My Patient Taking A Novel Oral Anticoagulant Needs Surgery, Device Implantation, Or Ablation

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Abstract

Atrial fibrillation (AF) is a highly prevalent chronic condition and a growing number of patients are on chronic anticoagulation therapy with novel oral anticoagulant (NOAC) agents: dabigatran, rivaroxaban, and apixaban. Many of these patients are expected to require invasive procedures. There is no clear consensus regarding the peri-procedural management of patients using NOACs, as to how to minimize both bleeding risk and thromboembolism risk. This review of the current available literature is designed to help formulate peri-procedural anticoagulation strategies for patients with AF taking NOACs who are being considered for catheter ablation, device implant, or other surgery.

To help frame the discussion, we offer 3 case vignettes that we will revisit to at the end of the review of the existing literature.

Case 1: A 62 year-old female with hypertension, diabetes, and symptomatic paroxysmal AF who is prescribed dabigatran for thromboembolism prevention. She has failed attempts at maintaining sinus rhythm with antiarrhythmic drugs. She is now being considered for catheter ablation of AF.

Case 2: A 76 year-old male with hypertension, diabetes, prior stroke, and ischemic cardiomyopathy who has persistent drug-refractory AF. He is maintained on chronic anticoagulation with dabigatran for thromboembolism prevention. He has an implantable cardioverter-defibrillator (ICD) which requires a generator change.

Case 3: A 58 year-old male with hypertension and paroxysmal AF who takes rivaroxaban for thromboembolic prophylaxis and is being considered for a knee replacement surgery.

Introduction

Atrial fibrillation is the most common arrhythmia in current clinical practice, affecting more than 1% of the general population and more than 5% of patients aged 80 years and older.[1] It is fast becoming one of the more prevalent chronic conditions in our aging society due to an increased burden of traditional risk factors for AF including obesity, hypertension, diabetes, and ischemic heart disease. Atrial fibrillation has a well-established role in causing cardioembolic stroke. Guidelines from the European and American cardiovascular societies recommend anticoagulation therapy as a mainstay in patients with AF who have moderate or high risk for cardioembolic stroke. A growing number of patients with AF are receiving chronic anticoagulation therapy with a NOAC. Patients with AF, given their high burden of co-morbidities, will oftentimes require invasive procedures. For example, in the Randomized Evaluation of Long term Anticoagulation Therapy (RE-LY) trial, 25% of patients required at least 1 surgical or invasive procedure, and nearly 15% of patients had 2 or more procedures during a mean follow-up of just 2 years.[2] Peri-procedural management of anticoagulation requires the

treating physician to weigh the risk of bleeding against the benefit of thromboembolism prevention. The emergence and anticipated routine clinical use of NOACs has the potential to greatly simplify peri-procedural anticoagulant management because of their relatively short elimination half-lives, rapid onset of action, predictable pharmacokinetic properties, and few drug-drug interactions.

The 2014 ACC/AHA/HRS guidelines recommend using the CHA_2DS_2-VASc score for estimating risk of a cardioembolic stroke. For patients with AF and a CHA_2DS_2-VASc score of 2 or greater, oral anticoagulants are recommended as a Class I recommendation. In patients with non-valvular AF the options for anticoagulation include warfarin (INR 2.0 to 3.0) (Level of Evidence:A), dabigatran (level of Evidence:B), rivaroxaban (Level of Evidence:B), or apixaban (Level of Evidence:B). For patients with non-valvular AF who are unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended (Level of Evidence:C).[3] Warfarin was the only oral anticoagulant agent available up until 2010, when dabigatran was approved by the FDA; warfarin remains the only option in patients with mechanical heart valves and those with dialysis dependent chronic kidney disease. Unfortunately, warfarin is challenging to use due to its narrow therapeutic index, need for frequent monitoring, and important interactions with many drugs. The availability of NOACs promises the delivery of equivalent benefit without the need for regular monitoring, and possibly a better safety profile by limiting the risks of overtreatment.

Disclosures:
Neither author has conflicts of interest to disclose.

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Table 1: Pharmacokinetics of NOAC agents

Characteristics	Dabigatran	Rivaroxaban	Apixaban
Pro-drug	Yes	No	No
Bioavailability	3-7%	66%(without food) 100% (with food)	50%
Elimination half life (hours)	12-17	5-9	12
% Renal elimination	80	66	27
Metabolism using CYP3A4 family	No	Yes	Yes

This review of the current available literature is intended to help clinicians formulate strategies in managing AF patients who are taking NOACs and are being considered for catheter ablation, device placement, or other surgery.

Pharmacology Of The NOACs

Table 1 gives a brief review of the pharmacokinetics of the NOACs.

Dabigatran

Dabigatran is an oral reversible direct competitive inhibitor of thrombin. Dabigatran was approved for thromboembolism prevention in patients with non-valvular AF in 2010. It was also approved for the treatment of deep venous thrombosis (DVT) and pulmonary embolism in 2014.

Dabigatran etexilate is a low-molecular weight non-active pro-drug that is administered orally and converted in the blood to its active form, dabigatran (a potent, competitive, and reversible direct thrombin inhibitor). Dabigatran binds to the active site of thrombin univalently, thereby inactivating both bound fibrin and unbound (i.e. free) thrombin. By inhibiting thrombin, dabigatran prevents a cascade of events: conversion of fibrinogen into fibrin, positive feedback amplification of coagulation activation, cross-linking of fibrin monomers, platelet activation and inhibition of fibrinolysis

Dabigatran inhibits human thrombin in a concentration dependent manner. Dabigatran binds to thrombin in a highly selective, rapid, and reversible manner. After oral administration, dabigatran etexilate is rapidly absorbed and hydrolyzed to its active moiety by non-specific ubiquitous esterases in the gut mucosa, liver, and plasma. After oral administration of dabigatran etexilate, peak plasma concentration (Cmax) of the active drug is reached within 0.5–2 hours and steady-state concentrations are achieved within 3 days of initiation. Up to 80 % of circulating unchanged dabigatran and small amounts of dabigatran glucuronides are excreted via the kidneys, the dominant elimination pathway.[4] Consequently, reduced kidney function results in elevated dabigatran plasma concentrations and a prolonged drug effect. Dabigatran shows a very low potential for drug–drug interactions and its absorption is not affected by food.

Rivaroxaban

Rivaroxaban is a potent, oral direct inhibitor of Factor Xa. The FDA approved rivaroxaban for stroke prophylaxis in patients with non-valvular AF in 2011. It was also approved for use in prophylaxis of DVT in adults undergoing hip and knee replacement surgery in 2011.

Rivaroxaban prevents thrombin generation by inhibiting Factor Xa; this is achieved by binding directly to the active sites of the serine endopeptidase. The pharmacodynamic profile of rivaroxaban in healthy subjects reveals a linear correlation between the Prothrombin Time (PT) and the plasma concentration of rivaroxaban. On pharmacokinetic evaluation of rivaroxaban in healthy volunteers, Cmax was achieved 2-4 hours after oral administration.

Rivaroxaban has a terminal elimination half-life of 5-9 hours in healthy young subjects and 11-13 hours in elderly subjects due to normal age related renal function decline. In individuals with renal dysfunction, rivaroxaban plasma concentrations were increased compared with healthy controls.[4]

Rivaroxaban is metabolized via CYP enzymes (CYP3A4 and CYP2C8), as well as CYP-independent mechanisms. As a result, the plasma concentrations of rivaroxaban are affected with concomitant CYP inducer or inhibitor drugs. Approximately 66% of ingested rivaroxaban is excreted via the kidneys and the remainder excreted in the feces as unchanged drug.

Apixaban

Apixaban is a pyrazole derivative, small-molecule, selective factor Xa inhibitor. It is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF having been approved for such use by the FDA in 2012. In 2014, the FDA approved apixaban for use in prophylaxis of DVT in patients who have undergone hip or knee replacement surgery.

Like rivaroxaban, apixaban is an inhibitor of Factor Xa. It is rapidly absorbed, reaching Cmax approximately 3 hours after a dose in healthy volunteers. Steady state concentrations are reached within 3 days. The pharmacokinetics of apixaban are affected by body weight, sex, and age.[4]

Apixaban is metabolized via O-demethylation and hydroxylation mainly by CYP3A4/5. The plasma concentrations of apixaban are affected with concomitant use of strong CYP inducer or inhibitor drugs. After oral administration, it is eliminated unchanged 50% in the feces and approximately 25% excreted in the urine.

Monitoring

Routine coagulation monitoring is not required in patients taking NOACs, as these drugs have predictable pharmacokinetics. However this assessment may be useful in situations such as acute bleeding, requirement for emergency surgery and suspected overdose.

Thrombin clotting time and ecarin clotting time can be used to evaluate the anticoagulation effect of dabigatran. Prothrombin time is relatively insensitive to dabigatran. The activated partial thromboplastin time (aPTT) assay shows a curvilinear dose-response relationship with dabigatran; therefore a normal aPTT level provides reassurance that there isn't a significant anticoagulant effect present.[5] The diluted thrombin time Hemoclot assay (available in Europe) provides direct assessment of thrombin activity and can be used for reliable quantitative assessment of dabigatran concentrations; values more than 65 seconds are associated with an increased risk of bleeding.

Anti-factor Xa assays using rivaroxaban and apixaban standards provide accurate measures of anticoagulant effect and are the preferred test to measure anticoagulant effects of these drugs. The PT may be prolonged in patients treated with rivaroxaban, but the effect is reagent specific.[6] The PT is not useful for apixaban because it is largely unaffected by the assay reagents at the current approved doses. The aPTT cannot be used to reliably detect the presence of rivaroxaban or apixaban.

Antidotes

No specific antidotes are currently available for dabigatran, rivaroxaban, or apixaban.[7] Dabigatran-specific monoclonal antibodies generated in mice using dabigatran-derived haptens coupled to

carrier proteins were recently developed. The obtained antidote has structural similarities with thrombin, and its affinity for dabigatran is about 350 times stronger than its affinity for thrombin. However, it has not yet been tested in humans.[8] Currently in development is a truncated form of enzymatically inactive factor Xa which, in a dose-dependent fashion, can reverse anticoagulation and correct the prolongation of ex-vivo clotting times by any of the Xa inhibitors.[9]

Management of bleeding should be individualized mainly according to the site and severity of bleeding but also to the patient characteristics, such as the indication for anticoagulation and stroke risk. In the absence of specific antidotes, general hemostatic agents should be considered.[10] In the setting of an overdose, activated charcoal can be used to decrease absorption of recently ingested dabigatran.[11] Activated charcoal may also help decrease the absorption of rivaroxaban and apixaban.[12, 13] In case of life-threatening bleeding or before emergency surgery, hemodialysis has been reported to help reduce the circulating levels of dabigatran.[14] There is limited preclinical data regarding the use of Prothrombin Complex Concentrate and recombinant factor VIIa to reverse the effects of NOACs, however clinical experience is limited. Fresh frozen plasma, tranexamic acid or desmopressin can also be considered in the setting of life threatening bleeding.[7]

Peri-Procedural Recommendations

Ablation

For purposes of this review, we will focus on the use of NOACs in the setting of catheter ablation of AF. It is estimated that more than 150,000 patients with AF undergo catheter ablation each year in the United States.[15] As procedural techniques evolve and the prevalence of AF increases, the number of ablation procedures performed is expected to increase rapidly. Patients undergoing AF ablation are typically anticoagulated per the current guidelines.[3] There are inherent additional procedural thromboembolic risks with ablation. Catheter manipulation can dislodge a previously formed thrombus in the left atrium. Passage of catheters into the left atrium and the insult of ablation on the left atrial tissue can trigger various aspects of the clotting cascade. Stunning of the left atrium results in decreased contractility and an increased risk of thrombus formation.

That being said, patients who have paroxysmal AF and few risk factors for stroke may or may not be chronically prescribed an anticoagulant and can safely be taken off their anticoagulant for several days prior to the planned ablation. The remainder of the discussion pertains mostly to patients with persistent AF and/or moderate to high stroke risk.

Many patients undergoing catheter ablation for AF take warfarin, though an increasing number use NOACs. The uninterrupted use of warfarin through the periprocedural timeframe is now widely accepted as safe and efficacious. However, there is no clear consensus regarding the periprocedural management with the newer anticoagulants.

There have been a number of studies comparing NOAC agents with warfarin. Most of these studies looked at dabigatran and results have varied between the different studies.

In a multicenter, observational study from a prospective registry including 290 consecutive patients undergoing AF ablation, patients receiving dabigatran therapy with the dose held on the morning of the procedure were compared against patients with uninterrupted warfarin therapy. The dabigatran group had a significantly higher major bleeding rate (6% vs 1%; p=0.019) and a greater composite of bleeding and thromboembolic complications (16% vs 6%; p=0.009) compared with the warfarin group.

Dabigatran use was confirmed as an independent predictor of bleeding or thromboembolic complications. Importantly, dabigatran was restarted just 3 hours after sheath removal, which might have contributed to the higher bleeding rates observed.[16]

In a randomized controlled trial studying the feasibility of dabigatran versus warfarin for peri-ablation anticoagulation in patients undergoing AF ablation, 90 consecutive patients were recruited with 45 patients in either group. Both dabigatran and warfarin were discontinued the day before ablation with no bridging therapy in either group and were resumed after confirming hemostasis of the venipuncture site. Occurrence of rebleeding from the venipuncture site was less common in the dabigatran arm than in the warfarin allocated patients (20% vs 44%; p=0.013). Thromboembolism rates were 0% in the dabigatran subset and 2.2% in the warfarin subset.[1]

In a case control analysis of 763 consecutive patients undergoing radiofrequency catheter ablation of AF, dabigatran held after the morning dose on the day before the procedure and resumed 4 hours after vascular hemostasis was compared with uninterrupted warfarin. The prevalence of major bleeding complications (2.1%) and minor bleeding complications (2.6%) in the dabigatran group were similar to those in the warfarin group (2.1% and 3.3%, respectively). There were no thromboembolic complications in either group.[18]

In a study of 999 consecutive patients undergoing AF ablation (376 taking dabigatran and 623 taking warfarin), a propensity score matched analysis was performed. Dabigatran was held 1 or 2 doses before the procedure and restarted at the conclusion of the procedure or as soon as patients were transferred to the ward for recovery. Total hemorrhagic and thromboembolic complications were similar in both groups, before (3.2% vs 3.9%; p=0.59) and after (3.2% vs 4.1%; p=0.53) propensity matching.[19]

In an analysis of 212 patients on dabigatran and 251 patients on warfarin evaluating the safety profile of uninterrupted dabigatran therapy during AF ablation, no significant difference in the risk of bleeding or thromboembolic complications were found between the two groups. Dabigatran was continued in the peri-procedural period with a dose given morning of the procedure and resumed the evening of the procedure in this study.[20]

In a recent meta-analysis which looked at 14 studies enrolling a total of 4782 patients (1823 treated with dabigatran and 2959 with warfarin) undergoing AF catheter ablation, no significant differences were found between patients treated with dabigatran and warfarin as regards thromboembolic events (0.55% dabigatran vs 0.17% warfarin; p=0.26) and major bleeding (1.48% dabigatran vs 1.35% warfarin; p=0.86).[21]

In a meta-analysis of ten cohort studies including 1501 patients receiving dabigatran and 2356 receiving warfarin comparing peri-procedural dabigatran with warfarin for anticoagulation in AF ablation. Dabigatran was held the morning of the procedure in 5 of the studies, held the night before in 1 study, held 12-24 hours prior in one, and held 2-48 hours prior in another study. There were equivalent major bleeding outcomes in the two groups (1.6% dabigatran versus 1.7% warfarin). Dabigatran demonstrated a significantly higher rate of neurological events in this analysis.[22]

There have been a few studies comparing rivaroxaban and warfarin in the setting of AF ablation. In a multicenter prospective study, uninterrupted rivaroxaban was compared with uninterrupted warfarin

in 157 patients undergoing AF ablation. There was no statistical difference between the two groups regarding major bleeding (1.9% rivaroxaban vs 2.5% warfarin). One patient in each group suffered a peri-procedural transient ischemic attack.[23]

In a prospective registry of patients undergoing AF ablation in 8 centers, uninterrupted rivaroxaban was compared with uninterrupted warfarin. Rates of major bleeding were 1.6% and 1.9% respectively between the two groups. Rates of embolic complications were 0.3% in each group.[24]

In a meta-analysis of 8 studies involving 3575 patients looking at the efficacy and safety of rivaroxaban compared with warfarin in patients undergoing catheter ablation for AF, similar rates of thromboembolic events (0.4% vs 0.4%; RR0.71, 95% CI 0.26 to 1.96, p=0.51) and major hemorrhage (1.2% vs 2.3%; RR 0.49, 95% CI 0.24 to 1.02, p=0.06) were noted between the groups. Direct efficacy and safety comparisons between rivaroxaban and dabigatran showed nonsignificant differences in rates of thromboembolism (0.5% vs 0.4%; RR 1.12, 95% CI 0.25 to 4.99, p=0.88) and major bleeding (1.0% vs 1.6%; RR=0.71, 95% CI 0.16 to 3.15, p=0.66).[25]

In a comparative analysis of 301 consecutive patients grouped into 3 per their peri-procedural anticoagulation regimen; uninterrupted warfarin with therapeutic INR(n=114),dabigatran(n=89) and rivaroxaban(n=98) undergoing AF ablation between Jan 2011 and Sep 2013, there was no significant difference in combined thromboembolism/bleeding risk among the groups(warfarin vs dabigatran vs rivaroxaban; 6.2% vs 6.7% vs 6.0%;p=0.82).Dabigatran or rivaroxaban was initiated at least 1 week prior to the ablation procedure. The last dose of dabigatran was given the morning 1 day prior to the procedure and the last dose of rivaroxaban was given the evening 2 days prior. Heparin infusion without bolus for a target ACT>350s was initiated 6 hours after sheath removal for both NOAC groups; NOAC was resumed on the morning after the procedure.[26]

In a prospective, non-randomized, single-center, observational study of 556 patients evaluating the efficacy and safety of peri-procedural anticoagulation with Vitamin K antagonists (VKA) (n=192), rivaroxaban(n=188) and dabigatran(n=176), there were no significant differences regarding thrombo-embolic events in 1.3% (VKA 2.1%; rivaroxaban 1.1%; dabigatran 0.6%; p=0.410); major bleeding in 2.3% (VKA 4.2%; rivaroxaban 1.6%; dabigatran 1.1%; p=0.112), and minor bleeding 1.4% (VKA 2.1%; rivaroxaban 1.6%, dabigatran 0.6%; p=0.464) with no fatal events observed. Patients were required to be on effective oral anticoagulation for at least 30 days before the procedure to be included. Interestingly, VKAs were stopped 5 days before the procedure and subcutaneous heparin (either LMWH or unfractionated heparin) started 48 hours after stopping VKAs. Dabigatran was interrupted 24-36hrs before and rivaroxaban 24-48 hours before the ablation. Subcutaneous heparin was started 24hours after the interruption of rivaroxaban and 12 hours after dabigatran. VKAs were restarted the evening of the procedure and NOACs 4-6 hours after the procedure.[27]

In clinical practice, strategies for NOAC use around the time of AF ablation have run the gamut between interrupted, minimally interrupted, and uninterrupted schedules.[28] Some centers withhold dabigatran for 5 days or more before the procedure. This is to ensure complete clearance by the time of the procedure. In such cases, bridging therapy with low molecular weight heparin (LMWH) or intravenous heparin is often warranted, particularly in patients with

persistent AF, in whom the ablation procedure will entail rhythm conversion from AF to sinus. A similar approach can be used with rivaroxaban and apixaban though there is less concern about a prolonged half-life in patients with renal impairment because these agents are only partially renally cleared. One popular option has been to transition to warfarin (in some centers, this transition occurs a month or more before the planned ablation) and perform the ablation on uninterrupted warfarin.

Can the above data be used to justify uninterrupted periprocedural anticoagulation with the newer anticoagulants? Some societies, such as the EHRA, have issued guidelines that argue against uninterrupted use of NOACs in the peri-procedural window.[29] The data regarding dabigatran is mixed and the lack of an easily available laboratory tool to monitor the level of anticoagulation with dabigatran (and the absence of a potent specific antidote) makes routine use of uninterrupted dabigatran difficult to recommend.

However, a minimal interruption of dabigatran appears to be effective and safe in patients undergoing AF ablation; the optimal strategy appears to involve holding dabigatran for 1-2 doses pre-procedure and restarting the medication 6-8hrs post-procedure. Uninterrupted rivaroxaban appears to be an acceptably safe alternative to uninterrupted warfarin for AF ablation, while data regarding apixaban are lacking.

Device Placement

It is well established that a strategy of uninterrupted warfarin treatment at the time of a pacemaker or ICD procedure markedly reduces the incidence of clinically significant device-pocket hematoma as compared to the strategy of withholding warfarin and using bridging heparin therapy.[30, 31] However there is no randomized prospective data regarding the NOACs in this clinical scenario.

In a substudy of the RE-LY trial, bleeding risk in patients anticoagulated with dabigatran or warfarin who underwent invasive surgery was evaluated. One-tenth of the included procedures were device implants or replacements; on average, dabigatran was last given 49 hours before invasive surgery. Anticoagulation with dabigatran was not associated with an increased risk of bleeding. [32]

In a small prospective observational analysis of 25 consecutive patients who were undergoing device implantation or replacement and were anticoagulated with dabigatran, no bleeding complications occurred within 30 days of surgery. The interval between the last dose of dabigatran and implantation was 26±16 hours (range 5-48) for the group with minimally interrupted anticoagulation and 5±3 hours (range 1-11) for the uninterrupted group. The interval between implantation and the first postoperative dose of dabigatran was 27±19 hours (range 2-48) in the minimally interrupted group and 8±3 hours (range 3-11) in the uninterrupted group. One minor bleeding event (development of a pocket hematoma which required no additional intervention or discontinuation of the anticoagulant) occurred in a patient who was receiving concomitant dual antiplatelet therapy.[33]

In a retrospective analysis of 257 patients undergoing device implantation, replacement, or revision, 14 received interrupted dabigatran (dabigatran held morning of the procedure), 48 received uninterrupted dabigatran, and 195 received uninterrupted warfarin. Bleeding complications occurred in 2.1% of patients with uninterrupted dabigatran, 0% of patients with interrupted dabigatran, and 4.6% on uninterrupted warfarin therapy. The differences were not statistically significant (p=0.69). In this study, bleeding complications

were strongly associated with concomitant antiplatelet medications. The authors concluded that the incidence of bleeding complications were similar during device implantation with uninterrupted dabigatran or warfarin. However this study was retrospective with unbalanced numbers in the comparison groups. Additionally, the number of patients with submuscular pockets was relatively small, limiting the breadth of conclusions that can be drawn regarding the safety of uninterrupted anticoagulation.[34]

The choice of management of NOACs in the peri-implant period needs to account for inherent bleeding risk, concomitant antiplatelet therapy, and risk of thromboembolism. With the paucity of quality data in patients at low risk for thromboembolism, most physicians currently tend to hold the NOAC for at least 1-2 half lives prior to the procedure and restart the medication post procedure after adequate hemostasis is obtained. In patients at very high risk of thromboembolism, conversion to warfarin therapy and performing the procedure on uninterrupted warfarin therapy should be considered.

Surgery

The risks of bleeding for surgical procedures must be weighed against the benefit of remaining on anticoagulants on a case-by-case basis. One of the best comparisons between warfarin and NOACs in the setting of surgery was an analysis of a subset of patients enrolled in the RE-LY trial; 4591 patients undergoing at least 1 invasive procedure were evaluated for bleeding from 7 days before until 30 days after invasive procedures. Among patients assigned to dabigatran, the last dose of the drug was given an average of 49 hours (range 35-85) before the procedure in comparison with 114 hours (range 87-144) in patients receiving warfarin. There were no significant differences in the rates of peri-procedural major bleeding between patients receiving dabigatran 110mg (3.8%) or 150mg (5.1%) or warfarin (4.6%). Among patients undergoing urgent surgery, dabigatran and warfarin were associated with similar rates of peri-procedural bleeding. Thromboembolic events in this study were rare and did not differ significantly in the warfarin and dabigatran groups.[32]

Broadly, surgical procedures can be divided into those which are bleeding-related and those that are not bleeding-related. For surgeries that are bleeding-related (i.e. evacuation of an intra-cranial hemorrhage or repair of a ruptured aortic aneurysm), management will almost always involve immediate cessation of the NOAC and possible administration of a reversal agent. The specific NOAC involved, the timing of the last dose, and drug-drug interactions should be noted. The laboratory should be contacted for the tests available at that particular institution for monitoring the anticoagulant effects of the NOAC in question. Perioperative management can be tricky in emergency situations given the lack of a specific antidote for the NOACs. However given their relatively short half lives, simply withholding further doses is likely to be sufficient in most cases. Currently available general supportive and hemostatic agents should be administered if necessary and surgery should be deferred for 12-24 hours, if possible.

Management of NOAC therapy for surgeries that are not bleeding-related is more nuanced and should be strongly influenced by the bleeding risk associated with the surgery. For some types of surgeries, such as orthopedic hip and knee procedures, the risk of venous thromboembolism must also be factored into the equation. In fact,

low dose rivaroxaban has been shown to provide superior outcomes to LMWH after total knee arthroplasty.[35] In surgical procedures with minimal clinically important bleeding risk such as superficial dermatological procedures, the European Heart Rhythm Association (EHRA) recommends that NOACs be discontinued 18-24 hours before the procedure and then restarted 6 hours post-procedure. For elective procedures with minor bleeding risk, such as biopsy of the prostate or hernia repair, the EHRA recommends discontinuing NOACs at least 24 hours prior to surgery. For procedures with a high risk of bleeding, such as major abdominal, cardiovascular, thoracic, orthopedic, intracranial or spinal operations, the EHRA recommends discontinuation of NOACs 48 hours before intervention.[29]

The Working group on Perioperative Hemostasis and the French study group on Thrombosis and Haemostasis recommend stopping NOACs 24 hours before surgery and restarting 24 hours afterwards for procedures with a low hemorrhagic risk. For procedures with a medium or high hemorrhagic risk, their suggestion is to stop NOACs 5 days before surgery and time the restart based on a post-operative clinical assessment of bleeding risk.[36]

The 2014 ACC/AHA guidelines for perioperative cardiovascular evaluation judge it reasonable to continue anticoagulation perioperatively in some instances in which there is minimal to no risk of bleeding. For patients with AF undergoing elective procedures during which hemostatic control is essential, such as major surgery, spine surgery, and epidural catheterization, discontinuation of anticoagulants for greater than 48 hours is suggested.[37]

With regard to restarting NOAC agents post-operatively, there are no specific guidelines. A synthesis of available expert opinion suggests that if the bleeding risk is considered low, NOACs at a therapeutic dose can be safely restarted 24 hours after the procedure. If the bleeding risk is considered high, they can be restarted 48-72 hours after the surgery after confirming adequate hemostasis. For surgeries requiring immobilization, starting LMWH 6-8 hours after surgery and reinitiating NOACs 48-72 hours later is reasonable.[38,39] For certain types of orthopedic surgeries, low dose rivaroxaban started just a few hours after the operation has been shown to be safe and effective.[35]

Given the rapid onset of action and short half-lives of the NOACs, bridging anticoagulation is usually not required. However, in patients who are not able to take oral medications after surgery (i.e. patients with post operative ileus or patients who underwent gastric resection), use of bridging therapy with LMWH may need to be considered.

Conclusion:

Peri-procedural management of NOAC therapy is challenging and requires a nuanced balancing of the risk of bleeding against the risk of thromboembolism. Ultimately, clinicians must make these management decisions on a case-by-case basis. However, we present some sets of general principles to guide this decision-making, based partially on the limited evidence available and based partially on a common-sense approach. More robust clinical data is required for more formal strategies to be incorporated in the guidelines.

Referring back to the vignettes that we presented in the abstract:

Case 1: A 62 year-old female with hypertension, diabetes, and symptomatic paroxysmal AF who is prescribed dabigatran for thromboembolism prevention. She has failed attempts at maintaining sinus rhythm with antiarrhythmic drugs. She is now being considered for catheter ablation of AF.

We recommend stopping dabigatran for 2 doses pre-ablation and restarting the drug on the evening of the procedure after ensuring adequate hemostasis at the vascular access sites.

Case 2: A 76 year-old male with hypertension, diabetes, prior stroke, and ischemic cardiomyopathy who has persistent drug-refractory AF. He is maintained on chronic anticoagulation with dabigatran for thromboembolism prevention. He has an implantable cardioverter-defibrillator (ICD) which requires a generator change.

This patient is at high risk for peri-procedural thromboembolism. We recommend switching the patient to warfarin therapy 4 weeks prior to the procedure and performing the procedure on uninterrupted warfarin therapy. Warfarin can be transitioned back to dabigatran 1-2 weeks post-procedure.

Case 3: A 58 year-old male with hypertension and paroxysmal AF who takes rivaroxaban for thromboembolic prophylaxis and is being considered for a knee replacement surgery.

We recommend that rivaroxaban be held 24 hours prior to the procedure. Given the need for immobilization and the risk of venous thromboembolism, we recommend restarting the rivaroxaban (at a lowered dose to 10mg) at 8 hours after the procedure and then resuming the full dose of rivaroxaban 48 hours after the procedure, in the absence of any clinically important bleeding.

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