed in a mammalian cell line with the use of recombinant DNA technology. The resultant humanized monoclonal antibody fragment bound dabigatran with an affinity that was 350 times as high as that observed with thrombin. [15] Its mechanism of action is illustrated in Fig. 1.

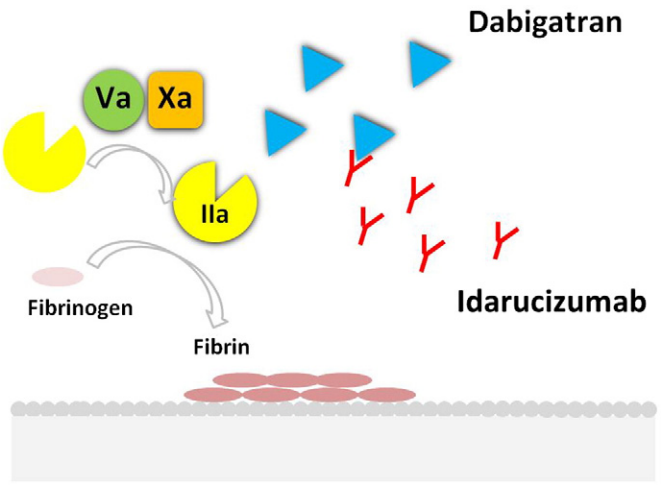


**Fig. 1.** Mechanism of action of idarucizumab. The prothrombinase complex consists of Factor Xa (Xa) and Factor Va (Va), and catalyzes the conversion of inactive prothrombin to the active protease, thrombin (IIa). This leads to fibrin generation and clot formation. The effect of the thrombin inhibitor dabigatran is reversed by idarucizumab, a humanized monoclonal antibody.

The interaction of idarucizumab with dabigatran is characterized by a rapid on-rate and a very slow off-rate, making binding effectively irreversible. In healthy volunteers, peak plasma concentrations of idarucizumab are achieved at the end of a 5-minute infusion, which ensures immediate availability in plasma for binding to dabigatran. [16] Idarucizumab reverses dabigatran in a dose-dependent manner. [17] In volunteers with normal renal function, idarucizumab has a half-life of ≈45 min and only 4% of the peak concentration remain in plasma after 4 h [16].

Due to its molecular weight, idarucizumab is eliminated mainly by renal excretion [16]. Proximal renal tubule receptors are responsible for reuptake of protein fragments. As a result of its predominantly renal excretion, idarucizumab clearance is attenuated in patients with renal impairment. Plasma concentrations of idarucizumab are increased 43.5% and 83.5% in subjects with mild or moderate renal impairment, respectively [18]. This may benefit patients with renal impairment as these same patients often have elevated dabigatran plasma concentrations. The idarucizumab-dabigatran complex is cleared in a manner analogous to that of free idarucizumab [19].

#### 3.1.2. Animal studies

Initial studies in rats demonstrated that a single bolus injection of idarucizumab completely reversed the anticoagulant activity of 200 ng/mL dabigatran within 1 min, as measured by thrombin time (TT) and activated partial thromboplastin time (aPTT) [15]. This reversal was maintained during the course of 25 min despite continual infusion of further dabigatran. Subsequent studies in a porcine blunt liver injury model showed idarucizumab to rapidly reverse the hemorrhagic effects of dabigatran. Administration of idarucizumab at 30, 60, or 120 mg/kg reduced blood loss in a dose-dependent manner and improved survival up to 100% compared with untreated controls ($P < 0.0001$ for all groups) [20]. With administration of idarucizumab 30, 60, or 120 mg/kg, plasma concentrations of unbound active dabigatran decreased by 75%, 80%, and 93%, respectively, compared with the pretreatment levels. The experiment highlighted a finding that was shown in subsequent trials - idarucizumab remains predominantly in plasma, and this initiates a shift in equilibrium of dabigatran molecules from tissues to the blood compartment where they bind to idarucizumab. When idarucizumab was compared to 4-factor prothrombin complex concentrate in a polytrauma model in which pigs were subjected to both liver injury and bilateral femoral fracture, it reduced hemorrhage and was associated with 100% survival. [21]. In a mouse model of ICH, idarucizumab prevented intracerebral hematoma enlargement, and substantially reduced the excess mortality of the anticoagulated animals [22]. These preclinical studies supported the potential of idarucizumab to attenuate dabigatran-induced bleeding in humans.

#### 3.1.3. Volunteer studies

In phase I and II clinical trials, anticoagulation was assessed using diluted thrombin time (dTT), thrombin time (TT), activated partial prothrombin time (aPTT), ecarin clotting time (ECT), activated clotting time (ACT), and thromboelastography parameters. In volunteers who included the elderly and renally impaired subjects, idarucizumab reversed the anticoagulant effect of dabigatran within 5 min in a dose-dependent manner [23], [24], [25]. Of note, idarucizumab administration in the absence of dabigatran had no effect on coagulation parameters or endogenous thrombin potential, suggesting that it is unlikely to be intrinsically prothrombotic [16]. Further, these trials showed idarucizumab to be well-tolerated, without thrombotic, serious or severe side effects.

#### 3.1.4. Clinical phase 3 study

Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE AD) is a global, prospective, cohort study. It is an open-label, single-arm, phase III trial of idarucizumab administration in patients who