

UBLED AF (Uninterrupted Blackpool EDOxaban vs Warfarin vs Rivaroxaban in Atrial Fibrillation/Flutter ablation) Study

Narendra Kumar¹; Noha Elbanhawy¹; Moinuddin Choudhury¹; Rahul Potluri²; Shajil Chalil¹; Khalid Abozguia²

¹Cardiology Department, Lancashire Cardiac Centre, Blackpool Teaching Hospitals NHS Trust, Blackpool, UK, FY3 8NR.

²Department of Cardiology, Bedford Hospital, Bedfordshire Hospitals NHS Foundation trust, Bedford, UK.

Abstract

Aim: Catheter ablation in patients with atrial fibrillation (AF)/atrial flutter carries a risk of thromboembolism and major bleeding. In light of recent prospective trial data on the safety and efficacy of uninterrupted edoxaban in patients undergoing AF/flutter ablation, real-world data was aimed for validation.

Methods: A total of 228 patients who underwent AF/atrial flutter ablation over 14 months at our centre were retrospectively analyzed. All patients received uninterrupted oral anticoagulation for at least 4 weeks prior to ablation and 3 months post-ablation. Both bleeding and thromboembolic events were assessed at 24 hours comparing patients on warfarin, rivaroxaban and edoxaban.

Results: Mean age of patients were 68.5 +/- 8 years in the warfarin group (N =86), 63.4 +/- 10.6 years; in the edoxaban group (N =63) and 62.3 +/- 11.6 years in the rivaroxaban group (N =79). CHADSVASc scores were 2.43 +/- 1.34, 1.68 +/- 1.34 and 1.64 +/- 1.38 respectively. The mean left atrial sizes were 42.7 +/- 6.8 mm, 42.0 +/- 6 mm and 41.1 +/- 6.5 mm respectively. The study endpoint was death, acute thromboembolism or major bleeding. There was 1 pericardial effusion (1.2%) in the warfarin group, 1 pericardial effusion and 1 transient ischaemic attack (2.5%) in the rivaroxaban group and 1 pericardial effusion needing drainage (1.6%) in the edoxaban group. There were no significant differences in the study endpoints between groups.

Conclusion: This real-world study demonstrated no significant difference in safety and efficacy between uninterrupted edoxaban, warfarin and rivaroxaban in patients undergoing AF/flutter ablation.

Introduction

AF ablation is technically challenging and is associated with peri-procedural risks including thromboembolic events (<1%), bleeding complications related to tamponade (1-2%) and vascular complications (2-4%). The increased risk of thromboembolic complications is likely related to the exacerbation of the baseline pro-thrombotic state by catheters in the left atrium (LA), endothelial denudation, char formation and tissue inflammation from ablation in the LA. Minimizing these complications with optimal peri-procedural anticoagulation with an appropriate balance between bleeding and thrombosis is critical to the safety of the procedure. Optimal peri-procedural anticoagulation protocols to minimize these complications are still largely debated and are non-uniform.^{1,11,12}

Key Words

Catheter Ablation; Atrial Fibrillation; Edoxaban; Complications; Anticoagulation.

Corresponding Author

Narendra Kumar, Lancashire Cardiac Centre,
Blackpool Victoria Hospital, Whinney Heys Rd, Black pool FY3 8NR, UK.

Studies have started focusing on the use of direct oral anticoagulants (DOACs) in the peri-procedural period and compared them to warfarin in terms of bleeding and thromboembolic complications. In a meta-analysis of 70 studies with 4962 patients, it was concluded that DOACs were both safe and effective when used in an uninterrupted fashion in patients undergoing AF ablation²⁻⁴. The incidence of cerebral thromboembolic events was low with these agents and not significantly different from uninterrupted VKAs, whereas major bleeding was significantly reduced with DOACs.^{2,9,10}

There is still shortage of real world clinical data have evaluating the uninterrupted rivaroxaban and apixaban individually in patients undergoing AF ablation³⁻⁵. Recently, ELIMINATE - AF study compared the safety and efficacy of edoxaban with warfarin in patients undergoing AF ablation with endpoints of death, stroke or major bleeding.

Complimenting this data, UBLED AF study aimed to evaluate real-world data observed from our own centre on the safety and efficacy of

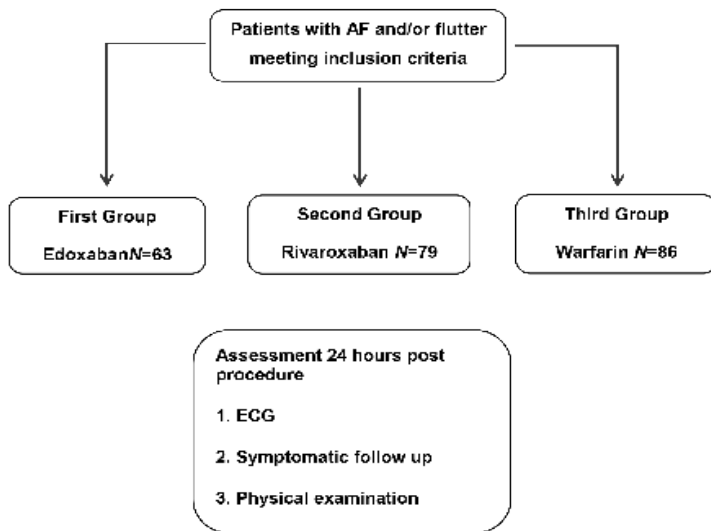


Figure 1: Study Method and Follow-up Flow Chart

Patients on uninterrupted anticoagulation 4 weeks prior to and 3 months post AF/flutter ablation with edoxaban were compared with those on rivaroxaban and warfarin. Records of assessment at 24 hours post-procedure were used to evaluate the occurrence of complications.

uninterrupted edoxaban in the peri-procedural period in cases of AF and atrial flutter ablation compared to warfarin and rivaroxaban.

Methods

A total of 228 patients who underwent AF and atrial flutter ablation on uninterrupted anticoagulation using edoxaban, rivaroxaban and warfarin over 14 months were reviewed retrospectively in this observational study. Patients on twice a day dosage of dabigatran and apixaban were excluded because our local practice was to interrupt anticoagulation on the day of the procedure with these DOACs.

The first group consisted of all patients on edoxaban, the second group all patients on rivaroxaban and third group those on warfarin during their ablation. All anticoagulation was uninterrupted for at least 4 weeks prior to ablation and 3 months post-ablation. For patients on warfarin, INRs were maintained above 2 for at least 4 weeks before the procedure. Baseline evaluation included a transthoracic echocardiogram, blood tests and a 12 lead ECG (Figure 1).

Patients were instructed to take their medication in the evening prior to the procedure. All patients were hence on uninterrupted anticoagulation on the day of the procedure. It was resumed 4-6 hours after haemostasis following ablation.

Transoesophageal echocardiography was performed if indicated to rule out LA appendage thrombus and to guide trans-septal puncture during the procedure. During the ablation procedure, a bolus of 100 IU/kg body weight of unfractionated heparin was given around the time of trans-septal puncture. The activated clotting time (ACT) was maintained between 300 to 400 s while catheters remained in the LA. The technique of the procedure was at the discretion of the operator but remained similar between the 3 operators involved.

Bleeding events were defined as any bleeding requiring blood transfusion, haematomas requiring surgical intervention, and

pericardial effusions. Cerebrovascular accidents and transient ischaemic attacks were considered thromboembolic complications after ruling out intracranial haemorrhage.

The documentation of the reassessment of patients at 24 hours post AF and atrial flutter ablation was reviewed carefully which was part of standard care and which recorded any adverse events up until that time.

Formal ethical approval was not required due to the local, retrospective and observational nature of the study. However, appropriate protection of patient information and data was ensured.

Statistical Analysis

Data between the warfarin, rivaroxaban and edoxaban groups were analysed using multivariate analysis with age and gender as covariates. Warfarin and rivaroxaban were used as references, respectively. Statistical analyses were descriptive. All continuous variables were expressed in terms of mean and standard deviation. Categorical data were expressed as numbers and proportions. Probability values of <0.05 were considered to be statistically significant. All analysis was performed using SPSS software.

Results

Table 1: Patient Characteristics

Patient Characteristics	Warfarin N=86	Edoxaban N=63	Rivaroxaban N=79
Age (years)	68.5 +/- 8.0	63.4 +/- 10.6	62.3 +/- 11.6
Gender, n (%)			
Male	52 (60.5)	45 (71.4)	56 (70.9)
Female	34 (39.5)	18 (28.6)	23 (29.1)
Medical History, n (%)			
HTN	40 (46.5)	24 (38.1)	24 (30.4)
DM	8 (9.3)	6 (9.5)	4 (5.1)
CVA/TIA	4 (4.7)	2 (3.2)	5 (6.3)
CAD/PVD	16 (18.6)	9 (14.3)	12 (15.2)
CHF	15 (17.4)	8 (12.7)	11 (13.9)
CHADS ₂ Sc	2.43 +/- 1.34	1.68 +/- 1.34	1.64 +/- 1.38
Baseline ECG, n (%)			
SR	36 (41.9)	31 (49.2)	45 (57.0)
AF/AT	50 (58.1)	32 (50.8)	34 (43.0)
LA diameter (mm)	42.7 +/- 6.8	42.0 +/- 6.0	41.1 +/- 6.5
Antiplatelet Drugs, n (%)			
Aspirin	3 (3.5)	4 (6.3)	4 (5.1)
Clopidogrel	4 (4.7)	1 (1.6)	2 (2.5)
Ticagrelor	1 (1.2)	0	0
Antiarrhythmic Type Drugs, n (%)			
Flecainide	11 (12.8)	7 (1.1)	14 (17.7)
Sotalol	7 (8.1)	2 (3.2)	2 (2.5)
Dronedarone	5 (5.8)	0	1 (1.3)
Amiodarone	9 (10.5)	1 (1.6)	6 (7.6)
Rate Limiting Drugs, n (%)			
Beta-blockers	70 (81.4)	44 (69.9)	60 (76.0)
Ca ²⁺ -channel blockers	12 (14.0)	6 (9.5)	6 (7.6)
Digoxin	17 (19.8)	9 (14.3)	7 (8.9)

Continuous variables reported as a mean +/- standard deviation (SD) and categorical data as numbers and proportions.

Table 2: Procedure Characteristics

Procedure Characteristics	Warfarin N=86	EdoxabanN=63	Rivaroxaban N=79
AF Ablation Only, n (%)	70 (81.4)	42 (66.7)	53 (67.1)
Flutter Ablation Only, n (%)	13 (15.1)	18 (28.6)	17 (21.5)
Combination AF/Flutter, n (%)	3 (3.5)	3 (4.8)	9 (11.4)
AF type, n (%)			
Paroxysmal	27 (31.4)	21 (33.3)	35 (44.3)
Persistent	46 (53.5)	24 (38.1)	27 (34.2)
Type of Anaesthesia, n (%)			
Local	46 (53.5)	36 (57.1)	48 (60.8)
General	40 (46.5)	27 (42.9)	31 (39.2)
Ablation Energy Used, n (%)			
Laser	13 (15.1)	18 (28.6)	21 (26.6)
Cryoablation	4 (4.7)	9 (14.3)	2 (2.5)
RF*	69 (80.2)	36 (57.1)	56 (70.9)
Type of Procedure, n (%)			
De novo	53 (61.6)	46 (73.0)	70 (88.6)
Redo	33 (38.4)	17 (27.0)	9 (11.4)
INR (if applicable), n (%)			
Less than 2	2 (2.3)	N/A	N/A
2-3	81 (94.2)	N/A	N/A
More than 3	3 (3.5)	N/A	N/A
Closure, n (%)			
Manual only	6 (7.0)	4 (6.3)	3 (3.8)
Z-suture only	5 (5.8)	12 (19.0)	4 (5.1)
Femstop only	71 (82.6)	44 (69.8)	71 (89.9)
Combination	4 (4.7)	3 (4.8)	1 (1.3)
Fluoroscopy Dose (MGy)	71.8	49.7	57.4
Fluoroscopy Time (min)	16.5 +/- 10.6	14.8 +/- 9.2	14.8 +/- 10.4

Continuous variables reported as a mean±standard deviation (SD) and categorical data as numbers and proportions, *RF = radiofrequency.

A total of 228 adult patients with non-valvular AF/atrial flutter who underwent elective catheter ablation over 14 months were studied. Baseline patient characteristics were similar (Table 1). The warfarin group (N=86) included 52 males and 34 females with a mean age of 68.5 ± 8 years and a mean CHADSVASc score of 2.43 ± 1.34. The edoxaban group (N=63) included 45 males and 18 females with a mean age of 62.3 ± 10.6 years and a mean CHADSVASc score of 1.68 ± 1.34. The rivaroxaban group (N=79) included 56 males and 23 females with a mean age of 62.3 ± 11.6 years and a mean CHADSVASc score of 1.64 ± 1.38. The mean LA sizes were 42.7 ± 6.8 mm, 42.0 ± 6 mm and 41.1 ± 6.5 mm respectively (P=0.473). Proportions of comorbidities, baseline ECG rhythm and medications are shown in table 1.

Procedural characteristics were also similar (Table 2). The proportion of patients who underwent AF ablation only in the warfarin group was 81.4%, in the edoxaban group 66.7% and in the rivaroxaban group 67.1%. The proportion of patients who underwent atrial flutter ablation only in the warfarin group was 15.1%, in the edoxaban group 28.6% and in the rivaroxaban group 21.5%. The remaining patients underwent both AF and atrial flutter ablations during the same procedure. Other features compared in table 2 are AF type, anaesthesia type, ablation energy type, de novo versus redo procedure, INR level (for warfarin

only), closure method, fluoroscopy dose and fluoroscopy time. There was a single case of TIA noticed in patient on uninterrupted Rivaroxaban. On an overall basis, as per table 3, 2 patients on rivaroxaban had minor acute bleeding complications (HR (95% CI); P value rivaroxaban vs warfarin 1.09 (0.07 – 17.45); 0.95 HR (95% CI) and P value rivaroxaban vs edoxaban 0.80 (0.05 – 12.98); 0.87). There was single case of pericardial effusion (1.2%) in the warfarin group. However, 1 pericardial effusion and 1 transient ischaemic attack (2.5%) were observed in the rivaroxaban group and 1 pericardial effusion needing drainage (1.6%) in the edoxaban group. There were no significant differences in the study endpoints between groups.

Endpoints

There were no deaths in any group in this study. There was 1 bleeding event in each of the three groups in the form of pericardial effusions, resolving spontaneously except in the case of edoxaban where drainage was required. There was 1 thromboembolic event in the rivaroxaban group which was a transient ischaemic attack. The total event rate was therefore 1.2% in the warfarin group, 2.5% in the rivaroxaban group and 1.6% in the edoxaban group, with P values of 0.83 comparing edoxaban to warfarin, 0.51 comparing rivaroxaban to warfarin and 0.70 comparing rivaroxaban to edoxaban (Table 3).

Discussion

During the last decade, several new oral anticoagulants have been approved for clinical use including apixaban and edoxaban. NOACs have made their way into the guidelines for non-valvular AF due to multiple advantages compared to warfarin; e.g., chances for drug-to-drug interaction, the variation in dosage to response, and a narrow therapeutic window, to name a few.

There is lack of clinical studies which have compared traditional uninterrupted warfarin to all the new oral anticoagulants for patients who are undergoing atrial fibrillation or atrial flutter ablation. The current ACC/AHA/EHRA/APHRS guidelines support use of new oral anticoagulants compared to warfarin. All 3 operators at our centre used similar techniques for anticoagulation, trans-septal puncture and performing ablation in this study. Protocol for anticoagulation during the procedure with IV heparin was also standard within the department, using 100 IU/kg around the time of trans-septal puncture and maintaining an ACT target >300 seconds.

These data were collected several years ago, and the local practice was to continue the same anticoagulant for a patient already on warfarin. However, our practice has changed over the last few years where most patients get started in DOAC as per national and international guidelines. We compared uninterrupted edoxaban to VKAs and rivaroxaban in patients with atrial fibrillation or atrial flutter undergoing ablation procedure. No significant difference was found in acute complications including bleeding and thromboembolic events between all 3 groups (a total of 4 across all groups, including 1 pericardial effusion in each group and 1 transient ischaemic attack in the rivaroxaban group). In our observational study, the event rate for complications was very low across all groups. At local Institute, reversal agents are given for any cases that needed pericardiocentesis. The anticoagulation is immediately restarted once patient is stable and confirmed by a cardiac echo. The remaining cases were managed

conservatively without reversal. Anticoagulation was recommenced within 24 hours after confirmation with serial echo.

Randomised control trials have been conducted to assess the safety of uninterrupted rivaroxaban (VENTURE-AF)⁴, dabigatran (RE-CIRCUIT)³, apixaban (AXAFA-AFNET 5)⁵ and most recently edoxaban (ELIMINATE-AF) peri-procedurally.⁶

VENTURE-AF was the first randomised trial to compare rivaroxaban to VKAs in an uninterrupted fashion for peri-procedural anticoagulation in patients with non-valvular AF. It showed that the incidence of major bleeding was low (0.4%; 1 major bleeding event). Similarly, thromboembolic events were low (0.8%; 1 ischemic stroke and 1 vascular death). All events occurred in the VKA arm and all after catheter ablation. The study concluded that in patients undergoing catheter ablation for AF, the use of uninterrupted rivaroxaban was feasible and event rates were similar to those for uninterrupted VKA therapy.⁴ Similarly, in the randomised trial RE-CIRCUIT comparing dabigatran to VKAs, the incidence of major bleeding events during and up to 8 weeks after ablation was lower with dabigatran than with warfarin (5 patients [1.6%] vs. 22 patients [6.9%], $P=0.001$). Dabigatran was associated with fewer peri-procedural pericardial tamponades and groin haematomas than warfarin. The two treatment groups had a similar incidence of minor bleeding events. One thromboembolic event occurred in the warfarin group.³

In the randomised AXAFA-AFNET 5 trial, uninterrupted apixaban was compared to uninterrupted warfarin. The primary outcome was a composite of death, stroke or major bleeding, which were observed in 22 of 318 patients on apixaban and 23 of 315 patients on warfarin (non-inferiority $P=0.0002$). There was 1 death in each group and 2 strokes in the apixaban group. There were 2 tamponades managed with drainage in the apixaban group compared to 5 in the warfarin group. The study concluded that apixaban was non-inferior to warfarin in terms of safety and efficacy when used without interruption peri-procedurally.⁵

The ELIMINATE-AF trial was a prospective randomised study which was conducted to assess the safety and efficacy of once-daily edoxaban 60 mg (30 mg in patients indicated for dose reduction) vs VKAs in non-valvular AF patients undergoing catheter ablation. In this study, a total of 614 patients were randomised to edoxaban or VKAs (at a 2:1 ratio) to obtain 417 patients fully compliant with the protocol. The primary efficacy endpoint was a composite of all-cause death, stroke and major bleeding with a primary safety endpoint of major bleeding.⁶ The primary endpoint in the 'per-protocol population was observed in 1.3% of edoxaban (N=4) and 3% of VKA patients (N=3) between the start of ablation and the end of treatment. In the intention-to-

treat population, which included patients who received at least one dose of the study drug but did not necessarily undergo ablation, the primary endpoint was seen in 2.5% of edoxaban (N=10) and 1.5% of VKA patients (N=3). Pericardial tamponade occurred in 3 patients on edoxaban and 2 patients on VKA. Puncture site bleeding occurred in 3 edoxaban patients and 1 VKA patient. There were 2 intracranial bleeds and 1 gastrointestinal bleed in the edoxaban group. There was 1 ischaemic and 1 haemorrhagic stroke, both in patients on edoxaban. Small cerebral micro-emboli were detected in 13.8% (16 patients) of those who received edoxaban and 9.6% (5 patients) of those in the VKA group ($P=0.62$). The overall hazard ratio was 1.68 (confidence interval 0.46 - 6.47). The study concluded that uninterrupted edoxaban therapy represented a valid alternative to uninterrupted VKA treatment in patients undergoing AF ablation.⁶

In a 2017 meta-analysis of databases comparing DOACs to warfarin in patients undergoing AF ablation, the risk of clinical thromboembolic events was exceedingly low and not significantly different between groups and it also showed that silent cerebral events could occur in 1 in 10 patients despite uninterrupted anticoagulation.^{2,7,8} In terms of major bleeding, it was halved with uninterrupted DOACs compared with uninterrupted VKAs and this difference was persistent in a subgroup analysis of randomised and cohort studies with matched controls.

Our real-world data, therefore, supports the randomised trials, namely both ELIMINATE-AF and VENTURE-AF trials, to suggest that edoxaban is similar in safety and efficacy to warfarin and rivaroxaban when used peri-procedurally during AF / atrial flutter ablation.

Study Limitations

This was an observational study subject to confounding and selection bias. The event rate was low and therefore subject to error. This was a single-centre study; however, a strength is that all 3 operators had similar techniques for anticoagulation, trans-septal puncture and performing ablation. A complete dataset for the ACT measured during each procedure was not available; however, standard practice was similar in all cases with IV heparin given at 100 IU/kg maintaining an ACT target >300 seconds. Patients on dabigatran and apixaban were excluded since they are both administered twice daily and local practice at this hospital is to omit the morning dose of these DOACs on the day of the procedure; thus, we were not using them in an uninterrupted fashion.

Conclusion

In this single-centre observational study, there was an overall low number of acute bleeding and thromboembolic complications with no significant difference among all 3 groups. This real-world study further suggests that edoxaban carries a similar safety and efficacy profile

Table 3: Acute Complications

Acute Complication	Warfarin N=86	Edoxaban N=63	Rivaroxaban N=79	HR (95% CI); P value warfarin vs edoxaban	HR (95% CI); P value rivaroxaban vs warfarin	HR (95% CI); P value rivaroxaban vs edoxaban
Total, n (%)	1 (1.2)	1 (1.6)	2 (2.5)	0.73 (0.04 - 12.11); 0.83	2.18 (0.23 - 20.97); 0.51	1.59 (0.16 - 15.56); 0.70
CVA/TIA, n (%)	0	0	1 (1.3)	NS	0.30	0.37
Bleeding, n (%)	1 (1.2)	1 (1.6)	1 (1.3)	0.73 (0.04 - 12.11); 0.83	1.09 (0.07 - 17.45); 0.95	0.80 (0.05 - 12.98); 0.87

HR = hazard ratio, CI = confidence interval, NS = not significant

compared to warfarin and rivaroxaban when used in an uninterrupted fashion peri-procedurally for AF/ atrial flutter ablation.

Disclosures

Dr K Abozguia has received honoraria from Daiichi Sankyo, Bayer and Boehringer Ingelheim; Dr S Chalil has received honoraria from Daiichi Sankyo, Bayer, Boehringer Ingelheim and BMS/Pfizer; all other authors have no conflicts to declare.

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