Review Article

Direct Oral Anticoagulant Agents: Pharmacologic Profile, Indications, Coagulation Monitoring, and Reversal Agents

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Vitamin K antagonists (VKAs), such as warfarin, have been used for thromboprophylaxis and for the treatment of thromboembolic events in patients with nonvalvular atrial fibrillation for over 60 years. The increasing use of direct oral anticoagulants (DOACs) in recent years has shown greater advantages and safer use over VKA, including reduced bleeding, fewer drug interactions, no food interactions, a quick onset and offset of activity, and predictable dose-response properties. Despite their advantages, there are a couple of major limitations that raise concerns among clinicians, including the need for more coagulation assays to monitor their effects and more specific reversal antidotes in life-threatening circumstances of bleeding. This review will discuss the important characteristics of the 5 Food and Drug Administration-approved DOACs (including anticoagulation monitoring for each) and the specific and nonspecific reversal agents to DOAC-associated bleeding. **Key Words:** Idarucizumab—aripazine—andexanet alfa—thromboprophylaxis—direct oral anticoagulants—DOAC—reversal agents—pharmacology of DOACs.

Introduction

Conventional anticoagulants, such as vitamin K antagonists (VKAs), have been in use for more than 60 years for thromboprophylaxis and for the treatment of venous thromboembolism and other thromboembolic events in patients with nonvalvular atrial fibrillation (NVAF).[1] In recent years, there has been an emergence of direct oral anticoagulants (DOACs, also known as nonwarfarin anticoagulants, nonvitamin K oral anticoagulants, or novel oral anticoagulants),[2] which demonstrate greater advantages and a more stable pharmacologic profile over VKAs,[3] such as warfarin (Coumadin [Bristol-Myers-Squibb, New York City, New York]). DOACs include direct thrombin (factor II) inhibitors (i.e., dabigatran) and direct factor Xa (FXa) inhibitors (i.e., rivaroxaban, apixaban, edoxaban, and betrixaban). Unlike VKA, DOACs significantly reduce the risk of intracranial bleeding (ICB) and do not require consistent coagulation monitoring.[2-4] They also have decreased drug and food interactions, a rapid onset and offset of action, and predictable dose-response properties.[3-5]

Despite these benefits, DOACs exhibit a few important limitations, including cost, shorter half-life (thus, disallowing a patient protection if a dose is missed), higher risk of gastrointestinal bleeding, and the shortage of available specific reversal agents and coagulation assays to monitor their anticoagulation effects.[6] Currently, the cost of DOACs is more expensive than VKA due to their ongoing improvements and recent approval for clinical use. The average cost of each of the 5 Food and Drug Administration (FDA)-approved DOACs (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) is approximately U.S. $436/month, or U.S. $5233/year per patient (with dosing ranging from 2.5 to 150 mg/tablet),[7-11]

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compared with warfarin's average retail price of U.S. $18.66/month.[7]

Importantly, there is a dearth of reversal agents to DOACs in life-threatening cases of bleeding or emergency surgery. Several specific reversal agents, including idarucizumab, andexanet alfa, and aripazine, have undergone randomized, double-blind, placebo-controlled clinical trials in recent years. Nonetheless, as thrombosis involves multiple mechanisms, polypharmacy is essential to appropriately address this issue and its associated complications. In addition to a need for more reversal agents, there is uncertainty surrounding proper laboratory monitoring of DOACs. Although monitoring of DOACs is not required, there are circumstances in which routine anticoagulation assessments would be useful, such as emergency surgery, reduced renal function, or major bleeding.[12] The uncertainty renders routine monitoring of DOAC activity difficult in clinical practice especially in emergency situations in which knowledge of anticoagulant activity is critical for decision making.

We have chosen to discuss only current FDA-approved uses of these agents because a discussion of all potential uses of these agents is beyond the scope of this review article. This article provides a review of the pharmacologic profile and anticoagulation monitoring of DOACs, as well as the characteristics and ongoing or completed clinical trials of specific and nonspecific reversal agents.

Direct Oral Anticoagulants (DOACs)

The limitations of VKA have prompted the recent developments of DOACs as alternatives, which specifically target the catalytic sites of enzymes in the coagulation cascade to inhibit their activity. Currently, there are 5 FDA-approved DOACs, including direct thrombin (factor II) inhibitor dabigatran and the FXa inhibitors rivaroxaban, apixaban, edoxaban, and betrixaban. Table 1 summarizes the key characteristics of the DOACs.

Dabigatran

Dabigatran was the first DOAC to be approved by the U.S. FDA for clinical use in 2010.[13] It is a nonpeptidic, reversible, and competitive inhibitor of the free and clot-bound forms of thrombin (II) in the coagulation cascade.[13] Its activity leads to a downstream inhibition of fibrin and disruption in stable clotting formation.

Use of Dabigatran

Dabigatran has been approved (1) to treat deep venous thrombosis and pulmonary embolism in patients who have been receiving a parenteral anticoagulant for 5-10 days, (2) to reduce the risk of stroke and thromboembolic events in patients with NVAF, (3) to reduce the recurrence risk of DVT and PE in patients who were previously treated

Table 1. *Summary of FDA-approved DOACs*

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Date of approval	2010	2011	2012	2015	2017
Mechanism of action	Direct thrombin (FIIa) inhibitor	Direct FXa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor
Half-life elimination	12-17 h	5-9 h	~12 h	10-14 h	19-27 h
Primary method of elimination	Renal (80%)	Renal (66%), intestinal (28%)	Renal (~27%), intestinal	Renal (~50%)	Intestinal (~85%), renal (11%)
Drug interactions (Risk X: avoid combination)	Sulfinpyrazone, urokinase, Vorapaxar	Cobicistat, CYP3A4 inducers and inhibitors, hemin, mifepristone, omacetaxine, St. John's wort, urokinase, vorapaxar	CYP3A4 inducers, hemin, mifepristone, omacetaxine, St. John's wort, urokinase, vorapaxar	Hemin, mifepristone, omacetaxine, rifampin, urokinase, vorapaxar	Hemin, mifepristone, omacetaxine, urokinase, vorapaxar
Coagulation monitoring	aPTT, ECT, TT, dTT	PT, anti-FXa activity	anti-FXa activity	PT, aPTT, anti-FXa activity	Not well studied, but anti-FXa activity is likely useful

Abbreviations: aPTT, activated partial thromboplastin time; dTT, dilute thrombin time; ECT, ecarin clotting time; FIIa, thrombin; FXa, factor Xa; DOACs, direct oral anticoagulants; PPIs, proton pump inhibitors; PT, prothrombin time.; TT, thrombin time.