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Safety and efficacy of DOACs vs acenocoumarol in patients undergoing catheter ablation of atrial fibrillation

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Background: Thromboembolic complications can be life-threatening during atrial fibrillation (AF) catheter ablation. The aim of our study was to evaluate the safety and efficacy of continuous treatment using direct oral anticoagulants (DOACs) as an alternative to uninterrupted acenocoumarol for periprocedural anticoagulation.

Hypothesis: Continuous treatment with DOACs has similar safety and efficacy compared to acenocoumarol.

Methods: We enrolled 474 patients (mean age, 58 years; 68.4% male) undergoing AF catheter ablation between June 2013 and December 2016. All patients were equally assigned to take acenocoumarol (group 1, 136 patients) or DOACs (group 2, 338 patients) for ≥2 months before the procedure. We compared thromboembolic and bleeding complications between the 2 groups.

Results: Our analysis showed no significant difference in major and minor complications between the 2 patient groups. Specifically, 3 of 136 patients (2.2%) using uninterrupted acenocoumarol had a major complication (1 patient [0.7%] had transient ischemic attack resolved 8 hours later, 1 [0.7%] had pericardial tamponade, and 1 [0.7%] had a subcapsular renal hematoma) and 2 patients (1.4%) had minor complications (1 [0.7%] pseudoaneurysm and 1 [0.7%] groin hematoma). In group 2, 1 of 338 patients (0.3%) had a major complication (transient ischemic attack). In the same group, 7 patients (2.1%) had a minor complication (1 patient [0.3%] presented with pseudoaneurysm, 4 [1.2%] with pericardial effusion <1 cm, 1 [0.3%] femoral arteriovenous fistula between the femoral artery and femoral vein, and 1 [0.7%] groin hematoma).

Conclusions: DOACs and acenocoumarol have similar safety and effectiveness regarding thromboembolic complications prevention without increasing bleeding complications.

KEYWORDS

Atrial Fibrillation, Radiofrequency Ablation, Periprocedural Anticoagulants, DOACs, Acenocoumarol

1 | INTRODUCTION

Radiofrequency catheter ablation is widely used for the treatment of atrial fibrillation (AF) in patients who have failed antiarrhythmic drug therapy due to inefficacy or intolerance.[1] Periprocedural management of anticoagulation is a common clinical conundrum that varies greatly between institutions. In the setting of AF catheter ablation, oral anticoagulation (OAC) is the cornerstone in reducing the risk of thromboembolic complications.[2] However, the use of OAC during AF ablation carries the risk of worrisome hemorrhagic events.

Di Biase et al first showed that performing left atrial catheter ablation without warfarin discontinuation reduces the occurrence of periprocedural stroke and minor bleeding complications compared with uninterrupted warfarin and heparin bridging.[3] Additionally, a meta-analysis has demonstrated that stroke incidence drops to 0.06% with uninterrupted warfarin during the perioperative period.[4] Moreover, Expósito et al showed that, during an average follow-up period of 5 years after right atrial flutter ablation, 10% of the patients experienced embolic events, mainly stroke. Of all patients who suffered stroke/systemic embolism following cavotricuspid isthmus ablation, 5 of the 12 had documented AF after their ablation for right atrial flutter.[5]

As a result, continuous warfarin therapy during AF ablation has been recommended in the recent American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines as an alternative to the bridging approach with heparin in patients on vitamin K antagonists (VKAs) prior to catheter ablation.[2] However, the use of warfarin is limited by a narrow therapeutic index that necessitates frequent monitoring and dose adjustments, resulting in substantial risk and inconvenience. Direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban, were recently approved for the prevention of stroke in patients with nonvalvular AF.[6–8] With the advantages of rapid onset, shorter action duration, and fewer drug interactions, DOACs also have become a new option for patients undergoing AF ablation. In recent years, many centers have studied the efficacy and safety of using DOACs during AF ablation.[2] The effect of DOACs after 24 hours is considered to be limited, and it is recommended that the intervention should be scheduled 18 to 24 hours after the last intake.[9] Accordingly, discontinuing DOACs <24 hours before the procedure is considered continuous DOAC treatment, whereas discontinuing the drug ≥24 hours before the procedure is considered interrupted DOAC treatment.

The aim of our study was to evaluate the efficacy and safety of DOAC treatment compared with uninterrupted acenocoumarol treatment during AF catheter ablation.

2 | METHODS

2.1 | Study subjects

Our study prospectively investigated 476 consecutive patients who underwent AF ablation for symptomatic paroxysmal or persistent AF from June 2013 to December 2016. We excluded 2 patients—1 patient in the acenocoumarol group (0.2%) and 1 patient taking dabigatran (0.2%)—because we identified intracardiac thrombus in the left atrial appendage during transesophageal echocardiography (TEE) before performing the procedure. As a result, our cohort consisted of 474 patients (mean age, 58 years; 68.4% male). The patients were separated into 2 groups. Group 1 consisted of 136 patients who had been on a classic vitamin K inhibitor, acenocoumarol, and group 2 consisted of 338 patients who had been on DOAC treatment (eg, rivaroxaban, apixaban, dabigatran) ≥2 months before left atrial ablation. The dose of DOACs was adjusted according to individual patient characteristics (eg, age, creatinine clearance), and the dose of acenocoumarol was adjusted according the international normalized ratio (INR; 2.0–3.0). We compared the safety of uninterrupted acenocoumarol with continuous anticoagulation with DOACs during AF ablation. TEE, as well as transthoracic echocardiography (TTE), was performed in all patients to rule out any left atrial thrombi. Paroxysmal AF was defined as AF that spontaneously terminated within 7 days, and persistent AF was defined as AF that lasted for >7 days. We investigated all the periprocedural thromboembolic or bleeding complications. The study protocol was approved by the local ethics review committees of our institution.

2.2 | Periprocedural anticoagulation strategy

All procedures in group 1 were performed under efficient VKAs (INR 2–3), and acenocoumarol was continued throughout the periprocedural period. In group 2, we prescribed dabigatran, apixaban, or rivaroxaban. The reduced doses of DOACs were prescribed according to each patients' characteristics and drug-dosage instructions.[2] However, a dabigatran dose of 110 mg b.i.d. was administered to 82 patients (72%) because of the delayed release of the standard dose in the Greek market. DOACs were discontinued <24 hours before the procedure, and as a result the procedure was performed with uninterrupted DOAC treatment. In particular, patients in the dabigatran and apixaban groups were instructed to withhold the morning dose on the day of the procedure. Patients in the rivaroxaban group were asked to take their rivaroxaban dose, as scheduled, on the evening prior to the procedure. No heparin was administered to any patient in either group before ablation. Activated clotting time (ACT) was measured from venous blood every 30 minutes until a value within the target range was achieved (ACT of 300–400 s), based on operator preference, for the duration of the left-sided procedure. After the procedure, all sheaths were removed.

2.3 | Catheter ablation procedure

We performed TEE in all patients on the morning of the procedure to assess left ventricular function and to exclude the presence of intracardiac thrombi. Ablation was performed by one of 2 experienced operators (M.E. or K.P.L.). The ablation procedure has been described in detail elsewhere.[9] After a single transseptal puncture, we reconstructed the 3-dimensional geometry of the left atrium using the CARTO 3 navigation system (Biosense Webster, Inc., Diamond Bar, CA). Wide circumferential lesions for antral isolation of large atrial areas around both ipsilateral pulmonary veins were applied using a 3.5-mm-tip ablation catheter (ThermoCool Navi-Star; Biosense Webster). The endpoint of ablation of pulmonary vein antrum isolation was the absence or dissociation of potentials in the isolated area as documented with the circular mapping catheter (Lasso; Biosense Webster). We additionally performed substrate modification in patients having persistent AF. Intravenous unfractionated heparin was administered by bolus injection just after transseptal puncture with an initial dose of 100 U/kg. Patients displaying AF at the end of the procedure underwent electrical cardioversion.

Following completion of ablation, all catheters were removed from the body. All groin sheaths were removed in a specialized

nursing unit, after ACT had declined to <180 s. A pressure bandage over the femoral vein puncture site was applied for a minimum of 12 hours after sheath removal. Pericardial effusion was excluded via TTE directly after the ablation procedure, as well as on day 1 post-ablation. Patients were routinely monitored electrocardiographically overnight and discharged the following day. Demographic, historical, procedural, and laboratory data were recorded for each group. All complications were identified and categorized as bleeding, thromboembolic, or other complications. The patients were advised to receive VKAs or DOACs for ≥2 months after the procedure. Subsequently, the continuation of anticoagulation therapy depended on the CHA_2DS_2-VASc score of each patient.

2.4 | Definition of complications

The analysis included comparisons of both thromboembolic and bleeding complications. Classification of the outcomes was: (1) major bleeding events, including cardiac tamponade, hematomas requiring surgical intervention, any bleeding requiring blood transfusion, massive hemoptysis, hemothorax, retroperitoneal bleeding, and any other life-threatening bleeding leading to prolongation of hospitalization; (2) minor bleeding events, including hematomas or any bleeding event that did not require intervention and pericardial effusions that did not cause hemodynamic compromise requiring intervention; and (3) thromboembolic events, including transient ischemic attack (TIA), stroke, peripheral embolic events, and deep venous thrombosis. We considered as major complications thromboembolic events, pericardial effusions causing tamponade and hemodynamic collapse requiring pericardial drainage, or major hemorrhagic complication causing hemodynamic collapse requiring transfusion. Minor complications were pericardial effusions <1 cm without hemodynamic compromise and without requiring pericardial drainage and hematomas or any bleeding event that did not require intervention, groin hematoma, or arteriovenous (AV) fistula.

2.5 | Statistical analysis

Continuous variables are presented as mean ± SD. Comparing groups, we used the Pearson χ^2 test for categorical variables and the *t* test or Mann-Whitney *U* test for parametric or nonparametric continuous variables, respectively. If there was a small value (<5) in one of the cells, the Fisher exact test was used. All data were analyzed using SPSS software (IBM, Armonk, NY). A *P* value <0.05 was considered to be statistically significant.

3 | RESULTS

Out of 474 patients prospectively assigned, 136 (28.7%) were treated with uninterrupted acenocoumarol (INR 2–3; group 1) and 338 patients (71.3%) with DOACs (group 2). Specifically, group 2 consisted of 110 (23.2%) patients who received rivaroxaban, 114 (24.1%) apixaban, and 114 (24.1%) dabigatran. The baseline characteristics of the patients are shown in Table 1. Overall, the 2 groups were well matched with respect to age, sex, body mass index, left ventricular ejection fraction, renal function, and AF type ($P > 0.05$). CHA_2DS_2-VASc and HAS-BLED scores were similar between the 2 groups ($P > 0.05$). Patients in group 1 had a statistically significant higher prevalence of coronary artery disease compared with group 2.

TABLE 1 Baseline characteristics

Characteristic	Acenocoumarol vs DOACs		P Value
	Acenocoumarol, n = 136 (28.7)	DOACs, n = 338 (71.3)	
Age, y	58.91 ± 10	57.69 ± 11.7	0.293
Male sex	95 (69.9)	229 (67.8)	0.656
BMI, kg/m^2	32.06 ± 40.4	27.74 ± 13.4	0.086
LVEF, %	59.42 ± 7.3	60.34 ± 6.7	0.646
Cr, mg/dL	0.85 ± 0.2	0.84 ± 0.2	0.714
CHA_2DS_2-VAS_C score	1.40 ± 1.1	1.26 ± 1.2	0.225
HAS-BLED score	0.79 ± 0.8	0.75 ± 0.8	0.683
Type of AF (paroxysmal)	79 (58.1)	221 (65.4)	0.136
CAD	14 (10.3)	13 (3.8)	0.006
Dyslipidemia	44 (32.4)	114 (33.7)	0.774
DM	9 (6.6)	27 (8.0)	0.610
HTN	67 (49.3)	139 (41.1)	0.106

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHA_2DS_2-VASc, congestive HF, HTN, age ≥75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (female); DM, diabetes mellitus; DOAC, direct oral anticoagulant; HAS-BLED, HTN, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR, age >65 y; HF, heart failure; HTN, hypertension; INR, international normalized ratio; LVEF, left ventricular ejection fraction; SD, standard deviation; TIA, transient ischemic attack.

Data are presented as n (%) or mean ± SD.

The periprocedural complications throughout a follow-up period of 90 days are depicted in Table 2. Specifically, 4 (0.8%) of 474 patients had major complications, and 9 (1.9%) patients had minor complications. There were no statistically significant differences for overall complications within 90 days after ablation between the study groups. In group 1, 3 patients (2.2%) suffered a major complication. In particular, 1 patient (0.7%) had a TIA that resolved 8 hours later, 1 (0.7%) had pericardial tamponade causing hemodynamic compromise requiring pericardial drainage, and 1 (0.7%) had subcapsular renal hematoma requiring blood transfusion and hospitalization for 15 days. About the minor complications, we had 1 patient with pseudoaneurysm (0.7%) and 1 (0.7%) with groin hematoma. On the other hand, only 1 patient (0.3%) from group 2 had a major complication. The patient presented with TIA during AF ablation that resolved 20 hours later. In the same group, 7 (2.1%) patients had a minor complication. Specifically, 1 patient (0.3%) presented with pseudoaneurysm, 4 patients (1.2%) with pericardial effusion <1 cm not requiring pericardial drainage, 1 patient (0.3%) with femoral AV fistula between femoral artery and femoral vein not requiring intervention that resolved with compression, and 1 (0.7%) with a groin hematoma not requiring intervention. The subanalysis of group 2 according to the specific type of DOAC showed that 2 patients (1.8%) using rivaroxaban and 2 patients (1.8%) using apixaban had a pericardial effusion <1 cm without hemodynamic compromise and not requiring pericardial drainage. Femoral AV fistula that resolved

TABLE 2 Comparison of the periprocedural complications in the 2 patient groups undergoing AF catheter ablation

	Acenocoumarol vs DOACs			
Complications	Acenocoumarol, n = 136	DOACs, n = 338	Total	*P* Value
Major complications	3 (2.2)	1 (0.3)	4 (0.8)	0.073
TIA	1 (0.7)	1 (0.3)	2 (0.4)	0.492
Tamponade	1 (0.7)	0 (0)	1 (0.2)	0.287
Subcapsular renal hematoma	1 (0.7)	0 (0)	1 (0.2)	0.287
Minor complications	2 (1.5)	7 (2.1)	9 (1.9)	1.000
Pseudoaneurysm	1 (0.7)	1 (0.3)	2 (0.4)	0.492
Pericardial effusion	0 (0)	4 (1.2)	4 (0.8)	0.582
Femoral AV fistula	0 (0)	1 (0.3)	1 (0.2)	1.000
Groin hematoma	1 (0.7)	1 (0.3)	2 (0.4)	0.492

Abbreviations: AF, atrial fibrillation; AV, arteriovenous; DOACs, direct oral anticoagulants; TIA, transient ischemic attack.

Data are presented as n (%).

with compression developed in 1 patient (0.9%) in the apixaban group. In the dabigatran group of 110 mg, 1 patient (0.9%) had a TIA that resolved 20 hours later, 1 patient (0.9%) had pseudoaneurysm, and 1 patient (0.9%) had a groin hematoma, both of them not requiring intervention (Table 3).

4 | DISCUSSION

To the best of our knowledge, our study is one of the largest prospective studies described in the literature comparing thromboembolic and bleeding complications between uninterrupted acenocoumarol and continuous use of DOACs during AF ablation. The main findings of the present study are: (1) there was no significant difference in thromboembolic and bleeding complications between patients treated with uninterrupted acenocoumarol or continuous oral anticoagulation with DOACs during left atrial ablation for paroxysmal or persistent AF; and (2) DOACs (rivaroxaban, apixaban, and dabigatran) are effective treatment options for preventing thromboembolic events without significantly increasing hemorrhagic complications. Mitigating risk of cerebrovascular accident or other thromboembolic events in patients undergoing left atrial ablation for management of AF has substantially improved in the era of performing procedures on uninterrupted or minimally interrupted anticoagulation.[4,10,11] In the context of this more widespread practice, periprocedural cerebrovascular accident rates have declined from 5% to 7% to as low as 0.11% to 0.22%, and without significant increases in serious bleeding events.[4,12] Di Biase et al went even further in challenging the notion that pre-ablation TEE may be unnecessary by completely omitting it from AF ablation procedures in 970 patients treated with uninterrupted rivaroxaban or apixaban.[10]

Warfarin was the mainstay of anticoagulation in AF catheter ablation procedures. Historically, warfarin was discontinued before the procedure, and patients were "bridged" with heparin before and after the ablation procedure. Although widely adopted, this approach of anticoagulation changed recently, and more physicians prefer continuous anticoagulation during AF ablation.[13] The efficacy and safety of continuous warfarin have been shown recently in the prospective and randomized Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation Patients Undergoing Catheter Ablation (COMPARE) study.[3] This was the first randomized study showing that performing catheter ablation of AF without warfarin discontinuation and with a therapeutic INR in patients at high risk for stroke significantly reduces the occurrence of periprocedural stroke/TIA with minor bleeding complications. Therefore, continuous warfarin is currently preferred over warfarin discontinuation and bridging with low-molecular-weight heparin.[13] Warfarin is used more frequently than acenocoumarol because of its longer half-life (36 hours), theoretically providing more stable anticoagulation, and avoidance of factor VII fluctuations that potentially occur during acenocoumarol treatment (half-life, 10 hours).[14] However, in our study we preferred to use uninterrupted acenocoumarol (INR 2–3) during left atrial ablation for AF, knowing its safety from our previous study comparing uninterrupted acenocoumarol and dabigatran 110 mg b.i.d.[15]

TABLE 3 Comparison of periprocedural complications in the 3 patient groups receiving DOACs

	(Total No. of Patients = 474)							
	Acenocoumarol, n = 136 (28.7%)		Rivaroxaban, n = 110 (23.2%)		Apixaban, n = 114 (24.1%)		Dabigatran, n = 114 (24.1%)	
Complications	N	%	N	%	N	%	N	%
None	131	96.3	105	98.2	111	97.3	111	97.4
Major complications	3	2.2	0	0.0	0	0.0	1	0.9
TIA	1	0.7	0	0.0	0	0.0	1	0.9
Tamponade	1	0.7	0	0.0	0	0.0	0	0.0
Subcapsular renal hematoma	1	0.7	0	0.0	0	0.0	0	0.0
Minor complications	2	1.5	2	1.8	3	2.6	2	1.8
Pseudoaneurysm	1	0.7	0	0.0	0	0.0	1	0.9
Pericardial effusion	0	0.0	2	1.8	2	1.8	0	0.0
Femoral AV fistula	0	0.0	0	0.0	1	0.9	0	0.0
Groin hematoma	1	0.7	0	0.0	0	0.0	1	0.9

Abbreviations: AV, arteriovenous; DOACs, direct oral anticoagulants; TIA, transient ischemic attack.

Another emerging anticoagulation strategy involves the use of novel oral anticoagulants, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban, all of which are approved for systemic anticoagulation in patients with nonvalvular AF. Recently, Calkins et al, in the Uninterrupted Dabigatran Etexilate in Comparison to Uninterrupted Warfarin in Pulmonary Vein Ablation (RE-CIRCUIT) trial, a randomized, open-label, multicenter, controlled study, showed that in patients undergoing ablation for AF, anticoagulation with uninterrupted dabigatran is associated with fewer bleeding complications than is uninterrupted warfarin.[16] Lakkireddy et al[17] also described a higher rate of major bleeding complications for dabigatran compared with warfarin, whereas most other published studies showed that dabigatran is equivalent to warfarin for periprocedural anticoagulation in left atrial ablation procedures.[18–21]

We also showed in our study the efficacy and safety of continuous anticoagulation with rivaroxaban and apixaban. It is interesting to highlight that patients treated with rivaroxaban and apixaban had no major complication regarding thromboembolic and hemorrhagic events. In concordance with our results, Lakkireddy et al demonstrated that uninterrupted rivaroxaban is as safe and efficacious in preventing bleeding and thromboembolic events in patients undergoing AF ablation as is uninterrupted warfarin therapy.[11] Tao et al also confirmed our results in their prospective study clarifying the safety and efficacy of using uninterrupted morning rivaroxaban for anticoagulation during AF ablation, especially with regard to asymptomatic cerebral embolism and anticoagulation parameters.[22] In addition, Kuwahara et al reported that apixaban 5 mg or 2.5 mg b.i.d. has similar safety and effectiveness to warfarin for the prevention of cerebral thromboembolism during the periprocedural period of AF ablation.[23] It is worth mentioning that out of 474 patients enrolled in our study, we had only 4 (0.8%) major complications, 3 in the group of uninterrupted acenocoumarol and 1 (0.2%) TIA in the dabigatran group. There was no major bleeding complication in the DOAC group regarding hemorrhagic complication severe enough to require blood transfusion or pericardial tamponade causing hemodynamic compromise.

Finally, in our study we identified with TEE only 2 out of 476 (0.4%) patients having intracardiac thrombus before the procedure when we prepared the patient with OAC ≥2 months before left atrial ablation. One patient was taking acenocoumarol targeting (INR 2–3) and the other dabigatran 110 mg b.i.d. This finding is in agreement with the study of Di Biase et al, who illustrated that AF ablation while on uninterrupted apixaban and rivaroxaban without TEE is feasible and safe. A recent meta-analysis demonstrated that periprocedural DOAC therapy was as effective as continuous warfarin therapy for preventing thromboembolism and had a lower incidence of bleeding complications.[24]

4.1 | Study limitations

The first limitation of this study is that it represents a nonrandomized post hoc analysis of registry data. However, all data were prospectively collected and the 2 study groups were well matched. Second, we did not perform analyses based on the time in therapeutic range, which is an important indicator that evaluates the anticoagulant effect of acenocoumarol or DOACs.

5 | CONCLUSION

Our study illustrates that performing AF ablation is feasible and safe regarding periprocedural thromboembolic and bleeding complications while the patient is on uninterrupted acenocoumarol or continuous dabigatran, apixaban, and rivaroxaban.

Conflicts of interest

The authors declare no potential conflicts of interest.

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