



How To Manage Oral Anticoagulation Periprocedurally During Ablations And Device Implantations

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Abstract

More than 150,000 patients undergo ablation for atrial fibrillation (AF) each year. Current guidelines recommend oral anticoagulation in all patients undergoing AF ablation. A large number of patients undergoing cardiac implantable electronic devices (CIEDs) are on long-term oral anticoagulation. These patients are at increased risk for thromboembolism with interruption of oral anticoagulation. Due to the increased risk for bleeding complications during the procedure combined with the need to prevent thromboembolism, periprocedural management of anticoagulation in these patients can be challenging. In this article we review the current evidence for periprocedural management of oral anticoagulation in patients undergoing ablation and CIED implantation.

Introduction

More than 150,000 patients undergo ablation for atrial fibrillation (AF) each year. Current guidelines recommend oral anticoagulation in all patients undergoing AF ablation. A large number of patients undergoing cardiac implantable electronic devices (CIEDs) are on long-term oral anticoagulation. These patients are at increased risk for thromboembolism with interruption of oral anticoagulation. Due to the increased risk for bleeding complications during the procedure combined with the need to prevent thromboembolism, periprocedural management of anticoagulation in these patients can be challenging. In this article we review the current evidence for periprocedural management of oral anticoagulation in patients undergoing ablation and CIED implantation.

Methods And Materials

Presently, there are 6 million patients in the United States on long-term anticoagulation to both prevent and treat thromboembolism (TE).^[1] These patients account for up to 35% of all patients undergoing cardiac implantable electronic devices (CIEDs) and nearly all patients undergoing ablation for atrial fibrillation (AF).^[2] Periprocedural management of oral anticoagulation (OAC) for these patients can be challenging given the need to balance bleeding risk with thromboembolic risk, both of which can adversely affect morbidity and mortality. The reported bleeding risk associated with device implantation and atrial fibrillation ablation is 4.9%^[3] and 2.7%^[4] respectively. Conversely, even a brief interruption of

anticoagulation has been associated with an up to 3-fold increase in systemic thromboembolic events.^{[5],[6]}

Current guidelines recommend discontinuation of OAC and bridging patients at moderate to high risk for TE with intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) in the perioperative period.^[7] Although clearly effective in preventing thromboembolic events, bridging has actually shown to increase bleeding complications by up to 25%.^[8] Furthermore, bridging can pose increased health care costs due to need for longer hospital stays for patients requiring UFH.^[9] Due to these concerns, several centers now routinely perform CIED implant and AF ablation with brief or no discontinuation of OAC. In this article, we aim to provide a systematic review of the current data available regarding optimal management of anticoagulation in the periprocedural setting for patients undergoing CIED implantation or AF ablation.

Cardiac Implantable Electronic Devices

One third of patients undergoing CIED implantation are receiving oral anticoagulation. The most common complication post CIED implantation is pocket hematoma, which occurs more often in patients on OAC.^[9] Hematoma increases risk for infection, potential need for reoperation and prolonged hospital stay in addition to patient discomfort. Given this risk, perioperative anticoagulation management continues to be challenging particularly in patients with moderate to high risk (>5%) for thromboembolic events.^[2]

New data demonstrates a lower risk of bleeding without increasing the risk for a TE event in patients who do not interrupt OAC for CIED implantation. BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) was a multi-centered, single blinded, randomized control trial which evaluated patients with a greater than 5% yearly risk of TE undergoing CIED implantation. This study enrolled 668 patients when the data

Key Words

Right Atrial Septal Pacing, Paced PQ Interval, Atrial Fibrillation, The Percentage Of Atrial Pacing.

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and safety monitoring board recommended termination of the study based on the evidence favoring continuation of OAC. Warfarin was uninterrupted in 334 patients with an international normalized ratio (INR) of 2.0-3.0 and 325 patients stopped warfarin 5 days before scheduled procedure and started LMWH bridge. LMWH was discontinued after the morning dose the day before surgery and resumed 24 hours post procedure. Primary outcome (documentation of a clinically significant hematoma), was seen in 16% of patients on LMWH as compared to 3.5% of patients who continued warfarin. Prolonged hospital stays secondary to hematoma, occurred more in patients on LMWH (94.7% versus 1.2%). Patients on LMWH required cessation of anticoagulation secondary to hematoma (14.2% versus 3.2%) and surgical evacuation more frequently than patients who continued OAC (2.7% versus 0.6%). There was a 7-fold increase in infection risk in patients who had a clinically significant hematoma (11% vs. 1.5%). Patient satisfaction was significantly higher in those patients who continued warfarin without bridging.^[10]

A meta-analysis of nearly 11,000 patients from 1400 studies compared uninterrupted anticoagulation (warfarin / antiplatelet therapy) with heparin bridging at the time of device implant.^[9] Endpoints included hemorrhagic complications, mainly pocket hematoma (greater than 2 cm) +/- need for reoperation and thromboembolic events, including myocardial infarction (MI), transient ischemic attack (TIA), cerebrovascular attack (CVA), deep vein thrombosis (DVT) and pulmonary embolism (PE). Pooled data demonstrated that continued OAC had a lower incidence of pocket hematoma as compared to those patients who underwent UFH or LMWH bridging. There was no significant difference in thromboembolic events or bleeding complications between the two groups. Those patients who continued anticoagulation also had shorter hospital stays and improved quality of life.^[9]

In 2012, Cano et al evaluated 129 patients with moderate to high-risk for TE (mechanical valve prosthesis, AF with CHADS₂ score of ≥2, mitral stenosis, previous stroke, active neoplasm or deep vein thrombosis within the past 3 months) in whom warfarin was continued without interruption (INR of 2-4) and 82 low risk patients in whom warfarin was interrupted for 72 hours prior to surgery. They also included a retrospective review of patients managed with a standard heparin bridging strategy serving as a control group. Patients classified by this standardized protocol had significantly lower rates of pocket hematoma (2.3% OAC vs 17.7% bridging). The low risk arm had no pocket hematomas for interrupted OAC versus 13% for bridging controls. Patients who were not bridged were discharged 3.34 days earlier as compared to those who underwent bridging.^[11]

While there are numerous studies supporting the safety of continuing warfarin during device implantation, there are no randomized, controlled trials evaluating novel oral anticoagulants (NOACs). These drugs include dabigatran (direct thrombin inhibitor), rivaroxaban, apixaban and edoxaban (direct factor Xa inhibitors). NOACs have become increasingly popular due to their short onset of action, reliability, lack of routine monitoring and convenience. One concern is the lack of antidotes for the direct factor Xa inhibitors, which are currently under development.

Jennings et al evaluated the strategy of uninterrupted dabigatran (D) in 48 patients, holding on the morning of the procedure in 14 patients versus uninterrupted warfarin in 195 patients. Bleeding complications occurred in 1 of 48 patients (2.1%) with uninterrupted dabigatran, 0 of 14 with interrupted D, and 9 of 195 patients (4.6%)

on warfarin (9 pocket hematomas), P = 0.69. [12] In 2014, Kosiuk et al studied 176 patients on either dabigatran or rivaroxaban undergoing CIED implant. Postoperative bleeding complications and thromboembolic events occurring within 30 days of procedure were included. 2% of patients on dabigatran had clinically significant pocket hematomas. 5% of patients on rivaroxaban had clinically significant pocket hematomas and one pericardial effusion. Three of the bleeding complications in the rivaroxaban group required surgical intervention. One patient on dabigatran had a TIA.^[13]

BRUISE CONTROL 2 is an ongoing randomized controlled trial evaluating whether continued versus interrupted NOAC at the time of device surgery in patients with moderate to high risk of TE events reduces the incidence of clinically significant hematoma. Secondary endpoints include hemothorax, tamponade, TE events and quality of life. Completion for primary outcome measure is expected December 2016.^[14]

Based on current literature, low risk patients (less than 5% risk for TE) on warfarin with an INR of less than 3.0 may hold warfarin 3-4 days preoperatively without UFH or LMWH bridging ([Table 1]). For those patients with an INR greater than 3.0, warfarin should be discontinued at least 5 days prior to planned procedure. Updated INR should be measured the morning of the procedure. For those patients who have a greater than 5% annual risk for TE, warfarin may be continued with an INR for 2.0-3.0. Updated INR should be measured on the morning of the procedure. Due to slow onset of therapeutic levels, warfarin may be resumed the evening of the procedure if no significant bleeding complications occurred.^{[9],[10]}

For low risk patients on NOACs, anticoagulation may be discontinued prior to planned procedure. The timing and duration of this cessation depends on both the type of anticoagulant (direct thrombin inhibitor versus direct factor Xa inhibitor) and the patient's renal function. For those patients with normal renal function, NOAC should be discontinued at least 24 hours preoperatively. For those with renal dysfunction, anticoagulation should be held up to 48-72 hours prior to procedure^{[13],[15],[16]}. Resumption of NOAC is typically recommended within 24-48 hours. (see [table 2])

High-risk patients on NOACs pose a more difficult decision.

Table 1: Classification of Thromboembolic Risk	
Risk group	clinical characteristics
High	<ul style="list-style-type: none"> • Mechanical Mitral Valve • Mechanical Aortic Valve • CVA/TIA within 3 months • CHADS₂ score greater than 5 • Rheumatic heart disease • Clotting Disorder • VTE or PE within 3 months
Moderate	<ul style="list-style-type: none"> • Bileaflet Aortic Valve • CHADS₂ greater than 3 • VTE within 6-12 months • Active Cancer
Low	<ul style="list-style-type: none"> • CHADS₂ score less than 2 with no prior history of TIA/CVA • VTE > 12 months without prior risk factors

CVA = cerebrovascular accident; TIA = transient ischemic attack; VTE = venous thromboembolism; PE = pulmonary embolism. Adapted from the standardized protocol for the perioperative management of chronically anticoagulated patients receiving implantable cardiac arrhythmia devices.^[14]

Transitioning them to warfarin around the time of procedure versus continuing NOACs may have to be individualized based on risks versus benefits. The results of ongoing BRUISE CONTROL 2 trial will help to better answer this question.^[14]

Ablation of Atrial Fibrillation

In the United States alone, more than 150,000 patients undergo radiofrequency catheter ablation (RFCA) for AF each year.^[17] A worldwide survey on methods, efficacy and safety of AF ablation demonstrated that 4.5% of patients undergoing ablation experienced a major complication. Major bleeding accounted for 2.8% of complications where as thromboembolic events accounted for 0.94%.^{[18],[19]} The management of anticoagulation during the perioperative period can have a significant effect on these events^[20]. Current guidelines recommend that warfarin be discontinued and patients be bridged with LWMH or UFH during the ablation setting.

Recent randomized trials however show that RFCA can be safely performed without interruption of anticoagulation. The COMPARE trial (Role of Coumadin in Preventing TE in Atrial Fibrillation Patients Undergoing Catheter Ablation) was a prospective, randomized multicenter study assessing the safety of continuous warfarin therapy in preventing thromboembolic events around the time of RFCA. A total of 1584 patients were included in the three-year study. In group 1, warfarin was discontinued 5 days prior to ablation and then bridged with LWMH until the evening before procedure. Transesophageal echocardiogram was performed prior to procedure. UFH was administered prior to transseptal puncture to maintain an activated clotting time (ACT) >350 seconds. A single dose of 325 mg of aspirin was given post procedure. LWMH at 0.5 mg/kg was resumed 3 hours post procedure and was continued until INR was greater than 2.0. In group 2, patients were on warfarin with 3 to 4 weeks of therapeutic INR.

Transesophageal echocardiogram was only performed on patients with a subtherapeutic INR on the day of the procedure. If INR was 3.0-3.5, patients received fresh frozen plasma. If INR was > 3.5, patients were excluded. All patients received UFH to maintain ACT >300 seconds. Protamine was given after the procedure and sheaths were removed once ACT was less than 200 seconds. Warfarin was resumed the night of the procedure in both groups. Ablation was performed in the standard fashion for patients with paroxysmal or persistent atrial fibrillation.

Thromboembolic events occurred in 4.9% of patients in group 1 and 0.25% of patients in group 2 ($p < 0.001$). The majority of the patients who had a thromboembolic event had long standing persistent atrial fibrillation. Major bleeding complications (pericardial effusion, groin hematoma and pseudoaneurysm) occurred in 0.76% of patients in group 1 and 0.38% of patients in group 2 ($p = 0.31$). This clearly demonstrated that uninterrupted warfarin around the time of RFCA significantly reduced the risk for thromboembolic events without increasing the bleeding risk. Warfarin discontinuation was associated with a 10 fold higher risk for cerebral TE without significant reduction in hemorrhagic events.^[20]

A meta-analysis published in 2012 reviewed 9 studies on RFCA of AF comparing patients on uninterrupted warfarin versus discontinued warfarin. 6 studies reported prospective design. The target INR for all studies was 2.0-3.5. Intracardiac echocardiography (ICE) was used in 5 studies. Irrigated catheters were used in 7 studies. The review included a total of 27,402 patients. Of these, 6400 continued warfarin. The majority of the continued warfarin patients (89%) were from large prospective or comparative studies. 21,002 patients discontinued warfarin and followed LMWH bridging. Uninterrupted warfarin therapy was associated with significant reduction in thromboembolic events (0.06% versus 0.94% in interrupted warfarin, $p < 0.001$, OR 0.1) and minor bleeding complications (4.5% vs 18.6%, $p = 0.002$, OR 0.38). Major bleeding complications, mainly cardiac tamponade, were seen in 0.55% of patients who continued warfarin and 1.25% who discontinued warfarin ($p = 0.30$, OR 0.67).^{[21],[22]}

Although the majority of studies evaluating anticoagulation and RFCA for AF have only included warfarin, there are increasing reports regarding NOACs. This review will focus on the larger sample size studies involving dabigatran, rivaroxaban and apixaban.

Dabigatran

Data from the The Randomized Evaluation of Long-term Anticoagulant Therapy (RELY) trial provided some reassurance on periprocedural safety of dabigatran. In this trial more than 4500 patients underwent >7500 procedures during a 2 year follow-up. The rate of major bleeding complications for patients who underwent procedures within 24 hours of discontinuing dabigatran was significantly less than those taking warfarin. Additionally, patients who held dabigatran were able to undergo procedure sooner as compared to patients holding warfarin due to the shorter half-life of

Table 2: Last Dosing of NOAC Prior to Surgical Procedure

	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
	LR	HR	LR	HR	LR	HR	LR	HR
CrCl > 80 ml/min	>=24 hours	> =48 hours	>= 24 hours	>= 48 hours	>= 24 hours	> =48 hours	> =24 hours	> =48 hours
CrCl 50-80 ml/min	> =36 hours	> =72 hours	>= 24 hours	> =48 hours	> =24 hours	> =48 hours	> =24 hours	> =48 hours
CrCl 30-50 ml/min	>=48 hours	> =96 hours	> =24 hours	> =48 hours	> =24 hours	>=48 hours	> =24 hours	> =48 hours
CrCl 15-30 ml/min	Not indicated	Not indicated	> =36 hours	> =48 hours	> =36 hours	> =48 hours	> =36 hours	> =48 hours
CrCl < 15 ml/min	Not indicated							

CrCl = creatinine clearance; LR = low risk; HR = high risk . Adapted from the EHRA Guidelines on use of NOACs^[14]

dabigatran.^{[5],[17]}

Bassiouny et al in a single center, cohort study of 999 patients undergoing AF ablation, compared continuous warfarin versus holding 1 to 2 doses of dabigatran preprocedure and resuming immediately post procedure.^[23] Arshad et al compared the strategy of continuous warfarin vs interrupted warfarin plus bridging vs holding 1 dose of dabigatran preprocedure and restarting that evening.^[24] There was no significant difference in bleeding or TE risks between the groups.

In 2012, Dr Lakireddy et al published their findings from a multicenter prospective registry including 290 patients from 8 high volume centers comparing the safety and efficacy of dabigatran with continuous warfarin in the peri-ablation period. Patients were matched equally in each group. Patients in the dabigatran group held one dose the morning of procedure and resumed 3 hours post procedure. Warfarin was continued throughout the procedure with therapeutic INR 2.0-3.5 for at least 30 days prior to procedure. As compared to the prior mentioned studies, this prospective registry yielded significantly higher rates of bleeding in patients on dabigatran compared to continuous warfarin ((6% vs 1% major bleeding, $p=0.019$ and 14% vs 6% total bleeding rates, $p=0.031$). Three thromboembolic complications (2.1%) occurred in the dabigatran group compared with none in the warfarin group ($p=0.25$). The increased bleeding risk in this study as compared to other studies may be due to the short discontinuation period of dabigatran prior to the procedure. Dabigatran taken the night before, with an average half-life of 12-14 hours, may have still been in effect at the time of procedure start. It was also resumed 3 hours post procedure and given rapid onset of action, patients were therapeutic at a much faster interval. This, in addition to the overlapping of UFH during transseptal puncture, could account for the increased bleeding reports. As compared to other studies above where dabigatran was held for 24-48 hours prior to procedure, there was a much lower risk of bleeding. Dosing prior to procedure in combination with UFH seems to be a higher predictor of bleeding complications as compared to resumption time.

Rivaroxaban

The VENTURE – AF trial (ActiVe-controlled multi-cENTER stUdy with blind adjudication designed to evaluate the safety of uninterrupted Rivaroxaban and uninterrupted vitamin K antagonists in subjects undergoing catheter ablation for nonvalvular Atrial Fibrillation), published in 2014, was a prospective, randomized, controlled, multicenter trial looking at 250 patients undergoing ablation for AF. Patients were started on rivaroxaban daily or warfarin with INR of 2.0-3.0 for minimum of 3 weeks pre-ablation. Primary endpoint was incidence of major bleeding within 30 days.

Secondary endpoints were post procedure thromboembolic events, minor bleeding and medication adherence. Both rivaroxaban and warfarin were continued throughout the procedure. UFH was administered with goal ACT of 300-400 seconds. Post procedure warfarin was continued per protocol. Rivaroxaban was resumed 6 hours post procedure if hemostasis was achieved. Bleeding events occurred in 21 patients on rivaroxaban as compared to 18 patients on uninterrupted warfarin. There was 1 ischemic stroke and 1 vascular death in the warfarin group, none in the rivaroxaban group. This study reassures that in patients undergoing RFCA for AF, the use of uninterrupted oral rivaroxaban was feasible and event rates were similar to those for uninterrupted VKA therapy.^[26]

In 2015, Vamos et al completed a systematic review and meta-analysis of the efficacy and safety of rivaroxaban compared with warfarin in patients undergoing RFCA. 16 studies involving 7400 patients were reviewed. Of those patients, 1994 received rivaroxaban periprocedurally. Only one study was a randomized controlled clinical trial. The remaining 15 studies were either observational retrospective or prospective studies. Rivaroxaban was administered daily and discontinued 24-48 hours prior to procedure although 6 studies used uninterrupted rivaroxaban. In general, rivaroxaban was resumed within 12 hours of the procedure. Warfarin was uninterrupted. Target activated clotting time was 300-400 seconds. There were fewer thromboembolic events in the rivaroxaban group compared to the warfarin group (0.2% vs 0.3%, $p=0.52$). Major bleeding events occurred in 1.15% of patients on rivaroxaban and 1.66% of patients on warfarin ($p=0.23$). Minor bleeding events were similar (4.96% vs 4.12%, $p=0.22$). One fatality was reported in each group, a ruptured cerebral aneurysm on rivaroxaban and one vascular death on warfarin. Overall, rivaroxaban was deemed a safe alternative to warfarin with no increased risk for bleeding.^[19]

Apixaban

In 2016, Kuwahara et al conducted an open label, randomized multicenter study evaluating the efficacy of either uninterrupted apixaban or warfarin in preventing cerebral TE during AF ablation. 200 patients were evaluated and assigned to take either apixaban or warfarin for at least one month prior to ablation. Neither drug was interrupted throughout the procedural period. All patients underwent brain magnetic resonance imaging (MRI) post ablation to screen for silent cerebral infarctions (SCIs). It was noted that during the ablation, the apixaban group required more heparin to maintain an ACT of greater than 300 seconds ($14,000 \pm 4,000$ units vs. warfarin $9,000 \pm 3,000$ units). The apixaban group had two SCIs, one major bleed and 3 minor bleeds where as the warfarin group had three SCIs and four minor bleeds ($p=1.0$), concluding similar safety and efficacy profiles for both drugs during the periprocedural period.^[27] Information regarding periprocedural use of edoxaban is currently limited.

When approaching a patient prior to AF ablation, risk for TE and risk for serious bleeding events need to be considered. There is enough evidence to recommend that warfarin be continued without interruption during the peri-ablation period. It is recommended that INR be checked weekly for one month preprocedure including the morning of procedure. TEE should be performed on all patients with labile INR. Patients with INR > 3.5, on the day of the procedure should be reevaluated prior to proceeding given increased bleeding risks. It is essential to be prepared for any major bleeding complications including readily available reversal agents (protamine, vitamin K) and blood products.

For patients on NOACs, data suggests continuing until the day before the procedure, if renal function is normal (see [table 2]). Due to the short half life, cessation of drug for 24 hours prior to start of procedure has proven safe and effective. Resumption of the drug post procedure varies amongst studies, but on average is within 6-10 hours once hemostasis is achieved. It is known that patients on long term NOACs require higher amounts of UFH to achieve and maintain safe ACT throughout AF ablation.^[17] A major impediment regarding the use of uninterrupted NOAC strategy for ablation had been the lack of reversal agents. Idarucizumab (Praxbind™) is a

humanized monoclonal antibody fragment that acts immediately after administration to completely reverse the effects of dabigatran and is currently available for use in the United States.^[28] Several agents (Andexanet alfa and Ciraparantag) are currently under evaluation for reversal of factor Xa inhibitors and are likely to be available soon.^[29]

Conclusion

Despite the current guidelines recommending cessation of OAC and bridging with either UFH or LWMH for patients at moderate to high risk for thromboembolic event undergoing CIED placement or AF ablation, there has been strong accumulation of evidence supporting the continuation of OAC during the periprocedural period. Warfarin has the most data supporting this, however evidence for minimally interrupted or uninterrupted NOAC strategy is growing. Patients who have continued OAC during the time of CIED implant or AF ablation with adequate precautions have not significantly increased bleeding or thromboembolic risks. Continuation of OAC has also been associated with shorter hospital stays, less health care costs and increased patient satisfaction.

Disclosure

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