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Review

Specific antidotes against direct oral anticoagulants: A comprehensive review of clinical trials data

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ABSTRACT

The Vitamin K antagonist warfarin was the only oral anticoagulant available for decades for the treatment of thrombosis and prevention of thromboembolism until Direct Oral Anticoagulants (DOACs); a group of new oral anticoagulants got approved in the last few years. Direct thrombin inhibitor: dabigatran and factor Xa inhibitors: apixaban, rivaroxaban, and edoxaban directly inhibit the coagulation cascade. DOACs have many advantages over warfarin. However, the biggest drawback of DOACs has been the lack of specific antidotes to reverse the anticoagulant effect in emergency situations. Activated charcoal, hemodialysis, and activated Prothrombin Complex Concentrate (PCC) were amongst the nonspecific agents used in a DOAC associated bleeding but with limited success. Idarucizumab, the first novel antidote against direct thrombin inhibitor dabigatran was approved by US FDA in October 2015. It comprehensively reversed dabigatran-induced anticoagulation in a phase I study. A phase III trial on Idarucizumab also complete reversal of anticoagulant effect of dabigatran. Andexanet alfa (PRT064445), a specific reversal agent against factor Xa inhibitors, showed a complete reversal of anticoagulant activity of apixaban and rivaroxaban within minutes after administration without adverse effects in two recently completed parallel phase III trials ANNEXA-A and ANNEXA-R respectively. It is currently being studied in ANNEXA-4, a phase IV study. Aripazine (PER-977), the third reversal agent, has shown promising activity against dabigatran, apixaban, rivaroxaban, as well as subcutaneous fondaparinux and LMWH. This review article summarizes pharmacological characteristics of these novel antidotes, coagulation's tests affected, available clinical and preclinical data, and the need for phase III and IV studies.

1. Introduction

Atrial fibrillation (AF) is a common arrhythmia seen in clinical practice and represents a significant clinical burden. Almost 20% of all ischemic strokes are attributable to AF [1]. Direct cost to Medicare for AF-related strokes in the first year is estimated to be $2.6 billion [2,3,4,5]. Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), affects more than 1 million patients each year globally. In the United States, the economic burden of this disease costs more than $1.5 billion a year [6,7].

Vitamin K Antagonist (VKA), like warfarin, has been the only oral anticoagulant available in the last 60 years. Coumadin has been used for decades to treat VTE and prevent stroke in patients with AF. Due to the slow onset of VKA's action, overlapping with a parenteral anticoagulant [e.g.: low molecular weight heparin (LMWH) or unfractionated heparin (UFH)] is needed for the first few days until therapeutic International Normalized Ratio (INR) with VKA is achieved. However, Coumadin as an anticoagulant has its limitations such as narrow therapeutic index, food–drug interaction, drug–drug interaction, interindividual variation due to hepatic enzymes variability and absorption variability, routine INR check, and close follow-up of the patients [8,9,10].

2. Direct Oral Anticoagulants (DOACs)

DOACs are a group of new oral anticoagulant medications, which directly inhibit the coagulation cascade. Non-warfarin oral anticoagulants (NOACs, formerly 'novel' oral anticoagulants and now sometimes referred to as non-vitamin K OACs, target-specific OACs or direct OACs) [11,12]. Until the beginning of this decade, there were no effective oral alternatives to warfarin. There are currently four approved DOACs in USA including direct thrombin inhibitor dabigatran and factor Xa inhibitors including rivaroxaban, apixaban, and edoxaban [16].

3. Dabigatran

Dabigatran (Pradaxa) was the first DOAC which was approved by the US Food and Drug Administration (FDA) for non-valvular AF in 2010 [13,17]. Subsequently, this was approved for treatment of DVT and PE in 2014. The effect of the drug peaks within 2–3 h of oral

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administration. Eighty percent of the drug is eliminated from kidneys and the rest is through liver [18,19].

4. Rivaroxaban

Rivaroxaban (Xarelto) was the first factor Xa inhibitor and second in the line of DOAC, which was approved in the USA for nonvalvular AF and VTE in 2011 [14,20,21]. The drug effect peaks within 2–4 h after oral administration. Rivaroxaban has two pathways of elimination; two-thirds of the dose undergoes metabolic degradation, and one-third is eliminated as unchanged drug in the urine [22,23].

5. Apixaban

Apixaban (Eliquis) is the third DOAC, approved in the USA for nonvalvular AF in 2012 [15,24]. The indication was subsequently extended to VTE treatment in 2014. This drug has a 15-hour half-life and no effect with food on its bioavailability. Thirty-five percent of the drug is excreted by the kidneys [25].

6. Other Xa agents

Edoxaban (Savaysa) is the latest drug in the class which was introduced in the USA in 2015. Betrixaban and other factor Xa inhibitors, are in evaluation and not yet approved by the FDA [26,27].

All the DOACs, their indications and brief mechanism of action are summarised in Table 1.

7. Specific target site of DOACs in coagulation cascade

The new DOACs target specific enzymes in the common pathway of the coagulation cascade, in contrast to warfarin, which attenuates thrombin generation by decreasing levels of vitamin K-dependent clotting proteins, factors II, VII, IX, and X [28].

Thrombin plays a central role in the coagulation system. Dabigatran connects to thrombin with high specificity and affinity, inactivating both fibrin-bound as well as unbound thrombin and preventing the conversion of fibrinogen to fibrin [29]. Rivaroxaban, apixaban, and edoxaban prevent thrombin formation by directly inhibiting free and clot-bound factor Xa, without requiring cofactors (such as antithrombin). These agents suppress synthesis of new plasma thrombin but have no effects on the activity of the existing thrombin [30,31].

8. Coagulation tests affected by DOACs

DOACs do not require monitoring of any coagulation tests when used in clinical practice. However, there are certain situations where the anticoagulant effect of these drugs needs to be determined, such as when patients require urgent invasive procedures, in actively bleeding patients, and in asymptomatic patients with excessively elevated INR [32]. Every one of the new oral anticoagulants prolongs individual coagulation tests in a dose-dependent manner. Some of the coagulation tests, affected by DOACs, also serve as surrogate markers to show the reversal of effects of these drugs with specific antidotes [33].

The unique mechanism of actions of DOAC makes the results of PT/INR tests unreliable in patients. Dabigatran inhibits coagulation by directly and specifically binding thrombin (factor IIa) [34]. The INR is relatively insensitive to dabigatran-induced anticoagulation, yielding normal or near-normal results at therapeutic dabigatran plasma concentrations and only slight increases in higher drug levels [35,36]. The thrombin time (TT) is probably the most sensitive to give interpretable information about dabigatran [37]. This has led to the development of a diluted thrombin time test (dTT) calibrated for dabigatran. The ecarin clotting time (ECT) is another available assay that is sensitive to dabigatran action within its therapeutic range [38]. The ECT and the dTT assays have a linear response to plasma dabigatran across its therapeutic range. However, aPTT only gives an approximate assessment of the effect of dabigatran on coagulation [39].

The FXa inhibitors rivaroxaban and apixaban have also been reported to give variable results with PT [40]. Direct factor Xa inhibitors don't influence TT, ECT, or the hemoclot test, but have a strong effect on anti-factor Xa assays [41,42]. There is a broad range of anti-Factor Xa chromogenic assays, which correlate with plasma concentrations of different factor Xa inhibitors, but these tests must be individually adjusted for each type of Xa inhibitor (e.g., apixaban, edoxaban or rivaroxaban) and as of yet they're not available worldwide [43,44,45].

The coagulation tests affected by DOAC's are summarized in Table 2.

9. Bleeding associated with DOAC compared with warfarin

The meta-analysis of primary studies in AF showed lower rates of major bleeding with the DOACs in comparison with warfarin in RE-LY [17] and ARISTOTLE [24] and neutral in ROCKET-AF [20]. The DOACs reduced the relative risk of intracranial bleeding in comparison with warfarin. However, they showed higher rates of major gastrointestinal bleeding with the DOACs compared with warfarin in the same studies [46].

A recent meta-analysis compared the bleeding risk of DOACs in 6 major clinical trials of acute VTE. The data included two studies with dabigatran (RE-COVER I and II), two studies with rivaroxaban (EINSTEIN-DVT, EINSTEIN-PE), one study with apixaban (AMPLIFY) and one study with edoxaban (Hokusai-VTE) [47–51]. The DOACs reduced the relative risk of major bleeding in comparison with standard treatment (relative risk 0.62, 95% confidence interval 0.45 to 0.85). Among major bleeding events, the reduction was consistent for fatal bleeding (0.36, 0.15 to 0.84) and intracranial bleeding (0.34, 0.17 to 0.69) [47,50,51].

Although, several meta-analyses and major published clinical trials suggested that DOACs do not increase the risk of significant bleeding, a lack of antidote always bothered clinicians in case of the emergency situation to reverse the bleeding. Bleeding associated with warfarin can be predictably managed with close monitoring of INR and reversal with FFP and vitamin K.

Neither FFP nor vitamin K is effective to reverse the effects of DOAC [37,47].

Table 1
Summary of currently approved DOAC's in USA.

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)
Mechanism of action	Direct anti-IIa	Direct anti-Xa	Direct anti-Xa	Direct anti-Xa
Indication	1.Stroke prevention in nonvalvular A.Fib 2.VTE treatment	1.Stroke prevention in nonvalvular A.Fib 2.VTE treatment 3.VTE prevention	1.Stroke prevention in nonvalvular A.Fib 2.VTE treatment 3.VTE prevention	1.Stroke prevention in nonvalvular A.Fib 2.VTE treatment
Half-life	12–14 h	7–13 h	8–15 h	9–11 h
Route of elimination	80% renal	70% renal	25% renal	35% renal
Onset of action	0.5–2 h	2–4 h	1–3 h	1–2 h