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Short Communication

New oral anticoagulants

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ABSTRACT

The quest for finding an ideal anticoagulant that can replace the commonly used VKA (warfarin) continues. There is now a plethora of data regarding the safety and efficacy of newer oral anticoagulants (NOAC) compared to warfarin for wide ranging clinical indications. These NOACs fall into 2 distinct categories due to their specific targeted action - Factor Xa Inhibitors and Thrombin Inhibitors. Rivaroxaban, Apixaban and Edoxaban belong to the group of Factor Xa Inhibitors while Dabigatran remain the sole Thrombin Inhibitor. In this review I have tried to explain many of the properties of an ideal anticoagulant that these NOACs possess. I have also discussed about some of the emerging antidotes for these NOACS. The detail analysis of all the available evidence comprising of nearly 50,000 patients in different clinical indications suggest that the NOACs are not inferior to VKA (warfarin) with regard to their efficacy but superior with regard to their safety profile.

1. Introduction

There is now increasing interest in the development of new oral anticoagulants (NOAC), as they have been shown to be equal in efficacy but superior in safety profile to the currently available vitamin K antagonists (VKA). However, they fall short of the properties that an ideal anticoagulant should possess (Table 1). An ideal antagonist should be safe and effective and can be administered orally with good pharmacokinetic and pharmacodynamic profile. There should be no interaction with commonly used drugs and they should not cause any adverse events. They should possess wide therapeutic index and antidotes should be available easily in order to neutralise their action during emergency. There is also a desire to eliminate the need for anticoagulation bridging and monitoring, and extend their use safely in the community. Last but not the least, they should be available cheaply. The debate, however, will continue for some time whether we should use Thrombin Inhibitors or Factor Xa Inhibitors until head-to-head trial results are available (Table 2). We analysed the safety and efficacy of all the NOAC compared to VKA in wide-ranging indications from all the available trials.

2. Methods

We selected Dabigatran (Direct Thrombin Inhibitor) and Rivaroxaban, Apixaban and Edoxaban (Factor Xa Inhibitors) for the purpose of this analysis (Table 3, Fig. 1). All the clinical trials and meta-analysis of the clinical trials provided the evidence for this. The trials that were included for analysis of efficacy were:

1. RE-COVER trial using Dabigatran
2. Einstein-DVT using Rivaroxaban
3. Einstein-PE using Rivaroxaban
4. AMPLIFY using Apixaban
5. Hokusai using Edoxaban

For the assessment of safety, the various trials used include RE-MEDY, RE-COVER II, AMPLIFY, J-ROCKET AF, Einstein-DVT,

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Table 1 – Unmet need.

Ideal anticoagulant
• Safe and effective
• Oral administration
• No interaction
• No adverse events
• Good pharmacokinetic and pharmacodynamics profile
• Wide therapeutic index
• Availability of antidotes
• Cheap

Table 2 – Novel anticoagulants.

Factor Xa Inhibitors (AntiXa)	Direct Thrombin Inhibitor (DTI)
Rivaroxaban	Dabigatran
Apixaban	
Idrabiotaparinux	
Edoxaban	

Einstein-PE, Hokusai-VTE, Rocket AF, ARISTOTLE, RE-LY and ENGAGE-AF-TIMI-48. We also reviewed recent literature regarding the availability of antidotes.

3. Results

A total number of 27,024 patients were analysed for assessment of efficacy – 13,513 patients were in the NOAC group and 13,511 were in the VKA group. With regard to efficacy in the prevention of VTE and PE, the NOACs were non-inferior to the VKAs, RR = 0.97 (0.83–1.14), $P = 0.50$. With regard to safety (Fatal Bleeding), there were 57,850 patients in the NOAC group and 44,757 in the VKAs group. The NOACs were superior to VKAs with a risk ratio of 0.53 (0.43–0.64), $P < 0.00001$. With regard to clinically relevant non-major bleeding events, there were 45,774 patients in the NOAC group and 38,750 patients in the VKAs group. The NOACs were superior to VKAs with a risk ratio of 0.78 (0.68–0.90). However, there was no difference between the NOACs and VKAs with regard to the major GI bleeding events (Tables 4 and 5).

Table 3 – Newer anticoagulants.

	Target	Dosing	Bioavailability	$t^{1/2}$	Monitoring	Excretion	Antidote
Dabigatran	Thrombin	BD	6.5	12–17	No	80% Renal	None
Rivaroxaban	FXa	OD	80	9–13	No	66% Renal 28% Intestine	Prothrombin complex
Apixaban	FXa	BD	50	12	No	25–29% Renal 47–56% Intestine	None
Idrabiotaparinux	FXa	OW	100	120[41]	No	Majority via renal	Avidin

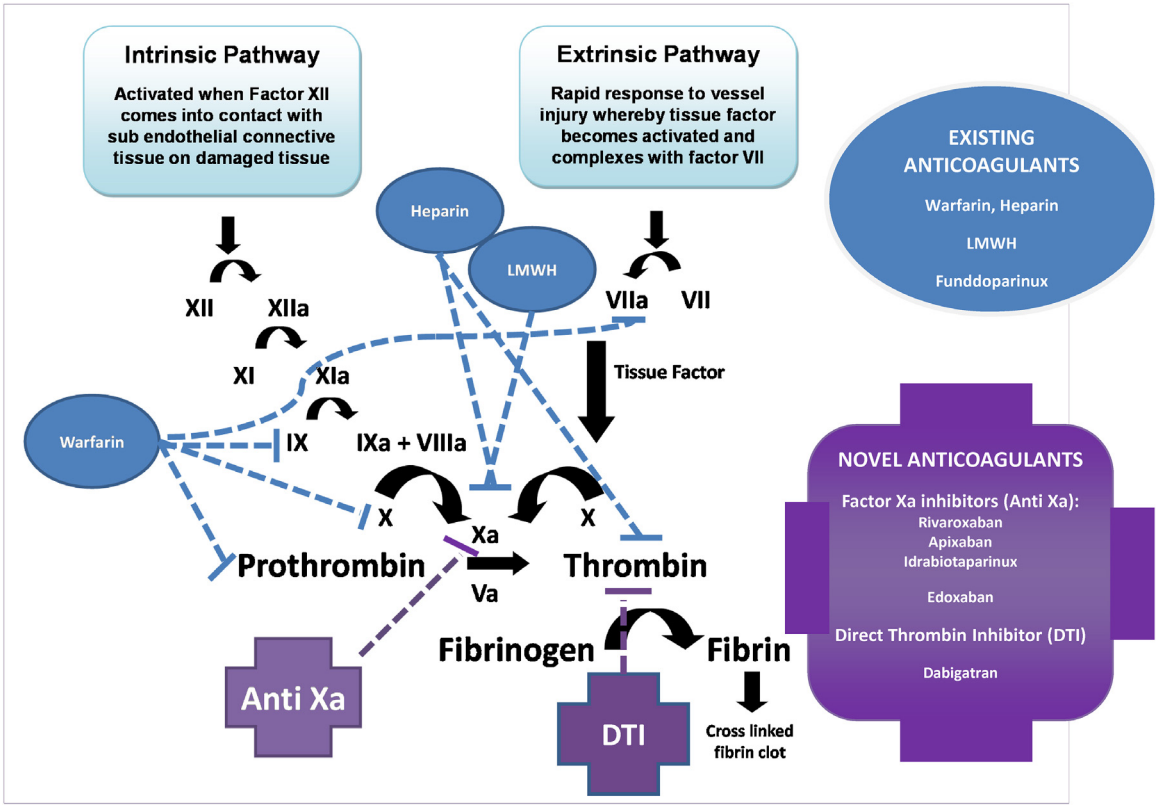

Fig. 1 – Coagulation cascade with actions of new oral anticoagulants.