JAFIB
Original Research
Journal of Atrial Fibrillation

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The Safety of Dabigatran Versus Warfarin in Patients Undergoing Atrial Fibrillation Ablation

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Abstract

The safety and optimal strategy of the use of dabigatran versus uninterrupted warfarin in atrial fibrillation ablation is currently unclear. We performed a retrospective analysis between July 2011-October 2012 of all patients undergoing an AF ablation who received uninterrupted warfarin therapy (199) and the routine cessation of Dabigatran therapy (126) 4 days pre-ablation. Major safety endpoints included: pericardial effusion (requiring pericardiocentesis), peripheral thromboembolism, CVA, and groin hematoma requiring blood transfusion. Minor endpoints included pericardial effusion and groin hematoma. Dabigatran was restarted the following day after ablation. The warfarin group was older, had a higher $CHADS_2$, CHA_2DS_2VASc and HASBLED scores and greater prevalence of aortic plaque. The major complication rate was 2.0% in the warfarin group and 2.4% in the dabigatran group (P= 0.83). The minor complication rate was 2.5% in the warfarin group and <1% in the dabigatran group (P= 0.27). In the dabigatran group, there was one renal thromboembolic event 4 days post-ablation. All patients in the warfarin group who suffered a major complication required a blood transfusion. Cessation of dabigatran therapy 4 days pre AF ablation has a comparable safety profile to uninterrupted warfarin therapy.

Introduction

Catheter ablation is increasingly being performed for patients with medically refractory, symptomatic atrial fibrillation (AF).[1] Atrial fibrillation ablation carries a significant risk of thromboembolism and bleeding due to thrombus formation in the left atrium and intraprocedural conversion from AF to sinus rhythm. Commonly, multiple strategies are employed peri-AF ablation to reduce the risk of thromboembolic complications, including the use of transesophageal echocardiography, intracardiac echocardiography, irrigated ablation catheters, and intraprocedural anticoagulation.[2]

Historically, patients treated with warfarin (WAR) would typically discontinue this medication and be bridged with low-molecular-weight heparin prior to ablation. Recent studies, however, have suggested that patients undergoing an AF ablation can safely undergo the procedure without discontinuation.[3] This strategy has become standard clinical practice.[4] The novel oral anticoagulant, dabigatran (DAG, direct thrombin inhibitor) has emerged as an increasingly common therapy for thromboembolism prevention in AF. However, strategies for its use in the setting of atrial fibrillation ablation have been varied and may be associated with an increased incidence of thromboembolism.[5,6,7] We sought to compare the safety and feasibility of uninterrupted warfarin versus discontinuing dabigatran 4 days prior to atrial fibrillation ablation.

Disclosures:
None.

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Material and Methods

Patients

We performed a retrospective, single-center study conducted at New York University Langone Medical Center from July 2011-October 2012. All patients who were referred for catheter ablation for symptomatic atrial fibrillation or atrial tachyarrhythmias post atrial fibrillation ablation and receiving either warfarin or dabigatran were included in the analysis. Patients were excluded from the study if they had a prosthetic heart valve, hemodynamically significant valvular disease, end stage renal disease or advanced liver disease. Written, informed consent was obtained in the usual fashion for catheter ablation.

Pre-Procedure

Patients receiving DAG discontinued the drug 4 days prior to catheter ablation and received no anticoagulation bridge. All patients were treated with DAG 150mg BID. Patients on WAR therapy were maintained at their current dose and had measured international normalized ratios of 1.6-3.2. Antiarrhythmic agents were discontinued five half-lives prior to the AF ablation and all patients underwent Transesophageal echocardiography (TEE) on the day of the procedure.

Intra-Procedure

The details of the wide-area circumferential area ablation and pulmonary vein (PV) isolation have been described elsewhere.[4] In brief, an 8-French duodecapolar catheter (Livewire, St. Jude Medical(SJM), St. Paul, MN, USA) was inserted into the left femoral vein and positioned in the coronary sinus via an 8-French short sheath (St. Jude Medical, St. Paul, MN, USA). One 11-French Agilis steerable introducer sheath (SJM) and an 8.5-French long sheaths (SJM) were inserted from the right femoral vein, and advanced into the LA using the transseptal puncture technique. Intravenous heparin was administered as a 100 units/kg bolus dose after a transseptal puncture, and then additional heparin was administered to maintain an activated clotting time value of 350–400 seconds. Protamine was used to reverse heparin at the end of the procedure. A single 7-French 20 mm diameter decapolar circumferential catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA) was placed within the pulmonary veins and used to construct a three-dimensional electroanatomical maps using a nonfluoroscopic navigation system (Ensite Velocity, St. Jude Medical, St. Paul, MN, USA). After, circumferential ablation lines were created around the left- and right-sided ipsilateral pulmonary veins using a 3.5-mm irrigated-tip catheter (ThermoCool, Biosense Webster). Radiofrequency energy was delivered with a maximum power of 35 W for 20 seconds at each site. The temperature was limited to 45˚C. The endpoint of the PV isolation was either the elimination or dissociation of the PV potentials recorded from the circular catheters placed within the PVs and exit block from the PVs. Transthoracic cardioversion was applied to restore sinus rhythm in the patients with persistent or long-standing persistent AF if they did not convert after additional lesions were applied to the septal left atrium, left atrial roof, lateral left atrium, as well as endocardial surface and epicardial coronary sinus. All patients requiring a redo ablation underwent left atrial mapping and ablation of the atrial tachycardia with confirmation of PV isolation. If PV isolation was not presents further lesions were delivered for completion of isolation. Finally, the cavotricuspid isthmus was ablated with an endpoint of bidirectional conduction block. The blood pressure was monitored noninvasively throughout the procedure.

Table 1: Baseline Demographics

	Dabigatran (n=126)	Warfarin (n=199)	p- value
Age (IQR)	62 (55-69)	65 (58-72)	0.001
Female n(%)	35(28)	68 (34)	0.21
AF Type-			0.99
Paroxysmal n(%)	36 (28)	57(29)	
Non-paroxysmal n(%)	90(72)	142(72)	
Prior AF ablation n(%)	42(33)	80(40)	0.21
Heart Failure n(%)	18(14)	26(13)	0.68
HTN n(%)	64(51)	117(59)	0.16
OSA n(%)	15(11)	22(11)	0.99
DM n(%)	19(15)	30(15)	0.98
CAD n/%	24(19)	38(19)	.98
TIA/CVA n(%)	11(9)	38(19)	0.08
CHADS (SD)	0.98 ±1.5	1.2 ±1.4	0.03
CHA_2DS_2VASc (SD)	2.1 ±0.34	2.7 ±0.2	<0.0001
CHA_2DS_2VASc >0 n/ %	18(14)	8(4)	<0.006
CHA_2DS_2VASc >1 n/ %	39(31)	36(18)	<0.007
CHA_2DS_2VASc >2 n/ %	70(56)	155(78)	<0.0001
Aortic plaque n(%)	74(59)	155(78)	<0.0006
HASBLED	0.29(0.49)	0.52(0.41)	<0.0004
ASA n(%)	19(15)	46(23)	0.06
Plavix n(%)	3(2)	8(4)	0.38
Anti-arrhythmic therapy n(%)	49(39)	68(34)	0.32
BMI kg/m2 (SD)	31 ± 6.1	30 ±7.5	0.18
LVEF % (SD)	57± 10	55 ±9.7	0.09
eGFR mL/min/1.73 m2	76±20	72±17	0.07
INR	1.1 (1.0-1.2)	2.2(1.8-2.5)	<0.0001

Post Procedure

Patients in the WAR group received their usual dose of warfarin the evening of the procedure. Patients in the DAG group received intravenous heparin 4-6 hours post sheath removal on the night of the procedure. On the following morning, the intravenous heparin was discontinued and DAG 150mg and a low-molecular heparin(enoxaparin) subcutaneous injection at 0.5 mg/kg were administered. The low-molecular weight heparin served as a bridge to therapeutic anticoagulation levels and was given for a total of 3 doses every 12 hours. Patients were evaluated for post procedure bleeding as well as signs and symptoms of neurologic thromboembolism in the first 2 weeks.

End Points

The endpoints were defined as major or minor. Major events included: death, thromboembolism, pericardial tamponade requiring pericardiocentesis and groin hematoma requiring transfusion. Minor events included: pericardial effusion and groin hematoma not requiring transfusion.

Statistical Analysis

The differences between the groups were examined using chi square tests for categorical variables. For comparisons of continuous variables, unpaired Student's t-tests were used, as appropriate. A multivariate logistic regression analysis was performed in the aim of identifying predictors for complications. All univariate predictors with a p value <0.1 were analyzed in a stepwise fashion and results are reported in Odd Ratios and Confidence Intervals. The statistical analyses were performed using SPSS 21 (Armonk, New York). For all analyses, a P value of <0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Population

Table 1.

There were significant baseline differences between the two groups. The WAR group was older, had a higher CHADS, CHA_2DS_2VASc and HASBLED score and a higher prevalence of aortic plaque. There was also a trend towards an increased prevalence of cerebrovascular accidents/transient ischemic attacks , aspirin use and lower GFR in the WAR group.

Outcomes

Table 2.

Overall bleeding complications were increased in the warfarin population, however this did not meet statistical significance. Also, all patients in the Warfarin group who suffered a major complication required a blood transfusion. One patient in the DAG group with

non-paroxysmal AF developed renal thromboembolism 4 days post AF ablation. The patient had reported abdominal pain and weakness and presented to the Emergency Department with notable findings of a creatinine elevation (1.0mg/dl to 1.4mg/dl) and findings on Computed Tomography of the abdomen significant for a wedged shaped infarct of the right kidney. The patient received IV heparin and was switched to warfarin. The patient's renal function improved over the next 2 weeks and no further complications were observed.

The majority of complications occurred in the first 48 hours (9/13) with 4 complications occurring after 48 hours. These 4 complications were 3 minor groin hematomas(2 in DAG, 1 in WAR group) and a pericardial effusion requiring a pericardiocentesis (WAR group). There were no cerebrovascular accidents or transient ischemic attacks. There were no significant differences in complication rates between patients with paroxysmal (Major-3, Minor-3) and non-paroxysmal AF (Major 4, Minor-3).

Univariate analysis revealed 3 variables (elevated INR 1.9 vs. 1.7, p=0.026; decreased LVEF 49% vs. 56%; p= 0.058; increased age 64 vs 62; p=0.059) as predictors of complications. However, multivariate logistic regression analysis did not show an independent single predictor of complications (INR OR 1.2 95%; CI 0.57-2.6, p=0.59, LVEF OR 0.95; 0.91-1.0; p=0.053, AGE OR 0.99; 95% 0.93-1.05 p=0.76).

Discussion

In our single-center retrospective study, we found the strategy of discontinuing dabigatran 4 days prior to AF ablation and restarting dabigatran therapy the following morning provided a similar safety profile when compared to uninterrupted warfarin.

Dabigatran is a newly developed oral anticoagulant that directly inhibits thrombin, and is less susceptible to dietary and drug interactions as compared to warfarin.[8] Furthermore, it does not require anticoagulation monitoring. The Randomized Evaluation of the Long-term Anticoagulation Therapy (RE-LY) trial demonstrated the noninferiority of dabigatran over warfarin with respect to a reduction in the occurrence of both stroke and systemic embolism among patients with AF.[9]

Since its approval, there has been a significant increase in the use of dabigatran and a reduction of warfarin prescriptions in the United States.[10] This rise in dabigatran therapy has resulted in multiple peri-procedural strategies aiming to reduce the incidence of thromboembolism and bleeding. Determining the optimal anticoagulant strategy for patients taking dabigatran and undergoing AF ablation is critical .

There have been conflicting results in the literature on the safety of dabigatran as compared to warfarin as an anticoagulation strategy peri-ablation.[5,8, 11-13] Most recently, 2 meta-analyses on this topic differ as to whether there is an increased incidence of neurologic/ thromboembolic events in patients receiving dabigatran.[6,11] Steinberg and colleagues noted a statistically significant increase in the prevalence of neurologic events 0.7% vs. 0.2% in patients receiving dabigatran vs. warfarin. In contrast , Providencia and colleagues noted no difference in the prevalence of thromboembolism 0.55% vs. 0.17%, in patients receiving dabigatran vs. warfarin. In our cohort, despite the higher than average CHA_2DS_2VASc score (2.5), as compared to prior studies (1.6-1.9), thromboembolism rates (0.8% vs. 0%) were similar in the dabigatran and warfarin groups respectively.

The increased incidence of thromboembolic events in other studies may be related to the subtherapeutic anticoagulation window(the time period between the initiation of dabigatran and its peak effect).[5]In our study, heparinization starting 4-6 hours post procedure (followed by the initiation of dabigatran and enoxaparin the following day) may have decreased the dabigatran subtherapeutic window and prevented thromboembolism. In prior studies, low molecular weight heparin, in the setting of warfarin therapy has been shown to be effective in the setting of AF ablation.[14] In contrast to our study, the majority of studies have held dabigatran for 1-2 doses prior to ablation and restarted the 1st dose within 24 hours.[6,11] Most notably, one of the largest retrospective case cohort studies found no increase in hemorrhagic or thromboembolic events utilizing a strategy of holding dabigatran(the evening prior to the ablation and the day of the procedure) and restarting the medication 4 hours after vascular hemostasis.[13] To our knowledge, we are the first to describe next-day enoxaparin administration as a bridge to therapeutic anticoagulant levels in the setting of dabigatran therapy post-AF ablation.

In the aforementioned studies, major hemorrhage peri-ablation has been estimated between 1.3%-1.8%.[6,11] There have been no significant signals indicating the risk of bleeding is higher in patients receiving dabigatran versus warfarin. However, definitions of major bleeding, the size of single center studies and adverse event rates have differed substantially. Importantly, the T1/2 life of dabigatran is 12-17 hours. However, in the elderly and in patients with impaired renal function, the plasma levels and T1/2 life increase. Recently, the European Heart Rhythm Association has recommended holding dabigatran > 72hours prior to a surgical intervention in patients with a creatinine clearance between 50-80 and at high bleeding risk.[15] Our study is the first to show cessation of dabigatran up to 4 days pre-ablation is as safe as uninterrupted warfarin therapy.

All patients within our cohort were candidates for warfarin or full dose dabigatran therapy. However, patients receiving warfarin were older, had a greater prevalence of aortic atherosclerosis and had higher calculated CHADS, CHA_2DS_2VASc and HASBLED scores. There was also a trend towards a greater prevalence of TIA/CVA, aspirin use and lower GFR . Interestingly, in prior studies comparing dabigatran vs. warfarin therapy, patients receiving warfarin show a similar trend towards having a greater baseline prevalence of TIA/ CVA, decreased renal function and greater aspirin use.[13,16-18] These differences likely impact the observed complication rate in prior retrospective studies. The exact cause of greater baseline comorbidity in warfarin patients is unknown, however reluctance to switch from

Table 2: Procedural Outcomes

	Dabigatran (n=126)	Warfarin (n=199)	p-value
Total Major and Minor Complications n (%)	4 (3.1)	9 (4.5)	0.52
Major complications n (%)	3(2.4)	4(2.0)	0.83
Death and CVA n (%)	0	0	1
Peripheral Thromboembolism n (%)	1(0.8)	0	0.21
Pericardiocentesis n (%)	2(1.6)	1(<1.0)	0.32
Groin Hematoma AND Transfusion n (%)	0	3(1.5)	0.17
Minor Complications n(%)	1(0.8)	5(2.5)	0.27
Pericardial effusion (NO Pericardiocentesis) n (%)	0	3(1.5)	0.17
Groin Hematoma (NO Transfusion) n (%)	1(0.8)	2(1.0)	0.85
Patients requiring blood transfusion n (%)			
(> 1 unit of blood products)	0	4(2.0)	0.11

warfarin to dabigatran, unfamiliarity with dabigatran use in sicker patients and lack of a reversal agents in patients with less perceived tolerance of hemodynamically significant hemorrhage may represent likely factors.

Study Limitations

This was a small retrospective non-randomized study. Our study has limited power in identifying predictors of bleeding and thromboembolic events due to the limited number of patients and small number of events.

Conclusions:

In patients receiving dabigatran therapy pre-AF ablation, a strategy of drug cessation 4 days prior to the procedure and resumption of dabigatran the following day has a comparable safety profile to uninterrupted warfarin therapy. Although a reliable, widely available antidote for dabigatran is not available, the outcomes of serious complications do not appear to be different amongst patients receiving dabigatran versus warfarin. Large randomized controlled trials will be needed to further assess the impact of interrupted dabigatran therapy on safety.

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