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ORIGINAL ARTICLE

'The role of novel oral anticoagulants in patients undergoing cryoballoon ablation for atrial fibrillation'

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Abstract *Aim:* Peri-procedural thromboembolic (TE) and hemorrhagic events are complications of major concern for patients undergoing cryoballoon (CB) ablation for atrial fibrillation (AF).

While peri-procedural anticoagulation management could decrease the incidence of these complications, data on CB ablation are scarce. The role of novel oral anticoagulants (NOACs) has not been thoroughly tested in this population.

Methods: In the present study, we sought to assess acute peri-procedural complications in patients undergoing CB ablation for AF under different anticoagulation regimens; anticoagulation administration was performed according to the CHA2DS2-VASc score guidelines. To the best of our knowledge, this is the first study that compares 1) uninterrupted warfarin, 2) bridging therapy with low molecular weight heparin (LMWH), 3) aspirin and 4) NOACs in this subgroup of patients.

Results: NOACs were as effective as uninterrupted warfarin in terms of bleeding complications and TE events. Surprisingly, the aspirin group had more hemorrhagic complications than both the warfarin and NOACs groups.

Conclusion: In the current study, the use of NOACs was an effective and safe approach in CB ablation.

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1. Introduction

Atrial fibrillation (AF) increases the risk of stroke and death. Patients undergoing catheter ablation are at their greatest risk for stroke in the peri-procedural period of AF ablation, even if they have low CHA2DS2-VASc score. Therefore, an adequate level of anticoagulation is needed throughout the entire procedural period. In fact, intra-procedural administration of unfractionated heparin (UFH) prior to or immediately following transseptal puncture as well as dose adjustment to maintain an activated clotting time (ACT) above 300 seconds is recommended in the current guidelines.[1]

In addition, a peri-procedural uninterrupted anticoagulation strategy with vitamin K antagonists seems to be a better option with respect to bleeding complications and stroke compared to the bridging strategy with Low Molecular Weight Heparin (LMWH).[2,3]

However, vitamin K antagonists are sometimes inconvenient to use because of their numerous interactions, which in turn require frequent laboratory monitoring.[4,5] As a result, many patients who receive warfarin still have inadequate anticoagulation when undergoing AF ablation.[6–8]

The relatively rapid onset and offset of New Oral Anticoagulants (NOACs) make them attractive for use in the peri-procedural setting of AF ablation. Nevertheless, their relative safety and efficacy needs to be better established when assessing their potential benefit in these settings. There are no prior reports on the use of NOACs in patients undergoing Cryoballoon (CB) ablation in AF.

In this study, we sought to assess the acute peri-procedural complications in patients undergoing CB ablation for AF with different anticoagulation regimens. To the best of our knowledge, this is the first study that compares 1) uninterrupted warfarin, 2) bridging therapy with LMWH, 3) aspirin and 4) NOACs in this subgroup of patients. The CB patients are a special population, particularly because the procedure involves the use of a 15 F sheath via the femoral vein.

2. Methods

2.1. Study population

From June 2012 until December 2013, 210 consecutive patients underwent CB ablation, and peri-procedural complications were analyzed according to the anticoagulation strategy.

Anticoagulation was administered according to the current guidelines with the CHA2DS2-VASc score.[1]

The study protocol was approved by the ethics committee of Universitair Ziekenhuis Brussel. All patients provided informed consent prior to the procedure. Patients were diagnosed with drug resistant paroxysmal AF. Paroxysmal AF was defined as the frequent occurrence of recurrent episodes of AF that self-terminated within 7 days. Data collected included demographic characteristics, such as the age, sex, height, weight, comorbid conditions, current medications and allergies (Table 1). The baseline international normalized ratio (INR) value was obtained for all patients before the procedure. A trans-thoracic examination (TTE), enabling assessment of left ventricular ejection fraction, intracavitary dimensions and valve function, was performed within 1 week prior to ablation. To exclude the presence of thrombi in the left atrial appendage, all patients underwent a transesophageal echocardiogram (TEE) on the day before the procedure. Moreover, all patients underwent a preprocedural computed tomography (CT) scan to assess the left atrial anatomy. Peri-procedural complications, including Thromboembolic Events (TE), bleeding events and cardiac tamponade, were recorded for all patients. A cerebrovascular event (CVA), transient ischemic attack (TIA), pulmonary embolism (PE), deep vein thrombosis and myocardial infarction were considered TE complications. Occurrence of blood loss requiring transfusion or resulting in a 20% or greater decrease in the hematocrit, hematoma requiring intervention or intracranial hemorrhage were considered major bleeding complications.

Table 1 Clinical characteristics.

	NOACs	Warfarin	Aspirin	LMWH	Control
Age (years)	66 ± 8	62 ± 11	59 ± 10	61 ± 12	46 ± 13
Male n (%)	22 (64%)	29 (59%)	40 (70%)	7 (58%)	35 (79%)
BMI	26 ± 4	27 ± 4	26 ± 4	26 ± 3	25 ± 3
Hypertension n (%)	22 (64%)	31 (63%)	32 (56%)	8 (67%)	5 (11%)
Dyslipidemia n (%)	19 (55%)	14 (28%)	14 (24%)	1 (8%)	6 (14%)
Diabetes n (%)	2 (6%)	6 (12%)	1 (1.7)	1 (8%)	1 (2%)
HF	3 (9%)	7 (14%)	0	0	0
CAD	3 (9%)	1 (9%)	3 (5%)	0	0
LVEF (%)	58 ± 4	55 ± 8	59 ± 4	60 ± 2	60 ± 3
LA size (mm)	42 ± 7	44 ± 6.6	42 ± 6	37 ± 4	38 ± 6
CHA2DS2-Vasc score	2.3 ± 1.4	2.1 ± 1.4	1.3 ± 1	1.5 ± 0.8	0.41 ± 0.58
HAS-BLED score	1.5 ± 0.7	1.4 ± 0.8	0.8 ± 0.7	1 ± 0.7	0.23 ± 0.42

NOACs: Novel Oral Anticoagulants, LMWH: Low Molecular Weight Heparin, BMI: Body Mass Index, HF: Heart Failure, CAD: Coronary Artery Disease, LVEF: Left Ventricular Ejection Fraction, LA: Left Atrium.

2.2. Statistical analysis

Data are presented as the mean ± standard deviation (SD) or as absolute values and percentages, where appropriate. The unpaired student's T or U-Mann Whitney test was used to compare continuous variables. The Chi square or Fisher's exact test was used for categorical variable comparison. A p value less than 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS software (SPSS v21, IL, USA).

2.3. CB ablation

The approach used for CB ablation of AF at our institution has previously been described in detail.[9]

All procedures were performed under general anesthesia. Two right-sided femoral venous accesses were obtained. In case of accidental puncture of the femoral artery, manual compression of the puncture site was performed for at least 10 minutes before new puncture of the femoral vein was attempted. After obtaining venous accesses, a 6-Fr decapolar catheter was advanced in the coronary sinus. Then, a single transseptal puncture was performed. A 0.32 Fr Emerald exchange wire (Cordis, Johnson and Johnson, Diamond Bar, CA, USA) was advanced in the left superior pulmonary vein (PV), and a steerable 15-F over-the-wire sheath (FlexCath Advance, CryoCath, Medtronic, MN, USA) was positioned in the left atrium (LA). A 20-mm diameter inner lumen mapping catheter (ILMC) (Achieve, Medtronic, MN, USA) was then advanced in each PV ostium to obtain baseline electrical information. After withdrawing the mapping catheter, a 28 mm CB (Arctic Front, Medtronic, MN, USA) was advanced over the wire up to the LA; it was then inflated and positioned in the PV ostium of each vein. For each vein, CB ablation consisted of at least one application that lasted for 3 minutes. To avoid phrenic nerve palsy, a potential complication observed during right-sided PV cryoablation, diaphragmatic stimulation was achieved by pacing the ipsilateral phrenic nerve with a 1000 ms cycle and 20 mA output. Isolation was verified 10 minutes after the last application.

2.4. Preprocedural anticoagulation

For patients who were receiving treatment with one of the NOAC agents and who were scheduled for CB ablation, our practice was to stop anti-coagulation as follows: a) the morning prior to ablation for dabigatran, b) two nights prior to ablation for rivaroxaban, and c) the morning prior to ablation for for apixaban (although experience with this agent is limited). For warfarin, uninterrupted administration was preferable. Nevertheless, some patients received LMWH as a bridging therapy, which was mainly due to fluctuating INR levels. Patients with a CHA2DS2VASc score of 0 were treated with aspirin or with no anticoagulation prior to the procedure. We do not alter our peri-procedural management based on renal function, except that we ensured that the drug was properly dosed for the patient's creatinine clearance.

2.5. Intraprocedural anticoagulation

Unfractionated heparin was given immediately after performing the transseptal puncture and achieving left atrial access. A 100 U/kg bolus was given intravenously. Additional doses of UFH were supplied, if needed, to maintain a target ACT of 300 to 400 seconds throughout the procedure. The baseline and maximum achieved ACT was determined in all patients. The ACT was measured at 15-minute intervals until therapeutic anticoagulation was achieved and then at 30-minute intervals for the duration of the procedure.

2.6. Post-procedural anticoagulation

The choice of the anticoagulant regimen was driven by the patient's pre-procedural therapy. Warfarin was started the same day following ablation and LMWH was used as a bridge until resumption of a target INR of 2—3. If warfarin was not interrupted before ablation, the use of LMWH was avoided.

All patients were dismissed the day following the ablation if they did not experience complications. After the intervention, patients were continuously monitored with ECG telemetry for at least 18 hours. Post-procedural clinical evaluation consisted of a physical examination at 6 hours following the procedure and before discharge. The patient's groin was examined for local puncture complications after sheath removal, before mobilization and at discharge the following day. Moreover, a TTE was performed in all individuals to exclude post-procedural pericardial effusion. Oral anticoagulation (OAC) was started the evening of ablation and continued for at least 3 months. OAC was discontinued after this period in patients with a CHA2DS2-VASc score below 2, as recommended by the guidelines.[1]

Because NOACs provide therapeutic anticoagulation within a few hours of administration, the use of these agents post-ablation obviates the need to send a patient home with bridging enoxaparin injections. Therefore, we started all NOACs 12 hours after the end of the procedure.

3. Results

Two hundred and ten consecutive patients who underwent CB ablation and potentially experienced peri-procedural complications were analyzed.

Forty (20%) patients received NOACs, 48 (24%) received uninterrupted warfarin, 12 (6%) received LMWH as a bridging therapy, 57 (28%) received aspirin and 44 (22%) were not given anticoagulation before the procedure (Table 2). In the NOACs group, 19 were given rivaroxaban (47%), 17 (43%) dabigatran and 4 (10%) apixaban. Nine patients were excluded from the study because they were taking dual antiplatelet therapy.

3.1. Acute bleeding events

In the NOACs group, no acute peri-procedural bleeding was observed (0%). In the uninterrupted warfarin group, 3

Table 2 Bleeding events.

	NOACs	Warfarin	Aspirin	LMWH	Control
Bleeding events n (%)	0	3	12	0	1
Groin hematomas	0	2	10	0	1
Tamponade	0	1	1	0	0
Alveolar hemorrhage	0	0	1	0	0

NOACs: Novel Oral Anticoagulants, LMWH: Low Molecular Weight Heparin, TE: Thromboembolic.

patients experienced bleeding complications (6.3%). In the aspirin group, 12 patients (21.1%) experienced bleeding complications. Finally, no patients in the bridging LMWH group and 1 patient (2.3%) in the control group had hemorrhagic complications (Figure 1).

The Fisher's exact test revealed a significant difference between the NOAC and aspirin groups in terms of bleeding events ($p = 0.04$), wherein there were fewer bleeding events in the NOAC group. There was no statistically significant difference between the NOACs vs Warfarin groups ($p = 0.07$), NOACs vs LMWH groups (no events in either group), and NOAC vs Control groups ($p = 0.282$). There was also a significant difference between the warfarin and aspirin groups ($p = 0.025$), wherein there were fewer bleeding events in the warfarin group.

3.2. Peri-procedural TE events

In terms of serious TE events, there was only one stroke in the NOAC group (2.9%) and there were two strokes in the LMWH group (16.7%) (Table 3). No significant differences were found between any of the groups. The comparisons for these groups were as follows: NOAC vs uninterrupted Warfarin group ($p = 0.182$), NOAC vs aspirin group ($p = 0.195$), NOACs vs LMWH group ($p = 0.126$), and NOAC vs control group ($p = 0.195$).

4. Discussion

Ablation of AF via CB has proven an effective procedure in achieving pulmonary vein isolation (PVI).[10–12]

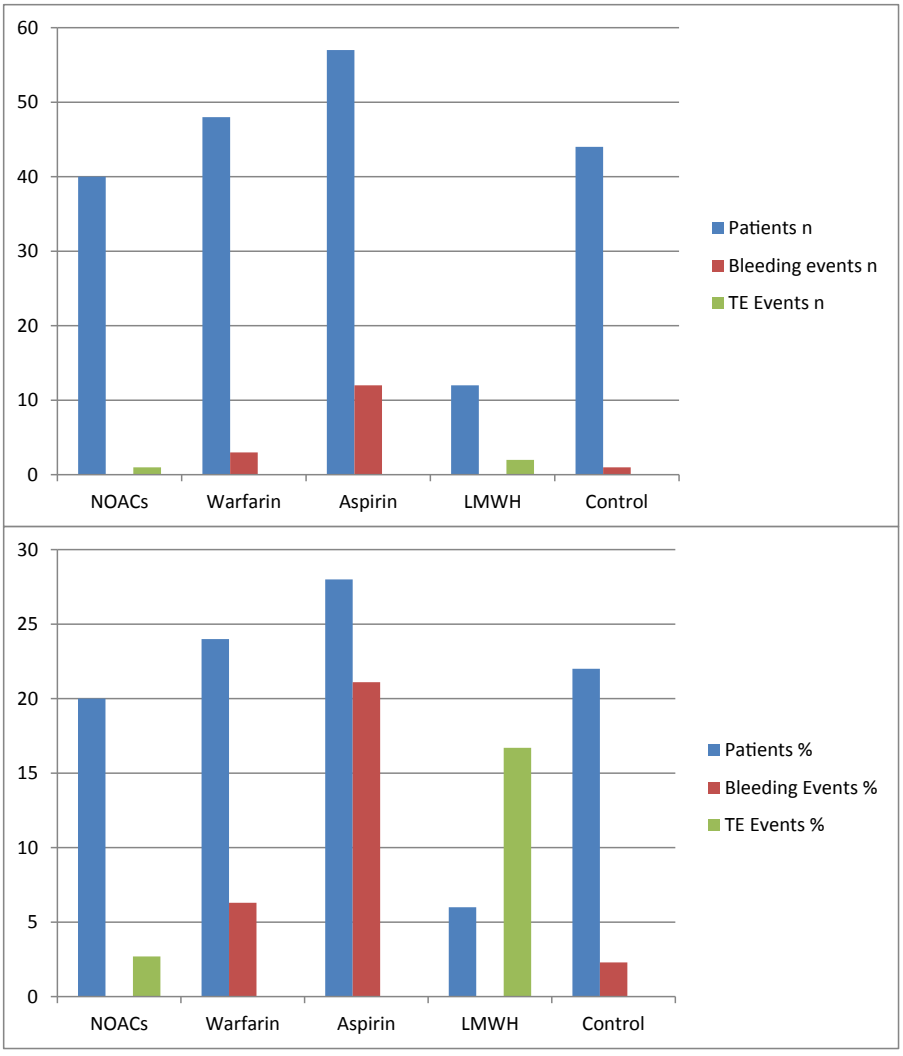

Figure 1 Absolute number and % of Patients, Bleeding events and TE events included in the study.

Table 3 Results.

	NOACs	Warfarin	Aspirin	LMWH	Control
Patients n (%)	40 (20%)	48 (24%)	57 (28%)	12 (6%)	44 (22%)
Bleeding events n (%)	0	3 (6.3%)	12 (21.1%)	0	1 (2.3%)
TE Events n (%)	1 (2.7%)	0	0	2 (16.7%)	0

NOACs: Novel Oral Anticoagulants, LMWH: Low Molecular Weight Heparin, TE: Thromboembolic.

Since then, CB ablation has become increasingly popular and is now widely accepted for treating symptomatic paroxysmal AF that is refractory to antiarrhythmic drugs (AADs).[13] Although there is some evidence that cryoablation is less thrombogenic than radiofrequency ablation ,[14] the post procedure anticoagulation regimen was not based on the ablation modality.

Patients undergoing catheter ablation for AF are at a higher risk of intra- and post-procedural thromboembolic (TE) events, including those identified as low-risk prior to ablation. Therefore, an adequate level of anticoagulation is needed throughout the entire procedural period. The current guidelines recommend intraprocedural administration of unfractionated heparin (UFH) prior to or immediately following transseptal puncture as well as dose adjustment to maintain an activated clotting time (ACT) above 300 seconds.[1]

Moreover, systemic anticoagulation therapy with warfarin, direct thrombin or Factor Xa inhibitors is recommended for at least 2 months following the ablation procedure.

Peri-procedural anticoagulation, although necessary, might contribute to some common procedural complications, including pericardial tamponade and vascular complications, which could be increased in patients for whom a 15-F sheath used for CB ablation.

The current study demonstrated that the use of NOACs is safe and comparable to vitamin K antagonists in terms of the peri-procedural complication rates. Of note, aspirin seems to perform worse than NOACs and warfarin when considering the peri-procedural complications in CB ablation. As a result, our study strengthens the value of NOACs in the peri-interventional setting of rather low-risk patients who often present for AF catheter ablation without adequate anticoagulation. The rapid onset of action of NOACs without the need for bridging also makes them attractive for use in the event of peri-interventional complications.

Among the NOACs, there are the most data on the safety of dabigatran when it is administered soon after AF ablation.[15, 16]

Dabigatran is the only NOAC that has been evaluated in the peri-ablation setting, but data are limited to few studies that have controversial results. Winkle et al. [16] analyzed patients undergoing AF ablation at a single-center in a retrospective fashion. No thromboembolic or bleeding complications occurred during the 30-day follow-up period, while dabigatran was switched to warfarin in three patients. Moreover, a study of 191 patients on dabigatran and 572 on uninterrupted warfarin again showed that both approaches are equally safe and effective.[17] In this study, anticoagulation was started more than four weeks before the ablation procedure in all patients, and dabigatran was held after the morning dose on the day before the procedure and then resumed 4 h after vascular hemostasis was achieved.[17]

In line with these data, two smaller studies have been published and suggest that peri-procedural dabigatran is safe in low-risk patients undergoing AF ablation. Eitel et al. [18] reported that anticoagulation with NOACs following AF catheter ablation is safe and effective based on long-term follow-up. Their rapid onset of action makes NOACs especially attractive in patients without effective anticoagulation on admission and in patients with peri-procedural complications.

On the other hand, Lakkireddy et al. [19] reported, in a 30-day follow-up, that thromboembolic events occurred in three patients on dabigatran (2.1%) and none on warfarin ($p = 0.25$), whereas, details on exact point of time and types of events are lacking. Furthermore, the dabigatran group had a significantly higher major bleeding rate (6 vs. 1%; $p = 0.019$), which was exclusively explained by a higher number of pericardial tamponades requiring drainage (six peri-procedural and three late tamponades in the dabigatran group vs. one late tamponade in the warfarin group). The exact reasons for the increased rate of thromboembolic and bleeding events remain unknown. It is possible that initiation of dabigatran in the pre-ablation setting might partially explain the increased bleeding rate.[19] Furthermore, one has to consider that pericardial tamponade—the only major bleeding events in this study—is mostly caused by technical factors.[1] The authors speculate that the overlapping pharmacodynamic effects of dabigatran and unfractionated heparin might explain the higher bleeding risk. However, despite the higher bleeding rate in patients on dabigatran, these patients also experienced more thromboembolic events.

Current guidelines recommend continuation of warfarin in the peri-ablation setting at low therapeutic levels (INR of 2−2.5).[1] However, patients often present for catheter ablation without adequate anticoagulation. Nevertheless, these patients need effective anticoagulation during as well as after ablation irrespective of their underlying thromboembolic risk.[1, 20, 21] This necessity arises from a presumed prothrombotic state, which is induced by activation of the clotting cascade and atrial stunning early after AF ablation, placing previously low-risk patients at a temporarily elevated thromboembolic risk.[22] Di Biase et al. [23] confirmed that a strategy of uninterrupted warfarin is a better option than bridging therapy in the peri-procedural setting of AF ablation.

As far as aspirin is concerned, studies suggest that hemostasis is unimpaired if at least 20% of the platelets have normal COX-1 activity and 12% of circulating platelets are replaced

every 24 hours.[24] Therefore, stopping aspirin 72 or more hours before the procedure may be adequate to minimize the risk of perioperative bleeding. Deveraux et al. suggested that if clinicians plan to use an anticoagulant agent for perioperative prevention of venous thromboembolism, starting or continuing aspirin throughout the perioperative period will provide no additional benefit; instead, it will increase the risk of major bleeding. However, these findings do not resolve the issue of the relative merits of aspirin versus other anticoagulant agents for perioperative thromboprophylaxis.

As stated above, CB seems to be less thrombogenic than RF ablation. Recent studies[25, 26] are consistent with our results on the safety of NOACs in this specific population. In the current study, there are no demographic variations between the different groups. However, it should be noted that the majority of the patients had low CHA2DS2VASc scores and low HASBLED bleeding scores, indicating a low-risk category for TE events and bleeding complications.

Rhythm over rate control and optimal anticoagulation remain important goals for AF patients, including for younger and older patients. [27] New techniques, such as the use of atrial appendage closure devices, provide additional therapeutic options. [28]

5. Conclusions

In the current study, the use of NOACs was an effective and safe approach in CB ablation.

6. Limitations of the study

There are some limitations in the current study. First, this is a retrospective analysis, and the sample of patients is relatively small. In addition, there are no long-term follow up data on TEs or bleeding complications. Moreover, the NOACs are considered as a single group, which may lead to false conclusions about the safety of regimens with apixaban, which are significantly less safe than dabigatran and rivaroxaban.

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