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Post-Procedural Dabigatran Versus Interrupted Warfarin Therapy Following Catheter Ablation for Atrial Fibrillation

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Abstract

Purpose: Patients undergoing catheter ablation for atrial fibrillation (AF) are at a higher risk of thromboembolic events post-procedure and therefore require therapeutic anticoagulation after ablation. Anticoagulation strategies include performing the procedure on or off therapeutic warfarin, though the latter approach requires post-procedure bridging therapy with low molecular-weight heparin (LMWH) until a therapeutic INR is achieved. The purpose of this study is to compare the safety and efficacy of post-ablation dabigatran as compared to warfarin with LMWH bridging.

Methods: We performed a single-center retrospective analysis of consecutive patients who underwent catheter ablation for AF between January 2010 and December 2012 and received either post-procedure warfarin with a LMWH bridge or dabigatran. Warfarin was started the night of ablation; LMWH was started the next morning and continued until the INR was ≥ 2.0 . Dabigatran was started the morning post-ablation.

Results: The analysis included 324 patients. Of these, mean age was 60 ± 9 years, 78% were male, 81% had CHADS₂ scores of 0 or 1, and 181 (56%) received dabigatran post-ablation. Patients who received dabigatran had lower CHADS₂ scores and were more likely to be in NYHA Class I. At 30-days post-procedure, there were 0 thromboembolic or bleeding complications in the dabigatran group versus 4 (2.8%) in the warfarin group ($p=0.037$). There were no deaths in either group at 30 days post-ablation.

Conclusions: Post-ablation dabigatran appears safe and efficacious compared to an interrupted warfarin strategy with LMWH bridging.

Introduction

Catheter ablation is now an established treatment modality for symptomatic atrial fibrillation (AF) in patients in whom anti-arrhythmic drug therapy has failed or is not preferred.¹⁻⁴ Because patients with AF are at a higher risk of thromboembolic complications, most patients require anticoagulation.^{3,4} This is particularly true at the time of catheter ablation for AF when cardioversion may be performed and when thrombus may form at the ablation sites and on the catheters and sheaths in the left atrium.⁵ However, there is no

consensus regarding the ideal management strategy of post-ablation anticoagulation.

During the ablation procedure, intravenous (IV) heparin is administered while the left atrium is instrumented. The standard of care is to prescribe some form of anticoagulation for at least two months afterward to reduce the risk of post-procedural thromboembolic events.³ Historically, patients on warfarin therapy discontinued its use several days prior to the procedure and were bridged with low molecular weight heparin (LMWH) either prior to and after the ablation procedure or post-ablation only.⁶ More recent literature has suggested that continuing warfarin without interruption is a viable alternate strategy.⁷⁻⁹ Still, many labs suspend oral anticoagulation just prior to catheter ablation for AF and resume the therapy following the procedure.

Dabigatran etexilate (Pradaxa) is a direct thrombin inhibitor approved for patients with non-valvular AF for the prevention of stroke and systemic embolization.¹⁰ Compared to warfarin, dabigatran carries with it a reduction in the risk of stroke, fewer food and drug interactions, requiring no INR monitoring, a reduction in

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None.

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the risk of intracranial bleeding, and achieving more rapid onset and offset. Its disadvantages include the lack of an approved reversing agent, higher risk of gastrointestinal bleeding, and higher per-pill cost.¹¹ A number of studies have now been published on the use of dabigatran periprocedurally.¹³⁻¹⁸ However, these have primarily used uninterrupted warfarin as a comparison group. As such, the safety and efficacy of dabigatran versus an interrupted warfarin strategy remains largely unclear.

The aim of the present study is to evaluate the outcomes of patients who received post-ablation dabigatran compared to warfarin with a LMWH bridge in patients undergoing catheter ablation for AF at our institution.

Methods

Study Design

We performed a retrospective cohort study of consecutive patients who underwent catheter ablation for AF at Northwestern Memorial Hospital (Chicago, Illinois) between January 2010 and December 2012. The study protocol was approved by the local institutional review board. All patients with at least 30 days of post-ablation follow-up data were included. Patients were excluded if an alternate (i.e. neither warfarin nor dabigatran) oral anticoagulant was used, if warfarin was continued periprocedurally without interruption, or if all anticoagulation was held post-procedurally due to a procedural complication.

The primary outcomes of our study were all-cause mortality and a composite endpoint of thromboembolic and bleeding-related events at 30-days. These included but were not limited to cases of cerebrovascular accidents, transient ischemic attacks, deep vein thromboses, pulmonary emboli, AV fistula formation, hematoma at catheter sites, and any internal hemorrhage that required blood transfusions or surgical interventions. A hematoma was classified as major if it required transfusion, surgical intervention, or hospital admission; all other hematomas were considered minor.

Periprocedural Anticoagulation

Patients on chronic warfarin therapy stopped warfarin 3 to 5 days prior to their procedure and were bridged with LMWH (e.g. dalteparin or enoxaparin based on formulary availability) subcutaneous injections if the INR was expected to be < 2.0 for more than 48 hours. LMWH was held for 2 doses before the procedure. Patients on chronic dabigatran therapy were instructed to hold 3 doses prior to their procedure with no other anticoagulants used in the interim. Patients on aspirin therapy continued aspirin until the time of their procedure. Most patients also underwent a transesophageal echocardiogram prior to ablation to assess for left-atrial appendage thrombus.

During the ablation procedure, while catheters and sheaths were in the left atrium, IV heparin was administered by an initial bolus of 100 Units/kg followed by repeat boluses every 30-60 minutes to maintain an ACT > 270 by as measured on an Abbott iSTAT1 machine. At the discretion of the individual provider, an IV heparin infusion without bolus was initiated 6 hours after sheath removal and discontinued on the morning after ablation.

Patients treated with post-ablation warfarin were started on warfarin the night of their catheter ablation. They were bridged with LMWH starting the morning after ablation and continued until a therapeutic INR of ≥ 2.0 was reached. Patients treated with dabigatran

post-ablation were started on dabigatran the morning after ablation. Dabigatran was dosed according to serum creatinine levels -- either 150mg twice daily or 75mg twice daily if the creatinine clearance was 15-30 mg/ml. Regardless of strategy, anticoagulation was continued for at least 2 months post-procedure.

Statistical Methods

Patients were analyzed according to post-ablation anticoagulation strategy only. Statistical analyses were performed using SPSS version 21.0 for Windows (SPSS, Inc., Chicago, Illinois). Univariate analyses were performed using chi-squared or Fisher's exact test (if $n < 6$) for categorical variables. Independent 2-tailed t-tests were performed for continuous variables. A p-value of < 0.05 was considered statistically significant. Multivariate analysis was not attempted due to the small number of outcome events.

Results

Patient Characteristics

Between January 2010 and December 2012, there were 378 patients who underwent catheter ablation for AF at our institution. 54 of these cases were excluded from our study: 35 received an alternate novel oral anticoagulant, 13 received uninterrupted warfarin therapy, and 6 received no anticoagulation post-ablation due to a procedural complication. Of the 6 who received no post-ablation anticoagulation, 5 were in the context of intra-procedural cardiac perforation and 1 was in the context of intra-procedural hemoptysis. Demographic characteristics are summarized in Figure 1.

324 patients were included in the final analysis. 181 patients (55.9%) received post-ablation dabigatran and 143 (44.1%) received warfarin with LMWH post-ablation. Of the patients who received post-ablation dabigatran, 179 (98.9%) were prescribed 150mg twice daily and 2 (1.1%) were prescribed 75mg twice daily. LMWH bridging dose was left to the discretion of the individual provider. Average weight of those who received LMWH was 96.8 ± 28.0 kg. 79.1% received dalteparin 100 IU/kg, 14.5% received dalteparin 50 IU/kg, 6.4% received dalteparin 200 IU/kg, and 0.9% received enoxaparin 1mg/kg.

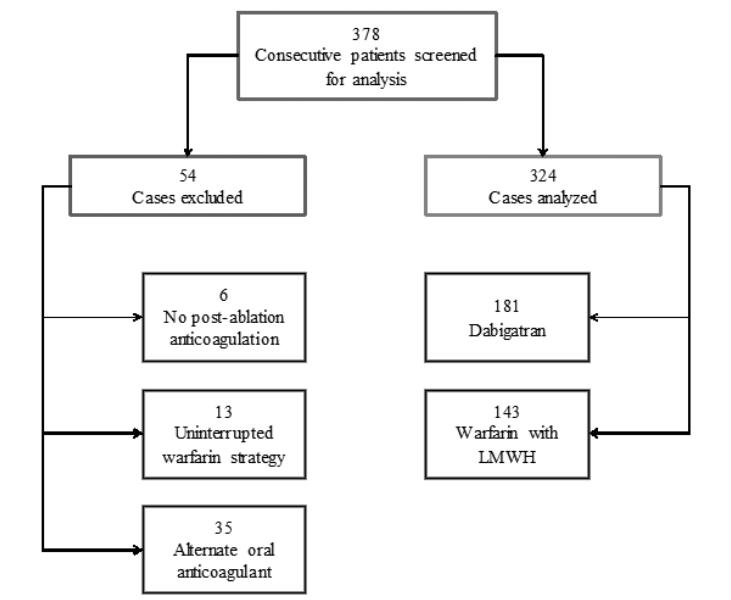


Figure 1: The description of cases excluded from the study and cases remaining for final analysis are shown here

Baseline characteristics of the dabigatran group and warfarin group are shown in Table 1. The mean age of both groups was 60 ± 9 years. The dabigatran group included a higher percentage of males and patients with paroxysmal rather than persistent AF, but the differences were not statistically significant. Those in the dabigatran group were more likely to have a CHADS₂ score of 0 or 1 ($p=0.022$), more likely reported as New York Heart Association (NYHA) Class I ($p=0.001$), and more likely to have had their ablation by cryoballoon ($p<0.001$). Patients in the warfarin arm were more likely to have undergone a prior catheter ablation ($p=0.002$). All 99 patients who were on dabigatran therapy prior to ablation continued dabigatran post-ablation. 32 patients previously on warfarin therapy were converted to dabigatran therapy post-ablation.

Outcomes and Cases

At 30-days post-procedure, there were 0 thromboembolic or bleeding complications in the dabigatran group versus 4 (2.8%) in the warfarin group ($p=0.037$). There were no deaths in either group at 30-days follow-up. Of the 4 complications included in the composite end-point, 1 patient suffered a transient ischemic attack (TIA), 2 patients had hematomas at the catheter insertion sites requiring surgical intervention, and 1 patient required blood product transfusions as a result of a hematoma (Table 2). These cases are briefly outlined as follows.

The patient who suffered a TIA post-ablation was a 45 year-old

Table 1: Comparison of Demographic and Procedural Variables by Anticoagulation Strategy

	Dabigatran (n=181)	Warfarin (n=143)	p Value
Male Gender	145 (80.1%)	107 (74.8%)	0.256
Age (years)	60.4 ± 9.4	60.2 ± 9.8	0.812
Hypertension	73 (40.3%)	66 (46.2%)	0.293
Diabetes Mellitus	18 (9.9%)	23 (16.1%)	0.099
Serum Creatinine (mg/dL)	$1.05 \pm .23$	$1.05 \pm .32$	0.828
Structural Heart Disease	37 (20.4%)	42 (29.4%)	0.063
Prior Stroke, Transient Ischemic Attack	9 (5.0%)	11 (7.7%)	0.312
Prior Valve Surgery	3 (1.7%)	4 (2.8%)	0.704
Prior CABG	6 (3.3%)	1 (0.7%)	0.139
Device (PPM/ICD)	16 (8.8%)	15 (10.5%)	0.616
Repeat Ablation	23 (12.7%)	37 (25.9%)	0.002
AF Type (Paroxysmal)	136 (75.1%)	98 (68.5%)	0.187
CHADS ₂ (Average)	0.66 ± 0.80	0.85 ± 0.95	0.045
0-1	157 (86.7%)	107 (74.8%)	0.022
2	19 (10.5%)	30 (21.0%)	
3-5	5 (2.8%)	6 (4.2%)	
NYHA Functional Class			0.001
I	172 (95.0%)	120 (83.9%)	
II	3 (1.7%)	18 (12.6%)	
III	2 (1.1%)	2 (1.4%)	
Pre-Ablation Warfarin	32 (17.7%)	108 (75.5%)	<0.001
Pre-Ablation Dabigatran	99 (54.7%)	0 (0.0%)	<0.001
Cryoablation	57 (31.5%)	13 (9.1%)	<0.001
Post-operative IV Heparin a	90 (49.7%)	58 (40.6%)	0.100

Abbreviations: CABG = coronary artery bypass graft; PPM = permanent pacemaker; ICD = implantable cardiac defibrillator; AF = atrial fibrillation, NYHA = New York Heart Association a Post-operative IV Heparin = unfractionated IV heparin without bolus started 6 hours after hemostasis

male with paroxysmal AF who was treated with LMWH (dalteparin 100 IU/kg) and warfarin periprocedurally. He presented to an ophthalmology clinic 9 days after ablation with sudden blurry vision in his right eye and was found to be in atrial flutter with a subtherapeutic INR. He had a negative CT Head and MR Brain. His visual symptoms resolved and he demonstrated no other neurologic signs or symptoms during this episode.

Of the patients who developed a groin hematoma, one was a 71 year-old woman who underwent a repeat ablation for paroxysmal AF. She developed an acute hematoma (11x14x17cm) two days after ablation while on ASA, warfarin, and unfractionated heparin. CT angiography showed an associated pseudoaneurysm, prompting surgical drainage and repair.

Another patient who developed a hematoma post-ablation was a 55-year old woman with persistent AF. She received periprocedural warfarin and LMWH (dalteparin 100 IU/kg). Two weeks after her ablation, while taking warfarin, she developed a left groin hematoma resulting in compressive neuropathy. The hematoma required surgical evacuation.

Finally, the third hematoma case was that of a 77 year-old woman with paroxysmal AF who underwent radiofrequency ablation with periprocedural warfarin and LMWH bridging post-ablation (dalteparin 100 IU/kg). Five days post-ablation, while still taking LMWH, she was found to have a right groin hematoma (9.2x7.1cm) and her hemoglobin had declined to 7.5 g/dL from a baseline of 13.9 g/dL. She was transfused 2 units of packed red blood cells and recovered fully without requiring surgical intervention.

Discussion

In this retrospective cohort study, our institution's overall complication rates were similar to those previously reported in the literature.¹² The use of dabigatran immediately following catheter ablation was associated with fewer thromboembolic and hemorrhagic complications as compared to the use of warfarin with LMWH bridging. Three bleeding complications and 1 thromboembolic complication were seen in the warfarin group, yielding a composite complication rate of 2.8% and thromboembolic complication rate of 0.7%.

There has been significant recent interest in examining the safety and efficacy of periprocedural novel oral anticoagulants for catheter ablation with no consensus at this time on an optimal anticoagulation protocol.²⁵ Lakireddy et al. first reported a multicenter experience comparing periprocedural dabigatran to uninterrupted warfarin. In their study, periprocedural dabigatran use was associated with an increased risk of bleeding and thromboembolism (16% versus 6%; $p=0.009$).¹³ Other studies have since shown no significant differences in complications between the use of dabigatran and a warfarin-based strategy.¹³⁻¹⁸ More recently, various meta-analyses of these studies have also been performed.¹⁹⁻²² These largely continue to demonstrate

Table 2: Comparison of Thromboembolic and Bleeding Complication Rates by Anticoagulation Strategy

	Dabigatran (n=181)	Warfarin (n=143)	p Value
All-Cause Mortality	0%	0%	
Composite Complication Rate	0%	2.8% (n=4)	0.037
Hemorrhage Requiring Transfusion		0.7% (n=1)	
Cerebrovascular Attack or Transient Ischemic Attack		0.7% (n=1)	
Hematoma at Catheter Insertion Site		1.4% (n=2)	

dabigatran as a noninferior anticoagulation strategy to warfarin, though one meta-analysis raises the concern for a higher rate of neurologic events with periprocedural dabigatran.¹⁹ It is important to note that the cohorts in these meta-analyses predominantly utilized uninterrupted warfarin as the control arm to post-ablation dabigatran. However, the 2012 HRS/EHRA/ECAS expert consensus statement for catheter or surgical ablation continues to support either an uninterrupted warfarin periablation strategy or an interrupted strategy with initiation of warfarin 4 to 6 hours following ablation and heparin or LMWH used as a bridge to an INR 2.0-3.0.³ Therefore, our study provides important data for centers that continue to utilize interrupted warfarin with LMWH periprocedurally.

Some aspects of our patient population merit discussion. Those who received dabigatran post-ablation had fewer cardiovascular co-morbidities than those in the warfarin arm, as demonstrated by their lower CHADS₂ scores and NYHA class. As our study cohort captures the time around when dabigatran was approved by the FDA for use in non-valvular AF, it is possible that providers were initially more selective in choosing appropriate candidates for dabigatran therapy post-ablation. It is worth noting that no patients previously given dabigatran were transitioned to warfarin post-ablation while 32 (22.9%) previously on warfarin were transitioned to dabigatran. This change could be due to patient preferences, ease of administration post-ablation, or provider comfort with the new anticoagulant. Finally, LMWH bridge dosing and the use of IV heparin immediately post-ablation were not standardized during our study period, potentially creating bias in our study results. Notably, 2 of the 3 bleeding complications occurred in the setting of a higher dalteparin dosing regimen.

Our study also revealed that cryoablation catheters were used in significantly more cases in which patients were given dabigatran post-ablation. Cryoballoon catheters are increasingly being used for catheter ablations because they may create more contiguous and potentially less thrombogenic lesion sets.²³⁻²⁴ As compared to our institution's standard irrigated tip radiofrequency ablation catheters used for ablation of AF, cryoablation catheters require larger sheaths (8.5 Fr versus 14 Fr). While the use of cryoablation catheters could have concurrently decreased the incidence of thromboembolic complications, these large 14 Fr catheters could have also increased the risk of hemorrhagic complications, particularly at the venipuncture sites in the groin. Interestingly, only 1 of the 3 cases with a hemorrhagic complication found in our study used these catheters during the procedure and all were in the warfarin arm.

Some limitations of this study deserve mention. The sample size of this study limited our ability to perform multivariate analyses to assess whether the type of anticoagulation served as an independent risk factor for adverse events. Given the small number of anticipated events, however, very large studies would be needed to generate enough events to support such an analysis. In addition, our institution's anticoagulation protocols could differ from that of other centers thus limiting the generalizability of the results.

Conclusions:

Our study suggests that the use of periprocedural dabigatran appears to be safe and efficacious following catheter ablation for AF as compared to an interrupted warfarin strategy with LMWH bridging. In order to monitor the safety of this approach, ongoing institutional and multi-center registries will be essential to developing

large cohorts of patients who are prescribed dabigatran or other novel oral anticoagulants following ablation.

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