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Journal of Radiology & Radiation therapy

Review Article

Beyond Warfarin; Newer Oral Anticoagulant Drugs (NOADS): A Primer for Interventional Radiologists

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Submitted: 27 January 2014

Accepted: 26 February 2014

Published: 03 March 2014

ISSN: 2333-7095

Keywords
- Interventional radiology
- Vascular procedures
- Hemorrhage
- Novel anticoagulants

Abstract

Recently three newer oral anticoagulants (rivaroxaban, apixaban, and dabigatran) have been introduced into clinical practice; while they are becoming more commonly seen in the primary care setting; they remain a gray area in the interventional community due to limited exposure. These drugs have been studied as a good alternative to warfarin, however there is a need amongst for radiologists performing percutaneous procedures to become more familiar with their clinical use, potential dangers during invasive procedures, and how to deal with complications as they arise.

ABBREVIATIONS

NOADS: Newer Oral Anticoagulant Drugs; INR: International Normalized Ratio; LMWH: Low Molecular Weight Heparin; VTE: Venous Thromboembolism; PT: Prothrombin Time; aPTT: Activated Partial Thromboplastin Time

INTRODUCTION

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

Recently three newer oral anticoagulants 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.

In this article these new agents are presented with emphasis on their clinical use, potential dangers during percutaneous procedure, and strategies for how to deal with complications as they arise.

Current NOADS

Dabigatran (Pradaxa®), Rivaroxaban (Xarelto®), Apixaban (Eliquis®)

Mechanism of action

Currently there are two mechanisms of action for NOADS:

1) Direct thrombin inhibitors (dabigatran) work 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].

2) Factor Xa inhibitors (rivaroxaban and apixaban) work by blocking the interaction of factor Xa with factor Va (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].

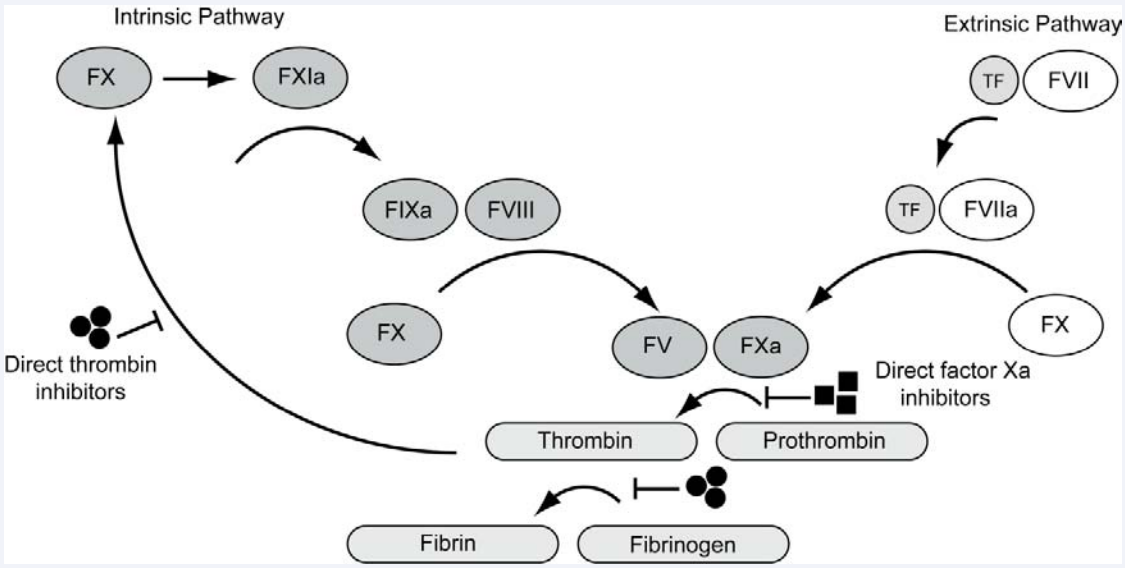

Figure 1 Site of action of NOADS.

Advantages of NOAD use

It is well known that tight control of the International Normalized Ratio (INR) is 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 be equal, if not superior, to warfarin in the management of conditions such as Venous Thromboembolism (VTE) and atrial fibrillation related stroke. There is also a lower incidence of intracranial bleeding with NOAD use in comparison to warfarin; this is comes without the need for regular laboratory monitoring [10-16]. In addition therapy can be started immediately without the need for Heparin or LMWH bridging.

Limitations

Dabigatran and apixaban, although shown to have lower rates of intracranial bleeding than that associated with warfarin therapy, have twice the risk of causing major gastrointestinal bleeding. Rivaroxaban is initially dosed twice daily, and while this is not a direct inducer of major morbidity, it can be indirectly problematic in patients with poor compliance.

The major limitation of the NOADS is lack of a known reversal agent, which is particularly problematic in the actively bleeding patient. This limitation is currently the biggest concern for radiologists performing percutaneous procedures. Several proposals have been made for a reversal agent, however there is no currently available reversal agent. A few of the proposed reversal methods will be discussed in brief later.

Pharmacokinetics

As a generalization NOADS start peaking within 2 hours of administration with an average half-life of around 12 hours. 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 rivaroxiban is prolonged from 5-9 hours to 11-13 hours. Dabigatran and rivaroxaban are excreted primarly 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 potential to increase 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. P-glycoprotein and CYP 3A4 inhibitor interactions occur with rivaroxaban; therefore caution should be taken when patients are receiving drugs such as ketoconazole, voriconazole and ritonavir as they may increase 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, 17-19].

CHALLENGES OF USING NOADS

In contrast to warfarin, there is no specific reversal agent that can be used for managing bleeding that result from NOAD use. These drugs are not routinely monitored, which leads to an increased risk of unwanted elevation of serum levels and associated risk of hemorrhage. Although there are laboratory evaluations available that indirectly monitor NOAD activity, there is no way of directly monitoring serum levels currently available. The indirect methods are discussed in further detail below.

Lab Evaluation

There is currently no gold standard for laboratory evaluation of these drugs however the following tests are currently available:

Thrombin Time and activated partial Thromboplastin Time (aPTT): 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 [19,20].

Ecarin clotting time: uses snake venom to measure direct thrombin inhibitors like Dabigatran but not the factor Xa inhibitors. This test however has a limited availability [18,21,22].

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 [18,22].

Rivaroxaban prolongs Prothrombin Time (PT), dilute PT, aPTT, Heptest and Prothrombinase Induced Clotting Time (PiCT) to varying degrees and therefore these tests have not been used clinically for monitoring. Apixaban has minimal effects of PT, therefore anti-Xa levels are needed to assess serum concentrations [18,22].

Role of NOADS 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 [23] as outlined below, is a very useful and easy guide to adapt to 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 NOADS:

A. 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.

B. Patients with poor compliance will face a higher risk of stroke with NOADs as compared to 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.

C. Patients with renal failure with creatinine clearance of less than 30mL/min.

D. Mechanical heart valve replacement. Valve thrombosis has been reported with dabigatran [4].

E. Patients older than 75 years.

F. History of gastrointestinal (g.i.) disease, especially lower g.i. bleeds. Dabigatran contains tartaric acid, necessary for its absorption and has a high concentration of the active drug in the colon.

G. Drug cost; although in many situations NOADS may be cost neutral or even cost effective.

Group 2: NOADS are superior to Warfarin.

A. Patients with good compliance but variable INR results. However it is imperative that potential noncompliance is thoroughly evaluated and excluded.

B. 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, NOADS may be superior to warfarin.

C. Newly diagnosed atrial fibrillation with no contraindications as mentioned above; the advantage being a relatively rapid onset of anticoagulation without heparin bridging. Frequent titration of dose with lab tests is not required with NOADS.

Group 3: Patients needing conversion from established warfarin to NOADS.

A. Due to the potential for increased efficacy and reduced risk of intracranial bleed, some patients may be good candidates for conversion to NOAD therapy. One suggested protocol is to start NOADS 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 [15,23-25].

Group 4: Conversion from NOADS to Warfarin.

For patients who are no longer candidates for NOADS, warfarin can be started as soon as these medications are stopped, with evaluation of the INR 3 or 4 days afterwards. 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 [23].

Pre-procedural management of patients on NOADS

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

Elective procedures and low risk interventions: In general stopping NOADS 48 hours prior to 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 hours, as this is adequate time for metabolism. Since the half-life is not dose dependent, this strategy is also applicable to NOAD overdose.

Emergency procedure: This will be discussed later in the management of bleeding secondary to NOADS [23].

Postoperative management

In general for low bleeding risk procedures, NOADS can be resumed in 24 hours, in higher risk cases they should be held for 48-72 hours 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 [23].

Strategies to manage NOADS 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.

Initial work up should consist of using commonly available lab tests to determine the etiology of bleeding. Although specific laboratory monitoring of NOADS has not been defined there are relatively simple initial steps that can be taken 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 vital signs and prompt resuscitation is paramount in the management of any acute life threatening bleed. 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 [26]. We have proposed an algorithm for management of hemorrhage for patients on NOADS (figure 2).

Nonspecific hemostatic agents

Although not well studied there are several proposed reversal

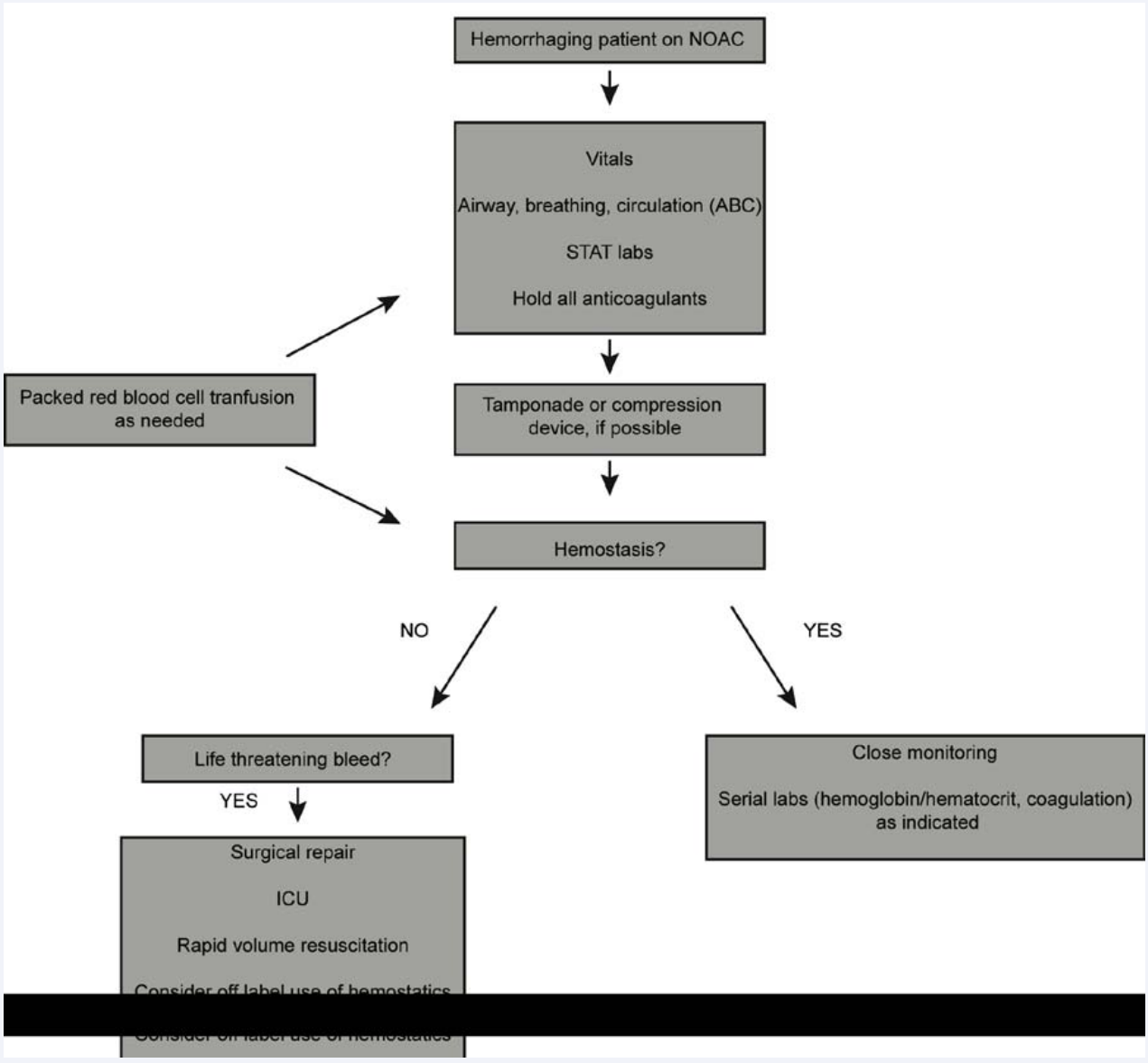

Figure 2 Management of acute bleeding with NOADS.

agents for NOAD associated hemorrhage

Recombinant factor VIIa: works via generation of thrombin by activating factor X (27-32).

Four factor prothrombin complex: contains high concentrations of inactive forms of factors II, VII, IX, X to stimulate thrombin formation.

Three factor prothrombin complex: similar to four factor, however this formulation contains less inactive factor VII.

Activated prothrombin complex concentrate: contains active factor VII, as opposed to the nonactive form, as well as factors II, IX, X. Combines effects of recombinant factor VIIa and four factor prothrombin complex [27,28, 33-38].

DISCUSSION AND CONCLUSION

NOADS provide a good alternative to warfarin for patients who have undergone careful selection based on the criteria described above. The lack of reversal agent is a significant concern for the radiologist performing a percutaneous procedure, however further research may reveal a more full proof strategy for managing NOAD associated hemorrhage. In the meantime close pre and post-procedural monitoring will help to reduce associated morbidity and mortality.

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Cite this article

Laroia ST, Morales SA, Laroia AT, Cohen DA (2014) Beyond Warfarin; Newer Oral Anticoagulant Drugs (NOADS): A Primer for Interventional Radiologists. J Radiol Radiat Ther 2(3): 1051.