ATRIAL FIBRILLATION

RESEARCH ARTICLE

The Use of New Anticoagulants in Electrophysiology During the Periprocedure Period

AYSHA ARSHAD, MBBS, JONATHAN S. STEINBERG, MD and SUNEET MITTAL, MD

The Valley Health System, Columbia University College of Physicians & Surgeons, New York, NY, and Ridgewood, NY

ABSTRACT. The introduction of new anticoagulants has ushered in a new and exciting era in the field of hemostasis and thrombosis. These drugs are the first major advance in this area since the vitamin K antagonist (VKA) warfarin was approved over 50 years ago for use as an anticoagulant. The drawback of warfarin has long been recognized, namely unpredictable and variable pharmacology and thus the need for regular anticoagulation monitoring and dose adjustment. The new anticoagulants act via direct thrombin inhibition (dabigatran) or factor Xa (FXa) inhibition (e.g. rivaroxaban, apixaban and endoxaban) (Figure 1).

KEYWORDS. anticoagulants, vitamin K antagonist.

The field of electrophysiology, which encompasses numerous types of interventional procedures, must rapidly accommodate the availability of these new drugs. This is particularly important in the periprocedure period where withdrawal of anticoagulation and need for bridging therapy has always been a challenge. Significant uncertainty already surrounds the treatment of patients who must discontinue VKA therapy before an invasive procedure. There is a paucity of well-designed prospective clinical trials to guide best practices; thus, one has to rely on observational studies to guide clinical decisions. To add to this, patients have different levels of thromboembolic risk and all pre- and post-procedure anticoagulation protocols must carefully weigh the risk of bleeding. Furthermore, there is uncertainty about the risk of thromboembolism associated with short-term warfarin therapy interruption. The aim of this manuscript is to describe different protocols that are currently in use for periprocedural anticoagulation related to electrophysiology procedures, the inherent pros and cons of each approach, and how the new anticoagulants may be incorporated in this setting.

Periprocedure risk stratification

All decisions regarding withdrawal of anticoagulation prior to an electrophysiology procedure require a thorough assessment of patient-specific thromboembolic and bleeding risk. Currently, periprocedure thromboembolic risk stratification is based largely on indirect evidence from studies performed in patients with atrial fibrillation (AF) who either were not receiving anticoagulation (e.g. placebo instead of a VKA in patients with chronic AF) or were receiving less effective treatment (e.g. aspirin instead of a VKA). A patient’s risk for a periprocedural thromboembolic event can be estimated based on their overall annual risk of thromboembolism, which can be a function of their underlying CHADS score: high risk (>10% annual risk; CHADS2 5–6), moderate risk (5–10% annual risk; CHADS2 3–4), and low risk (<5% annual risk; CHADS2 0–2). Conversely, assessment of bleeding risk is based mainly on surgical case series data as opposed to electrophysiology procedures. It is known, however, that certain interventional procedures such as cardiac device implantation are associated with a high risk for pocket hematoma because there is separation of the infraclavicular fascial layers and lack of suturing of unopposed tissues within the device pocket. In other procedures, such as lead extractions, withdrawal of all anticoagulation is often necessary to minimize the potential for catastrophic bleeding in the event of a complication. Catheter ablation may be
performed depending on the patient’s overall risk and type of ablation either after complete withdrawal of anticoagulation, with bridging, or on a therapeutic level of anticoagulation. This is a complex topic, which is discussed in detail later in this review. Anticoagulation management needs to balance the benefit of stroke prevention against the risk of bleeding. In addition, there is often suboptimal implementation of thromboprophylaxis among AF patients particularly in the perioperative period, most often due to an overperceived risk of bleeding.8,9 The HAS-BLED schema assigns a risk score to estimate the 1-year risk for major bleeding (intracranial, requiring hospitalization, resulting in a hemoglobin drop >2 g/l, and/or requiring a transfusion) in “real world” AF patients and may serve to potentially support clinical decision-making.10 HAS-BLED is an acronym for Hypertension [uncontrolled, >160 mmHg systolic], Abnormal renal/liver function (1 point for presence of renal or liver impairment, maximum 2 points), Stroke (previous history, particularly lacunar), Bleeding history or predisposition [anemia], Labile INR [i.e. therapeutic time in range <60%], Elderly (>65 years), Drugs/alcohol concomitantly (antiplatelet agents, non-steroidal anti-inflammatory drugs; 1 point for drugs plus 1 point for alcohol excess, maximum 2 points). The annual bleeding rate increases with the addition of each risk and is easily calculated to predict a patient’s individualized risk.

Periprocedural anticoagulation management protocols

Patients receiving a VKA or other antithrombotic drug who require an elective surgical procedure may benefit from management according to a standardized, institution-specific protocol. Although there are no randomized trials that show improved clinical outcomes with a standard management approach, observational studies of standardized perioperative anticoagulant therapy protocols (including heparin bridging regimens) have shown lower rates of thromboembolic events and bleeding.11 In addition, they seem to allow for more efficient use of health-care resources.12–14 Traditionally, there have been three major options for management in this setting (Table 1).

- Withhold VKA therapy for some time before the procedure (without substituting bridging therapy) and resume the VKA as soon as possible after the procedure.
- Withhold VKA therapy for some time before the procedure, institute bridging therapy with unfractionated or low-molecular-weight heparin, and resume the VKA as soon as possible after the procedure (with or without additional bridging therapy).
- Perform the procedure without interrupting VKA therapy.

Each of these approaches has its attendant strengths and weaknesses which merit further discussion.

Discontinuation of VKA therapy without periprocedure bridging therapy

The rationale for stopping VKAs prior to high-risk procedures or surgery is to minimize the risk and severity of periprocedure/operative bleeding. Given the elimination half-life of warfarin of 36–42 h, one can anticipate that discontinuation of warfarin for 5 days will
eliminate most of its anticoagulant effect. It should be noted that there may be delayed decay in some patients (e.g. elderly patients). Recent American College of Chest Physician guidelines recommend that VKAs be stopped approximately 5 days before surgery and then resumed approximately 12–24 h after surgery once adequate hemostasis has been achieved.

The major disadvantage of this approach is the potential for thromboembolism during the period that anticoagulation is interrupted. The 2006 American College of Cardiology, American Heart Association and European Society of Cardiology guidelines for the treatment of patients with AF suggest that anticoagulation can be interrupted safely for up to a week (level C recommendation “based on extrapolation from the annual rate of thromboembolism”). One observational study investigating periprocedural interruption of warfarin ≤5 days reported a 30-day thromboembolic event rate of 0.7% in a moderate risk population. In this study, the duration of warfarin therapy interruption was variable; however, more than 80% of patients had warfarin therapy withheld for 5 days or fewer.

Discontinuation of VKA therapy with periprocedure bridging therapy

For years, anticoagulated patients undergoing device implantation or catheter ablation have had VKA therapy interrupted and periprocedure bridging therapy administered with unfractionated or low-molecular-weight heparin. For patients deemed high risk for thromboembolism, several studies have described outcomes when low-molecular-weight heparin has been used as bridging therapy. These studies have uniformly shown that continuation of oral anticoagulation with warfarin is as safe as bridging and reduces hospital stay and costs.

This bridging approach has been based predominantly on data derived from case series and expert consensus as randomized clinical trials have not been conducted. No studies have been performed that have examined the efficacy, safety, dosing, or timing issues associated with re-anticoagulating patients with a VKA following bridging therapy. Additionally, the US Food and Drug Administration has not formally approved any agent for periprocedural bridging.

In the periablation period, the risk of periprocedural stroke/TIA with discontinuation of warfarin and heparin bridging has been reported to be as high as 1–5%. A large meta-analysis comparing a strategy of discontinuing warfarin and heparin bridging to continued warfarin in patients undergoing ablation of AF showed a striking decrease in thromboembolic and minor bleeding complications when warfarin was continued throughout.

In the peri-implantation period, continuation of oral anticoagulation therapy with an INR level of ≤2.5 does not impose increased risk of bleeding for device-related procedures. However, in several observational studies, bridging of anticoagulation in the periprocedural setting was associated with much higher bleeding risk. Intravenous heparin initiation 6 h or 24 h after pacemaker or defibrillator implantation is associated with a 20%
prevalence of pocket hematoma formation. \(^{31}\) Warfarin therapy or no anticoagulation is associated with a smaller 2–4% risk of pocket hematoma formation. \(^{32,33}\)

Two randomized trials have evaluated whether warfarin continuation is superior to warfarin interruption during PPM or IC implantation. The first trial randomized 100 patients undergoing PPM or ICD implantation to either continued or interrupted warfarin therapy. There was a trend toward reduced complications in patients randomized to continued warfarin. \(^{20}\) The second trial investigated hemorrhagic and thromboembolic complications at discharge, 15 and 45 days after the procedure. The trial concluded that implantation of devices during continued anticoagulation was as safe as bridging therapy and significantly reduced the duration of hospitalization. \(^{17}\)

In summary, there is incremental evidence from mostly observational but some randomized studies that for moderate to high risk patients undergoing a procedure, continuation of warfarin is superior strategy for thromboembolism prevention. \(^{34,35}\)

**Continued VKA therapy**

The advantages of continuing anticoagulation with a VKA through the periprocedure period are enhanced convenience, reduced cost, and reasonable safety profile given the availability of methods to reverse anticoagulation in the event of an emergency. Ablation of AF without interruption of warfarin (INR 2–3) appears to be safe and is becoming increasingly adopted by practicing electrophysiologists. \(^{36}\) Observational data suggest that compared with warfarin discontinuation and periprocedural bridging with heparin, AF ablation during a therapeutic INR is associated with reduced risk of periprocedural thromboembolic events. \(^{25,36–38}\) Surprisingly, ablation during a therapeutic INR was not associated with increased bleeding risk, including cardiac tamponade. \(^{25}\) A recently published case-control study which compared ablation during continued warfarin to dabigatran (which was withheld prior to the procedure), found continued warfarin to result in lower thromboembolic and bleeding risk, confirming the safety of performing complex procedures without interrupting warfarin. \(^{36}\)

The Heart Rhythm Society Consensus Statement on catheter ablation of AF recommends that a transesophageal echocardiogram (TEE) be performed prior to an AF ablation to exclude a left atrial appendage (LAA) thrombus in patients with persistent AF who present in AF; no specific recommendation is made for patients with paroxysmal AF. \(^{39}\) Contemporary studies in which warfarin has been discontinued prior to AF ablation have shown that a pre-ablation TEE discloses a LAA thrombus in 1.47–2.9%. \(^{40,41}\) An approach where ablation is performed on continued warfarin can likely obviate the need for a TEE, allowing convenience and efficiency without sacrificing safety.

The major risk inherent to performing ablation on continued warfarin is the greater potential for bleeding, which may occur during vascular access, transseptal puncture, ablation, catheter manipulation, or while removing sheaths after the procedure. If this occurs, reversal of VKA can be accomplished by administration of vitamin K and fresh frozen plasma. In addition, numerous reports have documented that pericardiocentesis can be performed safely in this situation as well. \(^{25,38,42}\)

In the device implantation setting, previous studies have demonstrated that continuation of warfarin in the periprocedural period may be safe. \(^{33,44}\) While the management of warfarin before device implantation varies widely, especially in individuals at high risk for embolic events, more recent reports have shown that warfarin discontinuation with heparin bridging is associated with more significant bleeding events than continuous warfarin. \(^{45,46}\) Two recently published randomized studies compared the two strategies, warfarin continuation versus bridging with heparin after discontinuing warfarin in high-risk patients. \(^{17,20}\) Both studies found that implantation of devices maintaining anticoagulation is as safe as bridging to heparin infusion, and interestingly in the second study, although the results were not statistically significant, there was a trend toward reduced complications in patients randomized to warfarin continuation. \(^{20}\)

This approach of continued anticoagulation may be best considered in patients deemed at moderate to high risk of thromboembolism; these patients include those with valvular atrial fibrillation, mechanical valves, those cardioverted recently or who require cardioversion during the device implantation procedure, those with a recent thromboembolic event, and those with a known coagulation defect that predisposes to thrombus formation (e.g. deficiency of protein C, protein S or antithrombin, or presence of antiphospholipid antibodies).

**Antiplatelet and anticoagulant therapy**

There are data showing dual antiplatelet therapy in combination with periprocedural use of heparin significantly increases the risk of bleeding following pacemaker or ICD implantation. \(^{48}\) The use of triple antithrombotic therapy (a dual-antiplatelet regimen plus warfarin) is expected to become more prominent, given an aging patient population. But although triple therapy can prevent both thromboembolism and stent thrombosis, it is also associated with significant bleeding hazards and continued warfarin in this particular situation in patients at moderate to high stroke risk has not been well studied and may be associated with excessive bleeding risk. \(^{49,50}\) Thus, the optimal strategy in these patients remains undefined.

**New Approaches to periprocedural thromboprophylaxis**

The U.S. Food and Drug Administration has recently approved two new agents for the prevention of stroke and systemic embolism in patients with non-valvular AF. In October 2010, dabigatran, a direct thrombin inhibitor that selectively and predictably inhibits both free and clot-bound thrombin was approved. In addition to preventing venous thrombosis, *in vitro* evidence
suggests that dabigatran, by virtue of its inhibition of tissue factor-induced platelet aggregation, may also be effective against arterial thrombosis. Its half-life is between 7 and 17 h; 80% of the drug is cleared by the kidneys. Dabigatran is a substrate for the P-glycoprotein transporter system. In November 2011, rivaroxaban was approved for the same indication. Rivaroxaban is a highly selective, reversible, oral direct factor Xa inhibitor. It inhibits prothrombinase-bound and clot-associated factor Xa. The mean half-life is 3.2–11 h. In humans, the elimination of rivaroxaban exhibits a dual mode. Renal and fecal eliminations of the unchanged drug account for almost half of the excretion of a dose. The other half undergoes metabolic transformation by CYP3A4 in the CYP450 system and also via CYP-independent mechanisms. Rivaroxaban is also a substrate for the transporter protein P-glycoprotein and breast cancer resistance protein.

There are new options for periprocedural management in the era of the new anticoagulants, but also new challenges. These challenges may include lack of reversibility should catastrophic bleeding occur. The relatively predictable half-life and rapid onset of action of these agents provide potential advantage. Use of new and novel oral anticoagulant therapy can follow two paths in the periprocedure period, but notably not involve bridging heparin therapy:

- continue oral anticoagulant therapy; or
- withhold oral anticoagulant therapy for some time before (and after) the procedure.

As there are no data regarding the safety of the first approach and given the absence of reversal agents, most experts agree that these agents must be temporarily withheld for a period of time before and after the procedure. In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 2 days, followed by either a single bolus of 50 IU/kg PC (Cofact) or a similar volume of saline. After a washout period, this procedure was repeated with the other anticoagulant treatment. Rivaroxaban induced a significant prolongation of the prothrombin time that was immediately and completely reversed by PCC, whereas dabigatran increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time. Administration of PCC did not restore these coagulation tests. These preliminary data as to reversibility of rivaroxaban are interesting but need further validation in a larger cohort of patients.

Drug-specific protocols

Based on drug pharmacology, dabigatran should be stopped at least 24 h prior to elective surgery. In patients with normal renal function, this allows the plasma dabigatran concentrations to fall to 25% of the steady-state trough concentrations, with a decrease to 5–10% at 48 h. Depending on the nature of surgery, renal function, and individual bleeding risk it may be necessary to discontinue dabigatran 2–4 days prior to surgery. In the RE-L study, patients who were treated with dabigatran and required surgery followed an empiric protocol that was anchored on whether major or minor surgery was being done and the extent of renal insufficiency. Thus, patients undergoing minor surgery stopped dabigatran 1 day before the procedure, whereby two doses of drug were withheld. Patients undergoing major surgery or who were receiving spinal/epidural anesthesia followed a more conservative approach whereby dabigatran was stopped 2–3 days before surgery, thus allowing four or five half-lives to elapse. This ensured minimal or no residual anticoagulant effect (3–6%) at the time of surgery. In patients with moderately to severely impaired renal function, dabigatran needs to be stopped for a greater duration to ensure that its anticoagulant effect has adequately dissipated. The perioperative management of patients receiving a factor X inhibitor is likely to be easier given their shorter elimination half-life (5 h for rivaroxaban; 8 h for apixaban). Thus, stopping rivaroxaban on the day before surgery, with omission of the evening dose only, should be sufficient to allow elimination of an anticoagulant effect. Similarly, apixaban can be stopped the day before surgery, with the omission of two doses before surgery. For both drugs, a longer period before surgery should be allowed in the elderly or those with known impaired renal function.

In the periablation period, there are only preliminary and emerging data on the use of these drugs. A recent multicenter observational study prospectively investigated the role of dabigatran in the periablation period. A total of 290 patients, including 145 patients on dabigatran and an equal number of matched patients on uninterrupted warfarin, were included in the study. Per protocol, dabigatran was held the morning of the procedure and resumed within 3 h of achieving hemostasis at the vascular access sites. Patients in the warfarin group underwent catheter ablation on uninterrupted warfarin therapy. Three thromboembolic complications (2.1%) occurred in the dabigatran group compared with none in the warfarin group (p=0.25). The dabigatran group had a significantly higher major bleeding rate (6% versus 1%; p=0.019), total bleeding rate (14% versus 6%; p=0.031), and composite of bleeding and thromboembolic complications (16% versus 6%; p=0.009) compared with the warfarin group. Dabigatran use was confirmed as an independent predictor of bleeding or thromboembolic complications (odds ratio, 2.76; 95% confidence interval, 1.22–6.25; p=0.01). Another recent observational study compared warfarin bridging with low-molecular-weight heparin to dabigatran. All patients were started on low-molecular-weight heparin immediately after the procedure, and dabigatran was started/restarted 22 h after the procedure. None of the patients experienced a bleeding or thromboembolic complication in the initial 30 days of the procedure. Given the different results in these two initial studies, particularly the data relating to dabigatran, there is a need for large randomized studies to confirm safety and to identify...
an optimal periprocedural anticoagulation protocol. There are no data on the anti FXa agents at this time.

**Recent experience in our center**

We started using dabigatran in the periprocedure setting shortly after the drug was approved in the United States. To further explore safety, we examined 94 patients who underwent AF ablation. Two matched cohorts, based on anticoagulation periprocedural regimen, were compared: (1) warfarin with low-molecular-weight heparin pre/post ablation and (2) dabigatran pre/post ablation. Warfarin was dosed to achieve INR of 2–3 and stopped 5 days pre-procedure; low-molecular-weight heparin at 1 mg/kg was used pre- and 0.6 mg/kg post procedure until INR >2. Dabigatran was dosed at 150 mg bid and continued until 12 h pre- and resumed 6–8 h post procedure. Both groups received intravenous heparin to AC >300 s during, and protamine immediately post procedure. We found vascular-related complications were lower in the dabigatran-treated patients (0% versus 11%, p < 0.02). Dabigatran was prematurely discontinued in only two patients (3%) for intolerance. No patient required reversal of anticoagulation and there were no thromboembolic complications in either group.

We have employed a similar strategy for the use of dabigatran in our device patients. It is held for 12 h pre-procedure and resumed 6–12 h post procedure. This protocol is based on drug pharmacology alone, as no study data exist for the use of this drug in this setting. We have not seen an increase in post-procedural hematoma or vascular complications in device patients nor any thromboembolic events. In 2011 there were 272 devices (PPM, CR, and ICDs) implanted at our institution. Three hematomas occurred requiring evacuation: one patient was on pradaxa (held per protocol) and two were on therapeutic anticoagulation with coumadin. Our preliminary experience suggests that the incidence of device hematomas in the dabigatran-treated patients is less than when the procedure is performed on warfarin.

**Future directions**

While these new agents appear advantageous over conventional anticoagulants, the quest for “the ideal anticoagulant” remains far from over. In addition to being fully effective in preventing and treating thromboembolism, an “ideal anticoagulant” should also not cause any bleeding, be reversed easily and be well tolerated. Its anticoagulant effect should be predictable and thus obviate monitoring of coagulation parameters.

**Recommendations**

The use of continued anticoagulation with warfarin in the periprocedural setting had been validated by contemporary observational series. This strategy is more effective, safer, and less costly than the alternative, bridging with heparin while interrupting warfarin in moderate to high-risk patients. The new anticoagulants are being used with greater frequency and their role in the periprocedural setting remains to be defined. Initial data have led to safety concerns but it is conflicting, and randomized trials will help clarify this issue. There is a need for surveys and prospective data collection of periprocedural anticoagulation management and its associated complications with a view to developing international consensus guidelines and options.

**References**


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