Surgical Neurology International

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Editor: **James I. Ausman,** MD, PhD University of California, Los Angeles, CA, USA

Editorial

The new era of anticoagulation

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Received: 11 December 15 Accepted: 30 December 15 Published: 19 February 16

For decades, warfarin, a Vitamin K antagonist, was the only oral anticoagulant available to physicians. However, over the last decade, newer agents with different mechanisms of action have become available for the treatment and prevention of thromboembolic events. Physicians must become familiar with the pharmacokinetics, mechanisms of action, indications, risks, and benefits of these agents to become comfortable using them in clinical practice. This review will serve to discuss these aspects of the novel non-Vitamin K oral anticoagulant agents.

Warfarin has been the mainstay of oral anticoagulation. It has been well studied and has proven efficacious in many situations. Its uses include reducing the rate of stroke in atrial fibrillation as well as treatment and prevention of venous thromboembolism (VTE). It is also used to prevent thrombus formation on mechanical valves. A significant advantage of warfarin is that its effect is reliably reversed by Vitamin K, fresh frozen plasma, or prothrombin complex concentrate. However, it has a narrow therapeutic window and a highly unpredictable dose response.[2] It has several interactions with prescription and nonprescription drugs, especially stimulants and inhibitors of the CYP-450 system. Its levels also vary with dietary intake of Vitamin K. Thus, the international normalized ratio must be closely monitored to ensure that patients are within the appropriate therapeutic range. This need for frequent monitoring is a significant deterrent to the use of warfarin, especially in the elderly population.[3] To address some of the limitations of warfarin, newer oral anticoagulants were developed and introduced.

The two main mechanisms of action of the novel oral anticoagulants (NOACS) are direct inhibition of thrombin and inhibition of factor Xa. Thrombin (factor IIa) is the final enzyme in the clotting cascade that cleaves fibrinogen to fibrin. It also activates other procoagulant factors and activates platelets. Inhibition of thrombin interrupts the final steps in the coagulation pathway.[9] Factor Xa acts one step upstream of thrombin in the clotting cascade, at the convergence point of the intrinsic and extrinsic coagulation pathways. It functions to cleave prothrombin to thrombin. As such, the inhibition of factor Xa prevents thrombin generation, which subsequently prevents clot formation.[15] Four NOACS are licensed currently in the United States: The direct thrombin inhibitor dabigatran, and the factor Xa antagonists: Edoxaban, apixaban, and rivaroxaban. These agents are now acceptable alternatives to warfarin for use in prophylaxis and treatment of VTE and stroke prevention in nonvalvular atrial fibrillation. They have rapid onset and offset of action and fewer interactions with medications and food. They have a more predictable anticoagulant effect which allows fixed dosing without the need for laboratory monitoring [Table 1].

Dabigatran etexilate (Pradaxa) is the only oral direct thrombin inhibitor currently approved for use. It is given as a fixed dose (150 mg twice a day) without monitoring. Dosing can be reduced to 110 mg twice a day in patients

Access this article online	
Quick Response Code:	Website: www.surgicalneurologyint.com
	DOI: 10.4103/2152-7806.177124

How to cite this article: Anklesaria Z, Al-Helou G. The new era of anticoagulation. Surg Neurol Int 2016;7:22. http://surgicalneurologyint.com/The-new-era-of-anticoagulation/

Table 1: Preprocedure management of the novel oral anticoagulants

NOAC	Mechanism	Commonly used dose	Preprocedure management
Dabigatran (Pradaxa)	Direct thrombin inhibitor	150 mg twice daily	Give last dose 2-3 days before procedure
Rivaroxaban (Xarelto)	Factor Xa inhibitor	15 mg twice a day for 21 days then 15-20 mg daily	Give last dose 2-3 days before procedure
Apixiban (Eliquis)	Factor Xa inhibitor	2.5-5 mg twice daily	Give last dose 2-3 days before procedure
Edoxaban (Savaysa)	Factor Xa inhibitor	30-60 mg daily	Discontinue 2-3 days before procedure

NOAC: Novel oral anticoagulants

at high risk for bleeding or with mild renal impairment. The peak effects are noted 2–3 h after ingestion. Renal excretion is the main elimination pathway, and as such, it is contraindicated in patients with creatinine clearance <30 ml/min. In patients with normal renal function, the half-life is approximately 12–17 h.[4] Dabigatran has been approved for treatment and prevention of VTE disease. Its efficacy for prevention of VTE in patients who have undergone hip or knee replacement surgery was studied in three trials: RE-NOVATE, RE-MODEL, and RE-MOBILIZE. A meta-analysis of these trials concluded that dabigatran at a fixed dose was noninferior to enoxaparin 40 mg daily for VTE prophylaxis. Bleeding rates were similar in both groups.[23] Dabigatran has also been shown to be as effective as warfarin for the treatment of acute VTE.[17] In a study of 18,000 patients, dabigatran at a dose of 110 mg was found to be as effective as warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation. It was also found to have lower rates of major hemorrhage. At a dose of 150 mg, it was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage as warfarin.[7] When compared to warfarin, dabigatran has been found to have a similar bleeding risk. However, there appears to be a slightly lower risk for intracranial hemorrhage and thus lower mortality, but a slightly higher rate of gastrointestinal bleeding.[19,21]

Dabigatran does not have a reliable effect on coagulation studies. It will prolong the thrombin time and the activated partial thromboplastin time (aPTT), but it will not reliably prolong the pro-thrombin time. Fortunately, monitoring is not required as drug levels are usually predictable for fixed doses.[8] The most commonly reported side effect of dabigatran is dyspepsia.[5] Until recently, dabigatran did not have a specific reversal agent but that changed with the introduction of the monoclonal antibody idarucizumab (Praxbind). Idarucizumab was studied in the RE-VERSE AD trial and was able to reverse the effects of dabigatran in over 90% of patients.[18] Praxbind is given intravenously as two separate doses of 2.5 mg about 15 min apart. Of note, it was given accelerated Food and Drug Administration approval and thus, the evidence that supports it is still controversial. Hemodialysis can also be effective in helping to remove dabigatran from the circulation.[6]

There are three oral direct factors X inhibitors available on the market. Rivaroxaban (Xarelto) is a direct factor X inhibitor that is given at a fixed dose of 10–20 mg twice daily depending on the indication. It is metabolized by the liver and the kidneys and has a half-life of 7–13 h. It reaches its peak efficacy 1–4 h after ingestion. It has been studied for VTE prophylaxis following orthopedic surgeries. Four Phase III studies have compared 10 mg/day of rivaroxaban with 40 mg/day of enoxaparin for thromboprophylaxis following hip or knee replacement surgery. In these studies, rivaroxaban was associated with fewer symptomatic VTE events and all-cause mortality. Bleeding events were similar in both groups.[22] Rivaroxaban also demonstrated similar efficacy when compared to low molecular weight heparin followed by warfarin for the treatment of acute VTE in a large prospective randomized controlled trial. EINSTEIN-DVT and EINSTEIN-PE were open-label randomized trials with 8281 patients with acute DVT or PE. They demonstrated the noninferiority of 15 mg BID rivaroxaban for 3 weeks followed by 20 mg once daily to enoxaparin followed by warfarin. Bleeding events were similar in both groups.[10] Rivaroxaban was also studied in a large double-blind trial for the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation. It was found to be noninferior to warfarin for this purpose. The major bleeding rates were similar for both drugs but intracranial, and fatal bleeding was less frequent in the rivaroxaban group.[17] Patients with a creatinine clearance of <30 ml/min were not included in these trials. Rivaroxaban is not used in patients with Child-Pugh B or C hepatic dysfunction. Drugs that are dual inhibitors of the CYP-3A4 and P-glycoprotein systems interact with rivaroxaban; therefore, concurrent use is contraindicated. Potent inducers of CYP-3A4 such as St. John's Wort may reduce the efficacy of rivaroxaban.[16]

Just as with dabigatran, routine monitoring of coagulation times is not required for patients on rivaroxaban. The aPTT and anti-Xa activity can be measured and may be prolonged but are not reliable in determining the efficacy of the drug.[11] Reversal is difficult given the lack of a specific antidote. Dialysis is not effective in clearing rivaroxaban given its high plasma protein binding affinity. Prothrombin complex concentrate and recombinant factor VII can be helpful in case of bleeding.[24] In the case of major bleeding, antifibrinolytic agents such as

tranexamic acid and epsilon-aminocaproic acid have been suggested for reversal. There is no good clinical data to support the use of any of these agents for reversal of the effect of rivaroxaban and, thus, they are not considered the standard of care.

Apixaban (Eliquis) is an oral factor Xa inhibitor with a half-life of 4–9 h. It reaches peak efficacy 1–4 h after ingestion. It is given as a fixed dose without monitoring. The dose varies according to the clinical indication, age, renal function, and weight and it is approved for use in end-stage renal disease. It is indicated for use in treatment and prevention of VTE's and stroke prevention in nonvalvular atrial fibrillation. The AMPLIFY study showed that a fixed dose of oral apixaban was as effective as enoxaparin followed by warfarin for the treatment of acute VTE. It was also associated with a clinically significant reduction in bleeding.[1] In the ARISTOTLE study, apixaban was found to be superior to warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation.[13] As with all novel anti-coagulants, monitoring of coagulation parameters is not required during treatment. Levels may be affected by strong dual CYP3A4 and P-glycoprotein inhibitors; such as azole antifungals or ritonavir. In the case of bleeding, reversal can be achieved with the use of prothrombin complex concentrate or recombinant factor VII. Similar to rivaroxaban, these are not reliable or evidence-based reversal agents.

Edoxaban (Savaysa) is another oral direct factor Xa inhibitor. It achieves peak concentration within 1–2 h. Fifty percent of the elimination of edoxaban occurs via the kidneys. It is given as a fixed dose of 30–60 mg once daily. It was found to be noninferior to warfarin for stroke prevention in patients with atrial fibrillation.[12] Like other NOACs, it was associated with lower rates of bleeding and death from cardiovascular disease. In the setting of VTE, edoxaban given once daily after an initial dose of heparin was found to be noninferior to warfarin given after heparin. It was also associated with significantly less bleeding.[14]

Despite a large amount of evidence demonstrating the efficacy and safety of the factor Xa inhibitors, the lack of a reversal agent is a significant limitation. To that effect, in a very recent study, a recombinant modified human factor Xa decoy protein called Andexanet alfa (andexanet) has been described. Andexanat binds and sequesters factor Xa inhibitors within the vascular space thus restoring the activity of factor Xa.[20] It is a potent and specific antidote to apixaban rivaroxaban and edoxaban. There are currently ongoing studies evaluating this potential reversal agent.

After decades of warfarin being the only anticoagulant available, the NOACS have finally provided physicians and patients with more options. There is a multitude of evidence supporting that they are as efficacious as warfarin. As experience accumulates, it is evident that they are less cumbersome to use and as safe as warfarin. NOACS are slowly but surely becoming the first line for the treatment and prevention of thrombosis in the 21st century.

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