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Review Article

# Management of Novel Anticoagulants in Total Joint Arthroplasty: A Practical Approach for the Orthopaedic Surgeon

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**Abstract**

Chronic anticoagulation is a common finding among patients undergoing total joint arthroplasty. Newer oral anticoagulants dabigatran, rivaroxaban and apixaban, target individual factors in the clotting cascade (factor Xa and factor IIa). Their stable pharmacokinetics provided improved efficacy and safety, with equivalent or superior anti-thrombotic properties. Currently, there is no guideline on managing patient on these novel anticoagulants in the Total Joint Arthroplasty (TJA) setting. Understanding the pharmacology, conventional laboratory tests and, reversal agents available to achieve a coagulation hemostasis is crucial to for the surgeon making the decision of surgery now or later. We reviewed the current literature on these drugs, their reversal agents and provided a practical approach to managing these patients in the peri-operative period for the practicing orthopaedic surgeon.

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- Reversal
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- Urgent

## ABBREVIATIONS

AF: Atrial Fibrillation; aPCC: Nano-filtered Activated Prothrombin Complex Concentrate; aPTT: Activated Partial Thromboplastin Time; Aristotle: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation study; AVERROES: Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment trial; CrCl: Creatinine Clearance; DVT: Deep Venous Thrombosis; ECT: Ecarin Clotting Time; FDA: Food and Drug Administration; FFP: Fresh Frozen Plasma; NOAC: Novel Oral Anticoagulants; PCC: Prothrombin Concentrate Complex; PT: Prothrombin Time; RECORD: REgulation of Coagulation in ORthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism studies 1 and 2; RELY: Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TJA: Total Joint Arthroplasty; TT: Thrombin Time; VTE: Venous Thromboembolism

## INTRODUCTION

In United States, approximately one million patients had a knee or hip replaced in 2009 and this number is projected to increase by over 600% by 2030 [1,2]. Chronic anticoagulation for Atrial Fibrillation (AF) is a common finding among patients undergoing Total Joint Arthroplasty (TJA). It is estimated that 3 million Americans are affected by AF and by 2050 this is projected to increase to 16 million [3,4].Other common indications for anticoagulation include treatment of DVT, prevention of recurrent VTE following an acute DVT, presence of a prosthetic heart valve and VTE prevention following hip and knee replacement. All these patients have the additional risk of hemorrhage, persistent wound drainage, hematoma formation, transfusion requirements, risk of peri-prosthetic joint infection and increased length of hospital stay [3]. Traditionally, chronic anticoagulation was managed with warfarin, which inhibits production of Vitamin K-dependent clotting factors II, VII, IX, and X. Due to ease of use, and improved efficacy and safety the novel anticoagulants targeting individual factors in the clotting cascade are gaining favor. These include factor IIA inhibitor dabigatran, and direct Xa inhibitors rivaroxaban and apixaban.

Management of these patients in relation to risk of thromboembolism and bleeding issues, especially in context of elective, urgent or emergent orthopedic surgeries is an area of evolving interest. Understanding the dosing, pharmacokinetics and reversal methods is important, especially as clinical data is limited and the treatment itself can cause significant harm. The purpose of this paper is to review the mechanism of action of these novel anticoagulants and to provide a practical perioperative approach to these increasingly prevalent medications for the practicing orthopedic surgeon.

## Dabigatran

Dabigatran (Pradaxa®) was the first Novel Oral Anticoagulant (NOAC) approved by the Food and Drug Administration (FDA) in October 2010, for arterial thromboembolic events in non-valvular atrial fibrillation, based on the RELY trial. It is an oral factor IIA (thrombin) inhibitor. From time of ingestion it takes 1.25-3 hrs to reach the peak plasma concentration. It has half-life of 12–14 hrs and is excreted predominantly by the kidneys (80%). It is renally dosed; 150mg twice daily if Creatinine Clearance (CrCl) >30 mL/min, half the dose (75mg twice daily) if CrCl 15-30 mL/min and not recommended for patients with CrCl<15 mL/min [5].

Dabigatran affects Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), Ecarin Clotting Time (ECT), and Thrombin Time (TT), the latter two measures providing the most accurate means to monitor appropriate drug levels [5,6]. Of the commonly available tests in hospitals, normalization of TT and aPTT is most accurate to assess coagulation hemostasis. Due to its pharmacokinetics the dose of drug, time of ingestion relative to the time of blood sampling and the patient's renal function, needs to be taken into consideration when assessing the patient's coagulation hemostasis.

For elective surgeries, peri-procedure recommendation for patients receiving dabigatran therapy is to discontinue it 3-4 days prior to an operation if CrCl is ≥50 mL/min or 4-5 days if CrCl<50 mL/min.[5]Currently there is no available antidote for dabigatran. In an in-vitro model, activated charcoal was able to reduce 99.9% of dabigatran absorption following recent ingestion [5]. There are case reports of acute hemodialysis successfully removing 60% of the drug after 6 hours [7]. In patients with end-stage renal disease up to 68% of active dabigatran was removed after 4 h of hemodialysis [5].

In cases of urgent surgery, Pernod et al proposed that if dabigatran concentration ≤ 30 ng/ml one can proceed with surgery. This is equivalent to a normal aPTT. This dictum is an extrapolation from the data of patients who underwent elective surgeries while on dabigatran, recorded in the RELY trial [8]. If aPTT is increased (probable drug level ≥30 ng/ml) it is recommended to wait up to 12 hours and re-check aPTT again and repeat the process if the surgery can be delayed. In patients requiring urgent surgical intervention, nano-filtered activated prothrombin complex concentrate (aPCC/ FEIBA®) 30-50UI/Kg is preferred over prothrombin complex concentrate (PCC/ Kcentra®, Bebulin® 25-50 UI/kg), per *in-vitro* and animal model studies and anecdotal case reports, even though they do not fully correct the abnormalities of hemostasis tests [5,8]. Hemodialysis should be discussed prior to surgery, understanding that it will take a long time to reach the threshold of 30ng/ml in these patients.

## Rivaroxaban

Rivaroxaban (Xarelto®), is an oral direct factor Xa inhibitor that was initially approved for prevention of stroke and systemic embolism in patients with non-valvular AF in 2011. Since then its clinical use has been expanded to include the prevention of VTE after elective hip or knee replacement surgery and for the treatment of DVT and prevention of recurrent VTE following an acute DVT. In phase III ROCKET AF study, rivaroxaban (20 mg daily if CrCl ≥50 ml/min and 15 mg if CrCl 15–49 ml/min) was shown to be equally efficacious compared to warfarin. It had similar safety rate of bleeding and adverse events but fewer intra-cranial hemorrhage and fatal bleeding events compared to those receiving warfarin [9]. It was based on the outcomes of the RECORD studies (comparing rivaroxabanto enoxaparin), rivaroxaban 10 mg daily was approved for the prevention of VTE after elective hip or knee replacement surgery [9].

The half-life of rivaroxaban is 5–9 hrs in young individuals and 11–13 hrs in the elderly [9]. It takes 2–4 hrs after ingestion to reach the peak plasma concentration; hence, it is important to know the timing and dose taken. Because of its short half-life and a rapid onset of action bridging with another anticoagulant is not required when rivaroxaban is discontinued before or initiated after surgery [9]. The recommendation is to hold it 24-48 hours prior to procedure and administer first dose 6–10 hours postoperatively or when hemostasis is achieved (Table 1).

PT is recommended for detecting the presence of rivaroxaban. Conventional assays are not sensitive at low concentrations and the degree of prolongation does not reliably predict the amount of drug present [5,10]. However, a normalized PT corresponds to approximately ≤30ng/ml drug concentration and is considered to be compatible with surgical management without increased risk of bleeding [8]. Once again, this is an extrapolation from the data of patients who underwent elective surgeries while on rivaroxaban, in the ROCKET AF study [8]. Commercially available chromogenic anti-factor Xa assays when used with a rivaroxaban calibration curve is most sensitive and specific for rivaroxaban plasma concentrations [5,9]. However, this is not available in all hospital labs.

If a bleeding complication occurs in a patient receiving rivaroxaban, the next rivaroxaban dose should be delayed or treatment discontinued as appropriate [9]. The urgency of the surgery needs to be weighed against the risk of bleeding complications on an individualized case by case basis. This is deferred to the clinical judgement of the surgeon. In cases of a severe, life-threatening bleeding or requiring emergent surgery, PCC (25–50 IU per kg bodyweight) is the recommended reversal agent [10]. Activated PCC and recombinant factor VIIa have been utilized in in experimental settings but there is concern due to the greater prothrombotic potential of these agents compared to PCC [9].

## Apixaban

Apixaban (Eliquis®) is another NOAC that acts to inhibit factor Xa. It is the first NOAC that has been shown to be superior

to warfarin in reducing stroke or systemic embolism, all-cause mortality, and major bleeding in patients with AF (ARISTOTLE study). Furthermore, in AVERROES study, patients with AF who were considered unsuitable for warfarin therapy, apixaban was more effective than aspirin for stroke prevention and had a similar rate of major bleeding [11,12]. Apixaban is dosed 5mg twice daily. It has a half-life of 8 -15 hrs, is highly protein bound and is excreted predominately fecal with 27% renal. Apixaban may prolong the PT, but this assay lacks sensitivity in comparison to the dilute PT test (modified PT) or the HepTest from American Diagnostica (a commercially available clot based anti-Factor Xa assay).[5]Barrett et al, demonstrated that chromogenic anti-factor Xa assays, provide the most accurate apixaban plasma concentrations [13]. A normal anti-factor Xa activity in patients receiving apixaban suggests very low drug levels and an intact hemostatic function, safe for surgical procedures [5] (Table 1).

Similar to other NOACs, apixaban has no antidote. In *in-vitro* testing PCC improved thrombin generation when added to blood of healthy donors on chronic apixaban. While there is no clinical evidence to support its use, a dose of 50 IU/kg PCC might be reasonable for severe/life-threatening bleeding in patients taking apixaban [5]. Unlike dabigatran, apixaban is not dialysable because of its high degree of protein binding. In the non-emergent circumstances, delaying the surgery for 24-48 hrs is considered effective to reduce drugs level to a range that does not cause any additional risk of bleeding from apixaban.

## CONCLUSION

NOACs such as dabigatran, rivaroxaban and apixaban are efficacious and safe, relative to warfarin. Because of their steady pharmacokinetics, regular coagulation lab testing is not required, unlike the traditional warfarin. They have been approved for the prevention of stroke and thromboembolic events in patients with non-valvular AF and rivaroxaban additionally for VTE prevention after total hip or knee surgery, DVT treatment and prevention

**Table 1**: Chronic Anticoagulants: Indication, dose and pharmacokinetics.

| Drug | Indication of use | Dose | Pharmacokinetics |
|---|---|---|---|
| **Warfarin** | 1. Stroke prevention in non-valvular atrial fibrillation | Dose adjusted to keep between INR 2 to 3 | Plasma levels peak: 1.5-3 days<br>Metabolism: Liver<br>Half-life: 20-60 hrs (patient specific) |
| | 2. VTE prevention following hip and knee replacement surgery | Dose adjusted to keep between INR 1.5 to 2 | |
| | 3. DVT treatment | Dose adjusted to keep between INR 2 to 3 | |
| **Dabigatran** | 1. Stroke and arterial thromboembolism in non-valvular atrial fibrillation | 150mg twice daily<br>*Renal dosing* | Plasma levels peak: 1.25 - 3 hrs<br>Excretion: Kidneys (80%)<br>Half-life: 12 - 14 hrs |
| **Rivaroxaban** | 1. Stroke prevention in non-valvular atrial fibrillation | 20mg daily<br>*Renal dosing* | Plasma levels peak: ~2 - 4 hrs<br>Excretion: Kidneys (66%)<br>Half-life: 9 - 13 hrs |
| | 2. VTE prevention following hip and knee replacement surgery | 10mg daily for 12 days (knee) or 35 days (hip)<br>*Initial dose 6-10 hrs after surgery*[¥] | Plasma levels peak: ~2 - 4 hrs<br>Excretion: Kidneys (66%)<br>Half-life: 9 - 13 hrs<br>Plasma levels peak: 1 - 3 hrs<br>Excretion: Predominantly fecal, Kidneys (25%)<br>Half-life: 10 - 14 hrs |
| | 3. DVT treatment | 15mg every 12 hrs for 21 days and then 20mg daily for 6 months or more. | |
| **Apixaban** | 1. Stroke prevention in non-valvular atrial fibrillation | 5mg twice daily | |

**Table 2:** Chronic Anticoagulant Management in the Perioperative Setting for Total Joint Arthroplasty Patients.

| Medication | Method of action | Perioperative Taper | Reversal Agent | Reversal Lab $ |
|---|---|---|---|---|
| Warfarin | Decreased synthesis of Vitamin K dependent clotting factors: II,VII, IX, X, Protein C and S. | **Elective**: Discontinue 5 days prior to surgery | **Urgent**: Single dose 2.5 to 5mg Vitamin K<br>**Emergent**: Vitamin K and FFP or PCC | Target INR <1.3 |
| Dabigatran | Inhibition of factor IIa (thrombin) | **Elective**: 3-4 days* or 4-5 days[ǂ] prior to surgery | **Urgent**: Activated charcoal following recent ingestion<br>**Emergent**: Hemodialysis, Activated charcoal following recent ingestion | Normalized TT[(a)]<br>aPTT<br>Dilute TT± |
| Rivaroxaban | Inhibition of factor Xa | **Elective**: Discontinue at least 24 - 48 hours prior to surgery | **Urgent**: PCC<br>**Emergent**: PCC, aPCC[+] | Normalized PT[(a)]<br>Chromogenic anti-factor Xa activity[±] |
| Apixaban | Inhibition of factor Xa | **Elective**: Discontinue at least 24 - 48 hours prior to surgery | **Urgent**: PCC<br>**Emergent**: PCC[+], aPCC[+] | Normal Dilute PT Test<br>Anti-factor Xa assay (HepTest)<br>Chromogenic anti-factor Xa activity[(a)] |

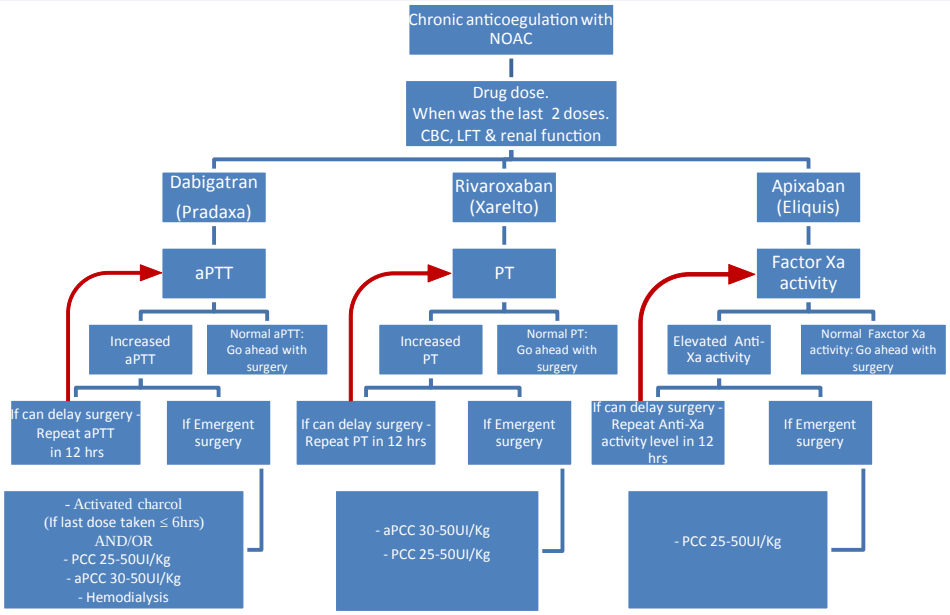


**Figure 1** Peri-operative management of patients on NOAC.
NOAC: Novel Oral Anticoagulant; CBC: Complete Blood Count; LFT: Liver function tests; PCC: Prothrombin Concentrate Complex (Kcentra® or Bebulin®); aPCC: Activated Prothrombin Concentrate Complex (FIEBA); PT: Prothrombin time; aPTT: Activated Partial Thromboplastin Time; TT: Thrombin Time; ǂ Preferred agent.

of recurrent VTE following an acute DVT. As the prevalence of chronic anticoagulation among patients undergoing total joint arthroplasty continues to increase, orthopaedic surgeons need to be aware of the mechanism of action, pharmacokinetics and reversal agents available for these NOACs. Aggarwal et al demonstrated that patients with preoperative AF undergoing TJA had an increased length of hospital stay, increased transfusion requirements, and an increased risk of periprosthetic joint infection and unplanned hospital readmission [3].

The recommended anticoagulation tests to evaluate hemostasis and drug reversal are normalization of aPTT for dabigatran, PT for rivaroxaban and chromogenic anti- Xa activity for apixaban (Table 2) [5]. Though several research projects are in the works to create an antidote for these drugs, none has yet been approved for human trials. The currently used for coagulation reversal agents for NOAC are non-activated prothrombin concentrate complex (PCC) and activated PCC (or aPCC). PCC, trade name Kcentra® and Bebulin® are available in USA. Kcentra® is 4 factor PCC (II, VII, IX and X) while Bebulin® only has 3 factors (II, IX and X). Most papers recommend the use of the 4 factor PCC at 25-50 UI/kg. In in-vivo studies and animal studies, the nano-filtered aPCC (trade name FEIBA®) has been able to reverse anticoagulation to some extent at dosage 30-50UI/Kg in patients on NOACs. Based on the current limited data the reversal agents recommended are PCC for rivaroxaban and apixaban (no human studies for apixaban) and aPCC for dabigatran [5,8,9]. Activated charcoal can be used for those who had taken dabigatran less than 6 hours to the time of presentation [5]. Hemodialysis is another option for dabigatran removal. But it takes hours 4-6 hours or more for approximately 60% drug removal [5,7] (Table 2).

In major orthopedic surgeries, such as TJA, a critical concern is bleeding. The use of reversal agents to overcome the anticoagulation effect adds the potential concern for thromboembolism secondary to these agents. Hence, the use of reversal agents needs to be made on individual basis, if the surgery cannot be delayed any further. For most patients a 24-48 hour delay is sufficient for it to be safe to proceed with surgery, if they were on rivaroxaban or apixaban, while 3-4 days delay is recommended for dabigatran. This duration need to be increased for the elderly and for those with renal failure. The pharmacokinetics is summarized in table 1.

There is no guideline on perioperative management of these patients, in elective, urgent or emergent surgeries. Pernod et al published a proposal on perioperative management of major bleeding risks in patients taking rivaroxaban and dabigatran. (Summarized in the relevant sub-sections).Adapting the approach proposed by Pernod et al, and utilizing the data available from current literature, we propose a peri-operative algorithm for urgent and emergent surgeries, in Figure 1, for the practicing orthopedic surgeon.

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