Periprocedural Management of Non-Vitamin K Oral Anticoagulants in Chronic Kidney Disease: A Review of Existing Heterogeneity and Contemporary Evidence

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Abstract
Non vitamin-K oral anticoagulants (NOAC) have considerably enhanced anticoagulation practice for non-valvular atrial fibrillation with specific advantages of fixed dosing, non-fluctuant therapeutic levels and obviation of therapeutic level monitoring. NOAC pharmacology is remarkable for considerable renal excretion. Heterogeneity in the precise time cut-offs for discontinuation of NOACs prior to elective surgical or percutaneous procedures arise from the non-linear variations of drug excretion with different levels of creatinine clearances as in chronic kidney disease. Multiple authors have suggested cut-offs leading to ambiguity among practicing clinicians. Recent data pertaining to systemic thromboembolism, stroke and major bleeding derived from randomized controlled clinical trials have simplified the periprocedural management of NOACs. This review focusses on heterogeneity in the management of NOACs in patients with CKD in this peculiar scenario and highlights the contemporary evidence to support a unified approach towards perioperative management of NOACs. Multiple antidotes targeted towards binding of specific NOACs have been developed and are in the testing phase, thereby offering immense potential for rapid and complete reversal of NOAC activity in emergent procedures and major bleeding episodes. Targeted research on thromboembolism, stroke and major bleeding following temporary periprocedural interruption of NOACs using multicentric registries could further expand the clinical utility of these agents.

Key Words: Non-Vitamin K Oral Anticoagulants, Chronic Kidney Disease, Bleeding Risk, Thromboembolism, Periprocedural.

Introduction
With the advent of non-vitamin K oral anticoagulants (NOACs), there has been a paradigm shift in anticoagulation for stroke prevention in non-valvular atrial fibrillation (NVAF). Distinct advantages of NOACs include fixed dosing, non-fluctuant therapeutic levels, elimination of the need for therapeutic level monitoring, lack of dietary restrictions and minimal drug interactions in comparison to warfarin. However, there is minimal objective data to support the optimal time at which NOACs need to be withheld and restarted for elective procedures in patients with chronic kidney disease. The timing is dependent on the creatinine clearance (CrCl) and bleeding risk associated with the surgical procedure. The clinical relevance of this timing is underscored by the fact that approximately 10% of patients receiving anticoagulation undergo surgical or invasive procedures mandating temporary interruption (TI) of these medications. There is a discrepancy between the recommendations from the manufacturers and the cut-offs suggested by multiple authors, thereby indicating a lack of consensus for the management of this often encountered clinical scenario. Earlier withholding of NOACs for elective procedures might predispose to suboptimal anticoagulation while withholding it later might predispose to higher intraprocedural bleeding risk. A similar dilemma is noted during resumption of NOACs after procedures. This article focusses on the pharmacokinetic profiles of the four commercially available NOACs and an approach to their management in the periprocedural setting.

Pharmacokinetics of Dabigatran and Discrepancies in its Usage in the Periprocedural Setting
Dabigatran is a potent oral direct thrombin inhibitor with a half-life of 12-17 hours which has shown to have lower rates of stroke and thromboembolism as compared to warfarin when used at a dose of 150 mg twice daily with similar rates of major hemorrhage in the Randomized Evaluation of Long-Term Anticoagulation Therapy
Discrepancies in the time of stoppage (in hours) of Dabigatran prior to elective surgeries*  

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*Package insert recommends discontinuing dabigatran 1-2 days (CrCl ≥ 50 mL/min) or 3 to 5 days (CrCl <50 mL/min) prior to elective surgical procedures. Longer but unspecified times are recommended for major surgery, spinal puncture, or placement of a spinal or epidural catheter or port.  

The non-linear variations in NOAC concentrations with different grades of CrCls complicates the process of arriving at precise cut-offs. Most of the studies with respect to dabigatran listed in table 1 present data which is fairly consistent across most grades of CrCls except in the 50-80 mL/min and <30 mL/min range, where discrepancies of approximately 12-48 hours are evident. Wysokinski et al. have recommended a conservative approach to withholding dabigatran (7 days) prior to elective surgery carrying high risk of bleeding in patients with CrCls <50 mL/min and ≥50 mL/min, respectively. In contrast, this is significantly different from multiple studies which recommend holding of NOACs 2-4 days prior to surgery at CrCls ≥50 mL/min and <50 mL/min respectively (Table 1). The European Heart Rhythm Association (EHRA) has also recommended stoppage of dabigatran at ≥96 hours prior to elective surgery carrying high risk for bleeding for the same CrCl cohort.  

The incidence of thromboembolic and bleeding complications in 4591 patients who underwent 7631 surgical procedures over a mean follow-up period of 2 years following periprocedural TI of dabigatran in the RE-LY trial has been published. This subgroup of patients comprised of different stages of CKD and a specific protocol was used to decipher the time at which dabigatran was withheld in the periprocedural setting (Table 2). Results from this study highlight the non-inferiority of dabigatran at either doses to warfarin in terms of 30-day post procedural thromboembolic events [Ischemic or hemorrhagic stroke: Dabigatran (D) 110mg vs. warfarin: relative risk (RR) 0.73, 95% confidence interval (CI) (0.28–1.92; P=0.53) and D150mg vs. warfarin, RR 0.71 95% CI, (0.27–1.85; P=0.48)] as well as bleeding of any magnitude in both elective and urgent surgeries [Major bleeding: D110 mg vs. warfarin: RR 0.83; 95% CI, 0.59-1.17; P=0.28; D150 mg vs. warfarin: RR 1.09; 95% CI, 0.80-1.49; P=0.58]. Moreover, patients anticoagulated with dabigatran demonstrated a 4-fold higher likelihood of completing the procedure within 48 hours of TI. Periprocedural bridging with heparin products was significantly lower with dabigatran [D110mg 15.3% vs D150mg 17% vs warfarin 28.5%, P<0.001]. Event rates were comparable to the randomized trial and moreover, this study offers the maximal sample size for assessment of thromboembolic and bleeding complications associated with anticoagulants in this scenario.  

A prudent approach to clinicians would be to follow the protocol in table 2 for management of dabigatran considering the well-validated nature of outcomes with this strategy. Additionally, a uniform interruption of dabigatran for 24 hours prior to the surgical procedure showed no difference in the aforementioned outcomes in comparison to warfarin. However, when this strategy was adopted, there were a disproportionately higher number of patients noted to have a standard and not a high surgical bleeding risk profile, thereby underwhelming in terms of statistical power for the latter scenario. In patients undergoing high bleeding risk procedures and having severely impaired renal function, a normal activated partial thromboplastin time (aPTT) or thrombin time (TT) essentially excludes drug levels associated with anticoagulants in this scenario.

Pharmacokinetics of Rivaroxaban and the Variations in Its Use in the Periprocedural Scenario  

Rivaroxaban is a direct oral factor Xa inhibitor with a half-life of 5-9 hours in healthy individuals of age 20-45 years and 11-13 hours in the elderly subgroup. Evidence substantiating the use of rivaroxaban emerges from the Rivaroxaban Once Daily Oral Direct Factor Xa
Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) involving 14,264 patients with NVAF. These results demonstrate non-inferiority to warfarin for stroke, thromboembolism and major bleeding along with lower incidence of intracranial and fatal bleeding in the rivaroxaban group. The rivaroxaban arm in this study comprised of patients with CrCl ≥50 ml/min or 30-49 ml/min who received 20 mg once daily or 15 mg once daily doses, respectively. Though a bulk of the safety and efficacy data has been derived from patients with compromised renal function in this study, patients with a lower CrCl of 15-30 ml/min have been approved to receive rivaroxaban 15 mg once daily despite paucity of randomized evidence to support it.

Evidence and Recommendations for Periprocedural Management of Rivaroxaban

The manufacturers recommend stopping of rivaroxaban at least 24 hours before any invasive procedure, irrespective of the bleeding risk associated with the procedure or the CrCl level. Table 3 summarizes the variations among different authors for the time at which rivaroxaban needs to be stopped prior to the procedure. Considering the increase in factor Xa inhibition and prothrombin time by 10-20% with reduction in CrCl below 50 ml/min, there is potential for excessive bleeding complications with this unified approach.

Robust evidence from a subset of 4692 patients with varying levels of CrCLs above 15ml/min who underwent 7555 TIs ranging between 3-30 days from the ROCKET – AF trial elicited no difference between rivaroxaban and warfarin in terms of major bleeding [Rivaroxaban 0.99% vs warfarin 0.79% per 30 days; hazard ratio (HR) 1.26; P=0.32], minor bleeding, strokes and thromboembolic episodes [Rivaroxaban 0.30% vs warfarin 0.41% per 30 days; hazard ratio (HR) 0.74, P=0.40] over a mean follow-up period of 24 months. Of these patients, 90% of TIs were initiated ≥3 days prior to invasive procedures. However, only 13% of these were surgical procedures with high bleeding risk. A total of 9% of patients with ≥2 risk factors for stroke underwent bridging therapy and there were no statistical differences between the rivaroxaban and warfarin groups among these patients.

For practical purposes, a unified approach of stopping rivaroxaban ≥3 days prior to invasive procedures of any bleeding risk in patients with CrCl<15ml/min is recommended. An exception would be those undergoing procedures with a high bleeding risk such as cardiac or neurosurgery and having CrCl<50ml/min, where withholding of rivaroxaban at least 5 days prior to the procedure is recommended. Normal prothrombin time, international normalized ratio or anti-factor Xa activity essentially excludes clinically significant blood levels and could be used to confirm clearance of rivaroxaban in high bleeding risk situations. Anti-factor Xa assays calibrated to the respective NOACs provide the best correlation to therapeutic levels of all oral Xa inhibitors but the assay availability is often limited.

Pharmacokinetic Profile of Apixaban in Normal and Compromised Renal Function

Apixaban is an oral direct factor Xa inhibitor with a half-life of 12 hours and 25% renal clearance. It has been evaluated for anticoagulation in NVAF in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) randomized controlled trial with 18,201 patients. Patients with CrCl<25 ml/min were excluded from the study and those with a serum creatinine of >1.5mg/dL received a reduced dose of 2.5 mg twice daily as opposed to those with better CrCLs who received a 5mg two times daily dosing. Results from this trial showed superiority to warfarin in terms of stroke and thromboembolism prevention, incidence of major bleeding and more importantly, mortality benefit. Present recommendations from the package insert recommend dose reduction to 2.5 mg twice daily if two of either criterion is met: body weight ≤60 kg, serum creatinine ≥1.5 mg/dL or age≥80 years. However, no dose reduction in individuals with isolated renal impairment, including those with end-stage renal disease on hemodialysis. However, there is lack of evidence to support lack of dose reduction in those with CrCl<25 ml/min.

Evidence-Based Management Strategy for Apixaban in the Periprocedural Setting

Table 4 summarizes the variations in the time cut-offs for withholding apixaban prior to elective procedures as suggested by different authors. The most substantial data on the periprocedural management of apixaban is derived from the sub-study of the ARISTOTLE trial comprising of 5924 patients with a total of 9260 analyzed procedures necessitating TI. Of 37.9% of patients who were on apixaban continued through the procedure without any interruption. Results from this study indicated no significant differences between apixaban (either doses) and warfarin in terms of 30-day post-procedural outcomes of major bleeding [Apixaban 1.62% vs warfarin 1.93% of procedures], minor bleeding and stroke or systemic embolism [Apixaban 0.35% vs warfarin 0.57% of procedures (odds ratio [OR] 0.601; 95% CI, 0.322-1.120] irrespective of the CKD stage. A total of 11.7% of patients in both groups underwent periprocedural bridging anticoagulation. However, this study comprised of only 13.1% major procedures defined as those requiring general anesthesia. Extrapolation of this data to those undergoing high bleeding risk procedures in the real world must be exercised with caution. The heterogeneity in the time at which apixaban was stopped prior to the procedure is to be noted (on the day of the procedure or anytime up to 7 days prior to it).

For practicing clinicians, this data offers substantial evidence for either non-interruption or holding of apixaban ≥24 hours for low bleeding risk procedures irrespective of the CKD stage and is therefore recommended. Until more comprehensive data is available, procedures involving a high risk of bleeding would mandate holding of apixaban, at least 48 hours prior to the procedure. Normal anti-factor Xa excludes systemic drug levels in high risk situations.

Pharmacokinetic Profile, Safety and Efficacy of Edoxaban in Non-Valvular Atrial Fibrillation

Edoxaban is an oral direct factor Xa inhibitor with a half-life of...
10-14 hours with a 50% renal clearance which has a targeted patient population of those with pre-existent renal dysfunction.7 Notably, edoxaban use is contraindicated in those with CrCl< 95 ml/min due to a higher incidence of ischemic strokes in patients taking the 60 mg once daily dose. Results from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF TIMI-48) trial demonstrated non-inferiority of edoxaban to warfarin in terms of stroke prevention and thromboembolism (systemic embolism: edoxaban 5 mg twice daily 1.18% vs. warfarin 1.5%, HR 0.79, 95% CI, 0.63-0.99, P<0.001; edoxaban 2.5 mg twice daily 1.61% vs warfarin 1.5%, HR 1.07, 95% CI, 0.87-1.31, P=0.05) and in addition, lower incidence of major bleeding (Edoxaban 5mg twice daily 2.75% vs. warfarin 3.43%, HR 0.80, 95% CI, 0.71-0.91, P<0.001; edoxaban 2.5 mg twice daily 1.61% vs warfarin 3.43%, HR 0.47, 95% CI, 0.41-0.55, P<0.001) and cardiac mortality.22 In this prospective trial, a significant portion of patients with CrCl 30-50 ml/min received a reduced dose of 30mg twice daily as opposed to the 60mg twice daily dosing for those with a higher CrCl value. Primary endpoints and bleeding risks as mentioned above were unaffected by dose reduction. Through the manufacturer recommends use of edoxaban at a reduced dose in patients with CrCl 15-50 ml/min, there is less evidence in terms of safety and efficacy in this range.

Recommendations for Periprocedural Management of Edoxaban

Presently, there is no randomized controlled trial evidence for bleeding and thromboembolic complications from TI of edoxaban in the periprocedural setting. In the absence of concrete evidence, stoppage of edoxaban at least 24 hours prior to the procedure is recommended in accordance with the package insert.3 aPTT and anti-factor Xa activity are sensitive indicators of therapeutic edoxaban levels.7 A unified approach derived from randomized controlled trials to the time at which NOACs need to be discontinued prior to the procedure is outlined in table 5.

Resumption of NOACs Following Temporary Interruption for Procedures and Indications for Bridging Therapy

Discrepancies have been noted in the optimal time at which NOACs should be restarted following elective surgery. In contrast to Wysokinski at al. who recommend re-initiation of NOACs ≥48 hours post-surgery, the EHRA recommends earlier reinitiation of NOACs 6-8 hours post-hemostasis or even bridging with heparin products until 48 hours after surgery when NOACs would be safe to use.6,12 Early post-operative reinitiation of NOACs might increase the risk of bleeding which could prove deleterious, particularly in the absence of well-validated reversal agents.

Ideally, NOACs should be initiated a time point after the procedure when hemostasis is complete. The decision to use periprocedural bridging therapy with short acting heparin products is a clinical decision which needs to account for 3 different factors:

1. The risk of thrombosis objectively derived from the CHADS2 Vasc scores;
2. The risk of bleeding associated with the procedure by itself;
3. And the adequacy of hemostasis.

It is highly recommended that clinicians assess adequacy of hemostasis in conjunction with the primary procedure operator before resumption of NOACs. Due to the fast onset of action of NOACs, bridging is not recommended except in cases of high CHADS2 vasc scores or in instances where the risk of re-bleeding is high (to facilitate reversal if indicated), wherein bridging with short acting heparin products may be considered until one reaches a point where NOAC resumption is considered safe. A rule of thumb is to initiate bridging therapy in those with high risk of thrombosis at 24-48 hours after the procedure until NOACs can be safely resumed.

Emergent Surgeries and Major Bleeding: Role of Antidotes Targeted Towards Specific NOACs

Enhancements in the understanding of NOAC pharmacology has paved way for the development of specific fast-acting antidotes which are presently being evaluated. Idarucizumab is a monoclonal antibody fragment targeted to bind dabigatran which has demonstrated complete reversal of anticoagulant activity within minutes of administration in a prospective cohort of 90 patients in the Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE AD) trial.22 Andexanet Alfa, a recombinant engineered variant of human factor Xa has been recently evaluated in a phase III trial with 33 patients for up to 90% reduction of apixaban anticoagulant activity within 2-5 minutes of administration. Preliminary results from the Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXA Inhibitors – Apixaban (ANNEXA-A) trial have shown no serious adverse prothrombotic effects.23 Similar results for rivaroxaban (ANNEXA-R) reversal are currently being evaluated. PER977 (Perosphere), has demonstrated near-complete reversal of edoxaban activity within 10-30 minutes of administration without prothrombotic effects.24 Notably, this agent is a non-specific antidote which has been shown to provide effective and rapid reversal of anticoagulant effects of both direct thrombin inhibitors and all commercially available oral factor Xa inhibitors.24 With the advent of multiple antidotes which provide rapid reversal of NOAC effects, one could expect further minimization of TIs of NOACs in the periprocedural setting.

Often, reversal agents such as fresh frozen plasma or prothrombin complex concentrates (PCC) have counterproductive prothrombotic effects such as systemic thromboembolism, myocardial infarction and stroke. A meta-analysis comprising of 27 studies evaluating use of PCC in vitamin K antagonist reversal for emergent surgeries

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<th>Agent</th>
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Procedures with high risk of bleeding include cardiac surgery, vascular surgery (excluding endovascular procedures) and neurosurgery where bleeding could be deleterious. Most other procedures are considered low risk for bleeding.

*Data derived from ROCKET-AF trial. †Data derived from ARISTOTLE trial. ‡Data derived from ENGAGE TIMI-48 trial.

Table 5: Unified Recommended Timing (in hours) for Discontinuation of Non-Vitamin K Oral Anticoagulants Prior to the Procedure

Table 4: Discrepancies in the time cut-offs for holding (in hours) Apixaban prior to elective surgical interventions*
or for severe bleeding showed a significant incidence of systemic thromboembolism (0.7–1.8%) and a mortality rate of 10.6%. These results further reinforce the need for specific NOAC reversal agents.

**Conclusion**

In conclusion, patients with CKD present a diverse population in whom considerable heterogeneity exists in the timing of stoppage of NOACs prior to the procedure. Data emerging from landmark prospective trials such as RE-LY, ROCKET-AF and ARISTOTLE have simplified the approach to this specific clinical scenario and considerably reduced the heterogeneity noted in this timing.\(^9,17,19,21\) Lesser emphasis is being placed on the level of renal compromise considerably reduced the heterogeneity noted in this timing.

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