

Beyond warfarin: The advent of new oral anticoagulants

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Abstract

New oral anticoagulants (NOAC) are the latest addition to anticoagulant armamentarium. Unlike traditional anti-coagulants like warfarin, lab monitoring and management of bleeding complications secondary to these agents is different. As more and more patients are being switched to these drugs, interventional radiologists in particular will benefit from a clinical review of NOAC.

Key words: Anticoagulants; new oral anticoagulants; warfarin

Introduction

For more than half a century, warfarin has been the most widely used oral anticoagulant in clinical practice. Its common use, side effects profile, and reversal techniques have been well established, making it a familiar drug in interventional practices with an overwhelming majority of practitioners being comfortable with its use.

Recently, three new oral anticoagulants (NOACs) have been introduced; while they are becoming more common to the clinical practices, they remain a gray area in the interventional community due to limited exposure.

As these drugs have become more widely prescribed, we must become familiar with their mechanism of action, dosing strategies, and potential complications in order to provide our patients with the safest care possible. In this article, we present these new agents with emphasis on their clinical use, potential dangers during invasive procedure, and how to deal with these complications as they arise.

Current NOACS

Dabigatran (Pradaxa®) - Boehringer Ingelheim

Rivaroxaban (Xarelto®) - Janssen

Apixaban (Eliquis®) - Bristol-Myers Squibb

Mechanism of Action

Currently, there are two mechanisms of action for NOACs:

- **Direct inhibition of thrombin:** Dabigatran works by binding to the active site of thrombin and the inactive form of fibrin-bound thrombin. An interesting characteristic of Dabigatran is its partially intrinsic coagulation reversibility; by quickly dissociating from its site of action, Dabigatran leaves a small amount of enzymatically active thrombin in the serum, which is potentially available for coagulation reversal^[1-4]
- **Inhibition of factor Xa:** Rivaroxaban and Apixaban work by blocking the interaction of factor Xa with factor Va

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[Figure 1] on the surface of activated platelets, thereby blocking the formation of the prothrombinase complex which converts prothrombin to thrombin. By blocking this pathway, the generation of fibrin is inhibited.^[5]

These mechanisms are in contrast to that of warfarin, which inhibits the activity of the vitamin K-dependent coagulation factors (II, VII, IX, X); this effect is achieved by warfarin's interference with the conversion of vitamin K to its epoxide, which is needed to carboxylate glutamate residues on the vitamin K-dependent clotting factors. By inhibiting carboxylation, the liver then produces coagulation factors with reduced procoagulant activity. Also, proteins C and S, which are natural anticoagulants, are inhibited by warfarin, which explains the need to bridge with heparin or low-molecular-weight heparin (LMWH) when starting warfarin.^[6]

Advantages of NOAC Use

It is well known that tight control of the international normalized ratio (INR) is the key to the success of warfarin therapy; however, controlling patients' INR can be a challenge. It has been estimated that INR levels are therapeutic only 50% of the time.^[7-9] One of the most attractive features of these new agents is that they have been shown to equal, if not superior, to warfarin in the management of conditions such as (VTE) Venous Thromboembolism and atrial fibrillation related stroke. There is also a lower incidence of intracranial bleeding with NOAC use in comparison to warfarin; so, there is no need for regular laboratory monitoring while using NOAC.^[10-16] In addition, therapy can be started immediately without the need for heparin or LMWH bridging. These advantages have led many physicians to reach for NOACs as first-line agents.

Limitations

One major limitation of NOAC use is the lack of a known reversal agent, which is particularly problematic in the actively bleeding patient. Several proposals have been made for a reliable reversal agent; however, this has yet to be determined. These will be discussed later.

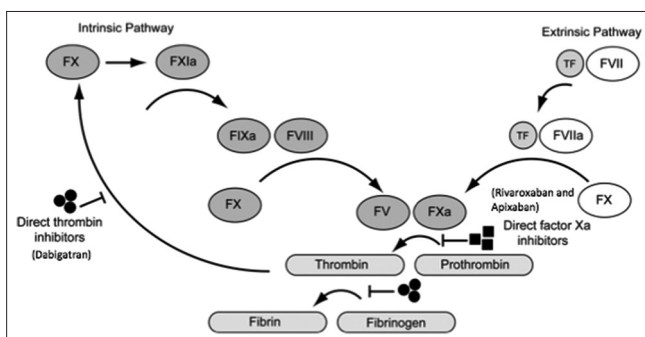


Figure 1: Mechanism of action of NOACs

Although Dabigatran and Apixaban have been found to have lower rates of intracranial bleeding than that associated with warfarin therapy, they have twice the risk of causing major gastrointestinal (GI) bleeding.^[17]

Pharmacokinetics

As a generalization, NOACs start peaking within 2 h of administration, with an average half-life of around 12 h. Dabigatran is only 35% protein bound in the plasma, as compared to Apixaban and Rivaroxaban which are 85% protein bound. In elderly patients, the half-life of Rivaroxaban is prolonged from 5-9 h to 11-13 h. Dabigatran and Rivaroxaban are excreted primarily through the urine, while Apixaban is predominantly eliminated through the fecal route.^[5]

Drug Interactions

Strong P-glycoprotein inhibitors (amiodarone, verapamil, quinidine, clarithromycin) should be used with caution in patients on Dabigatran, as these drugs have the potential to increase the serum levels of Dabigatran. On the flipside, an advantage of Dabigatran is that there is no effect on CYP pathway, which is a classic concern with warfarin. Interactions with P-glycoprotein and CYP 3A4 inhibitor occur in the case of Rivaroxaban; therefore, caution should be taken when patients are receiving drugs such as ketoconazole, voriconazole, and ritonavir, as they may increase the anticoagulation effect. Finally, there has been low potential for drug interactions with Apixaban; however, it is suggested that caution be taken with CYP inhibitors. There are no known food interactions for any of these drugs.^[5,18-20]

Challenges of Using NOACs

In contrast to warfarin, there is no specific reversal agent that can be used for managing a bleeding diathesis that results from NOAC use. These drugs are not routinely monitored, which leads to an increased risk of unwanted elevation of serum levels and the associated risk of hemorrhage. Although there are laboratory evaluations available that indirectly monitor NOAC activity, they are very complex and time consuming. These are discussed in further detail below.

Laboratory Evaluation

There is currently no gold standard for laboratory evaluation of these drugs. However, the following tests, although cumbersome, are currently available:

Thrombin time and activated partial thromboplastin time

These tests are sensitive to the systemic presence of Dabigatran, but cannot quantify the levels; in fact, the aPTT

plateaus with higher levels of Dabigatran. Although not fool proof, these tests offer rapid results that may assist in determining if bleeding is secondary to Dabigatran or another entity.^[20,21]

Ecarin clotting time

This test uses snake venom to measure direct thrombin inhibitors like Dabigatran, but not the factor Xa inhibitors. The test, however, has a limited availability.^[19,22,23]

Assays of factor Xa activity

A variety of assays have been proposed and the basic principle is the same as those used for monitoring heparin levels. Laboratories that are currently using these assays to monitor heparin levels can be adapted to apply these techniques for monitoring Rivaroxaban and Apixaban, as they are better indicators of plasma concentrations of these particular drugs.^[19,23]

Rivaroxaban prolongs prothrombin time (PT), PT, aPTT, and prothrombinase-induced clotting time (PiCT) to varying degrees, and therefore, these tests have not been used clinically for monitoring. Apixaban has minimal effects on PT; therefore, anti-Xa levels are needed to assess serum concentrations.^[19,23]

Role of NOACS in Clinical Practice

This topic is still hotly debated. However, when dealing with these drugs, it is important to keep the whole clinical scenario in mind. The schema presented by Shulman *et al.*,^[24] as outlined below, is a very useful and easy guide to adapt in clinical practice. The choice of anticoagulants can be divided into several broad groups based on the patient's clinical scenario:

Group 1- Patient population where warfarin is a superior choice compared to NOACs

- For patients already on warfarin with consistent INR results, there is little indication to switch to the newer drugs. For these patients, simply reducing the frequency of INR testing may improve the convenience and, hence, acceptability of warfarin treatment
- Patients with poor compliance will face a higher risk of stroke with NOACs than with warfarin, particularly given the short half-lives of Dabigatran and Rivaroxaban, as failure to take the medication quickly results in loss of anticoagulation effect. Lack of a suitable lab monitoring test further compounds this problem
- Patients with renal failure with creatinine clearance of less than 30 ml/min
- Mechanical heart valve replacement: Valve thrombosis has been reported with Dabigatran^[4]
- Patients older than 75 years

- History of GI disease, especially lower GI bleeds. Dabigatran contains tartaric acid necessary for its absorption and has a high concentration of the active drug in the colon
- Drug cost: Although in many situations, NOACs may be cost neutral or even cost effective.

Group 2- NOACs are superior to warfarin

- Patients with good compliance, but variable INR results. However, it is imperative that potential noncompliance is thoroughly evaluated and excluded
- Drug interactions: If the patient is already taking medications that have the potential to interfere with warfarin metabolism (e.g., antibiotic therapy, chemotherapy, amiodarone, acetaminophen, etc.) or there is a future plan to introduce these drugs, NOACs may be superior to warfarin. The pharmacokinetics of these drugs are discussed in [Table 1].
- Newly diagnosed atrial fibrillation with no contraindications as mentioned above. The advantage here is a relatively rapid onset of anticoagulation without heparin bridging. Frequent titration of dose with laboratory tests is not required with NOACs.

Group 3- Patients needing conversion from established warfarin to NOACs

Due to the potential for increased efficacy and reduced risk of intracranial bleed, some patients may be good candidates for conversion to NOAC therapy. One suggested protocol is to start NOACs only when INR has decreased below 2.3. Point-of-care INR monitors are also not used during transition, as Dabigatran may lead to elevated baseline INR.^[15,24-26]

Group 4- Conversion from NOACs to warfarin

For patients who are no longer candidates for NOACs, warfarin can be started as soon as these medications are stopped, with INR evaluated 3 or 4 days afterward. However, in patients with creatinine clearance of less than 15-30 ml/min, INR should be checked earlier to rule out excessive anticoagulation necessitating warfarin dose adjustment.^[24]

Table 1: Summary of NOACs

	Apixaban	Rivaroxaban	Dabigatran
Site of action	Factor Xa	Factor Xa	Thrombin generation
Half-life	6-12 h	5-9 h (healthy) 11-13 h (elderly)	12-17 h
Excretion	Fecal > renal	Fecal > renal	Renal > fecal
Time to peak concentration	3-4 h	2-4 h	1-2 h
Dosage	DVT prophylaxis: 2.5 mg PO/BID Atrial fibrillation: 5 mg PO/BID	DVT prophylaxis: 10 mg PO daily Atrial fibrillation: 20 mg PO daily	DVT prophylaxis: 150 mg PO/BID Atrial fibrillation: 150 mg PO/BID

Adapted from Zikria and Ansell, 2009. DVT=Deep venous thrombosis, PO=Oral route, BID=Twice a day

Pre-procedural Management of Patients on NOACs

Preoperative

As always, close communication with patient's primary team managing the anticoagulation is necessary.

Elective procedures and low-risk interventions

In general, stopping NOACs 48 h prior to the procedure is adequate. This short period of interruption usually does not require bridging therapy with heparin or LMWH.

Urgent, but not emergent surgery

If possible, the procedure should be delayed by 12 h, as this is adequate time for metabolism.^[5] Since the half-life is not dose dependent, this strategy is also applicable to NOAC overdose.

Emergency procedure

This will be discussed later in the management of bleeding secondary to NOACs.^[24]

Postoperative Management

In general, for low bleeding procedures, NOACs can be resumed in 24 h; in higher risk cases, they should be held for 48-72 h after surgery; in which case a heparin infusion should initially be used for anticoagulation. In cases where bowel paralysis is an issue, such as with post-gastrostomy placement, bridging with heparin may be needed, as patients cannot take oral medications.^[24]

Strategies to Manage NOAC-Induced Bleeding Complications

General consideration and preventive measures

As Dabigatran, in particular, is dependent on renal function for its elimination, it is imperative that kidney function be reviewed before its initiation and prior to any interventional procedure; precautions must also be taken in patients with acute renal failure. The issue of acute renal failure is especially important in the post-procedure period, as the development of contrast-induced nephropathy or hypovolemic prerenal insufficiency can occur in patients with major bleeding.

We also recommend using commonly available laboratory tests. Although specific laboratory monitoring of NOACs is cumbersome, there are relatively simple initial steps that we can take in patients with acute hemorrhage. For instance, a normal thrombin time and aPTT implies that the bleeding diathesis is not due to Dabigatran. Similarly, a normal PT or undetectable anti-factor X activity excludes hemostatic dysfunction secondary to Rivaroxaban and Apixaban.

Severe or Life-threatening Hemorrhage

Monitoring of the patient's vitals signs and prompt

resuscitation are paramount in the management of any acute life-threatening condition. If the source of hemorrhage can be determined and is endovascularly or surgically accessible, urgent intervention should be performed if appropriate. All anticoagulants should be discontinued until the source of hemorrhage is identified and bleeding has resolved.

If the bleeding is confirmed to be secondary to Dabigatran, hemodialysis can be done. Dialysis would not be effective for Rivaroxaban or Apixaban, as these drugs show up to 85% plasma protein binding.^[27] The use of nonspecific pro-hemostatic agents will be discussed later.

Nonspecific Hemostatic Agents

Recombinant factor VIIa

It works through generation of thrombin by activating factor X.^[28-33]

Four-factor prothrombin complex

It contains high concentrations of inactive forms of factors II, VII, IX, and X to stimulate thrombin formation.

Three-factor prothrombin complex

It is similar to four-factor complex; however, this formulation contains less inactive factor VII.

Activated prothrombin complex concentrate

It contains active factor VII, as opposed to the inactive form, as well as factors II, IX, and X. It combines the effects of recombinant factor VIIa and four-factor prothrombin complex.^[28,29,34-39]

Conclusion

NOACs are an exciting addition to clinical practice as they provide a convenient and effective alternative to warfarin. As these agents have become more common, interventionalists will need to have a strong understanding of the drugs and how to manage the potential complications that may arise.

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Conflicts of interest

There are no conflicts of interest.

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