

Non-vitamin K Oral Anticoagulants in Hypertrophic Cardiomyopathy Patients Undergoing Catheter Ablation of Atrial Fibrillation

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Abstract

Introduction: Patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF) require chronic anticoagulation due to a high thromboembolic risk. Evidence supporting use of non-vitamin K oral anticoagulants (NOACs) in patients with HCM remains sparse, and there are no data regarding the use of NOACs in HCM patients undergoing catheter ablation of AF. **Methods:** Observational non-randomised study in 4 European Centres. We aimed to investigate the safety and efficacy of NOACs compared with vitamin-K antagonists (VKAs) in patients with HCM undergoing catheter ablation for AF. **Results:** One hundred thirty-seven HCM patients (mean age 55.0 ± 13.4 , 29.1% female) underwent 230 catheter ablations for AF (1.7 ± 1.0 per patient). A total of 55 patients (39.4%) underwent 70 procedures (30.4%) on NOAC, while the remaining were on VKA. Warfarin (97.6%) and rivaroxaban (56.4%) were the most frequently used agents in the respective groups. No procedure-related deaths were reported. We observed no significant difference in the rate of thromboembolism (VKA 0.6%; NOAC 0%; $p=1.0$) or minor bleeding (VKA 0.6%; NOAC 1.4%; $p=0.54$). There was a non-significant trend towards a lower incidence of major bleeding (VKA 6.8%; NOAC 1.4%; $p=0.09$). **Conclusion:** These preliminary data suggest that NOACs are at least as safe and effective as VKAs in patients with HCM undergoing catheter ablation for AF.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most frequent monogenic cardiovascular disease and affects 1 out of every 500 individuals [1]. Atrial fibrillation (AF) is a common feature of HCM, with an estimated prevalence of 22.5% [1]. Given the high thromboembolic risk in HCM patients with concomitant AF, life-long oral anticoagulation is recommended, regardless of the CHA₂DS₂VASc score [2-3].

Non-vitamin K anticoagulants (NOACs) have emerged as a valid and more practical alternative to vitamin

K antagonists (VKAs) [4]. Even though data supporting the use of NOACs in patients with HCM and AF are sparse, recent observational studies suggest that NOACs might be safely used in this population [5].

Catheter ablation is an established treatment for AF and is also used in subjects with HCM [1]. Peri and post-operatively patients are exposed to an increased risk of thromboembolism [6]. Complications can occur in up to a fifth of HCM patients undergoing AF ablation [7]. Although observational studies suggest that ablation can be safely performed in HCM patients on VKA [1], the safety and efficacy of such a procedure while on NOACs has not yet been established. The aim of this study was to address this knowledge gap.

Methods

Study design

Observational study in four European centres. We included all patients aged over 18 with confirmed diagnosis of HCM undergoing a catheter ablation for AF. According to the guidelines of the European Society of Cardiology [2], HCM was defined as a wall thickness ≥ 15 mm in one or more left ventricular myocardial segments (on either echocardiogram or cardiac magnetic resonance imaging) that is not explained solely by loading conditions. Participants needed to be on effective oral anticoagulation (VKA, apixaban, edoxaban, rivaroxaban, or dabigatran) for at least 30 days before the procedure to be considered for inclusion. Patients on VKA had a target INR of 2-3. Peri-procedure interruption or continuation of the oral anticoagulants, with or without heparin bridging, was based on the local protocol of each centre at the time of the ablation. In patients elected to VKA interruption with heparin bridging, the VKA was substituted 3 days before the procedure with enoxaparin 100 IU/kg twice a day or dalteparin 200 IU/kg daily. All patients provided written informed consent prior to the procedure. The study complied with the Declaration of Helsinki and the research protocol was approved by the local ethics or audit committees.

Catheter ablation

Procedures were performed under sedation or general anaesthesia, according to each institution's protocol. Venous access was obtained via the femoral vein, with use of vascular ultrasound at operator's discretion. In the absence of patent foramen ovale, a single or dual transseptal puncture was performed under fluoroscopic guidance. Transesophageal echocardiography (TOE) was used based on operator preference. Patients received intravenous heparin to maintain an activated clotting time of 300–350 seconds. Pulmonary vein isolation was the main procedural end-point, and was performed as a first step in all procedures. Additional substrate modification was at operator's discretion. Patients were evaluated before discharge, at 30-days, and 3-months after the procedure, additional visits and further testing were allowed in case of symptoms.

Thromboembolic and bleeding events

The following safety and efficacy endpoints were assessed [8]:

1. All-cause peri-procedural death.
2. Thromboembolism, which was defined as a composite of stroke, transient ischaemic attack (TIA), systemic or pulmonary embolism. A stroke was defined as a sudden focal neurological deficit of presumed cerebrovascular aetiology lasting for 24 hours, not due to another identifiable cause and confirmed by computed tomography or magnetic resonance imaging of the brain. If symptoms were short lasting (<24 h) and no evidence of necrosis was found on brain imaging, the event was considered to be a TIA. A systemic embolic event was defined as an abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism (e.g. atherosclerosis, instrumentation, or trauma). A pulmonary embolism was diagnosed when dyspnoea or other suggestive clinical presentation was accompanied by a confirmation of a new pulmonary perfusion or intra-luminal defect.

3. Major bleeding, which was defined as composite of cardiac tamponade, bleeding requiring intervention (e.g., either thrombin injection or surgery) or transfusion, massive haemoptysis, haemothorax, retroperitoneal bleeding, fatal bleed, or any other bleeding leading to prolongation of hospitalisation.
4. Minor bleeding, which was defined as a composite of puncture site bleeding, thigh ecchymosis or haematoma, pericardial effusion with no haemodynamic compromise, minor gastrointestinal bleeding, epistaxis, or any bleeding treated conservatively with no need for transfusion, surgery, or prolonged hospitalization.

The criteria for definition of major or minor bleeding are strongly based on the recommendation from the *International Society on Thrombosis and Haemostasis* [9], but adapted for catheter ablation of AF [8].

Statistical analysis

The chi-square test and Student's t-test were used for comparison of categorical and continuous variables, respectively. Levene's test was used to check the homogeneity of variance; equivalent non-parametric tests were used when Kolmogorov–Smirnov was in favour of the absence of normal distribution. Results with $P < 0.05$ were regarded as significant. PASW Statistics version 18.0 was used for descriptive and inferential statistical analysis.

Results

One hundred thirty-seven patients (mean age 55.0 ± 13.4 , 29.1% female) underwent 230 catheter ablations for AF (1.7 ± 1.0 per patient). A total of 55 patients (39.4%) underwent 70 procedures (30.4%) on NOAC, the remaining were ablated while on VKAs. Warfarin (97.6%) and rivaroxaban (56.4%) were the most frequently used agents in the respective groups. VKA interruption regimen with low-molecular weight heparin bridging was adopted in 56 catheter ablations (35%). NOAC use was uninterrupted pre-procedure in all patients but one (no heparin bridging was performed either). Pre-procedural TOE was performed for 40 and 125 ablations in the NOAC and VKA group (57.1% vs. 78.1%, respectively; $p < 0.001$); 3 procedures in the VKA group were deferred due to the presence of intracardiac thrombus ($p = 0.55$), despite at least two INR measurements > 2 in the 4 weeks pre ablation. Most patients had paroxysmal AF (57.5%) at baseline, and mean AF duration was 3.3 ± 3.1 years. Mean CHA₂DS₂VASc and HAS-BLED score were 1.5 ± 1.5 and 0.8 ± 0.9 , respectively. As many as 10.4% had a history of stroke or TIA, and 3.6% was on concomitant single antiplatelet therapy. Mean left atrial diameter was 47 ± 7 mm.

Some differences were found at baseline population between the two groups: left ventricular ejection fraction, wall thickness and outflow tract gradient were higher in subjects on NOAC; patients on VKA more frequently presented with persistent AF or had history of previous surgical myectomy. Detailed baseline characteristics are reported in Table 1.

Procedural outcomes

The overall rate of complication was 9.3%. No procedure-related deaths were reported. A low incidence of thromboembolism (0.7%) was observed, with only one patient on interrupted VKA (with heparin bridging) suffering from an ischemic stroke immediately after the ablation with minor neurological sequelae. No thromboembolic events were reported in the NOAC group.

There was a numerically higher rate of major bleeding with VKA versus NOAC (6.8% vs. 1.4%, respectively; $p = 0.09$); after excluding patients on interrupted VKA with heparin bridging the numerical difference was confirmed (5.8% vs. 1.4%, $p = 0.16$). The overall rate of pericardial effusion requiring pericardiocentesis was 4.0%, and was numerically higher in the VKA versus NOAC group (4.5% vs 1.4%, respectively; $p = 0.11$). Puncture complications fulfilling major bleeding criteria were observed in 3 patients (1.3%) on VKA. The incidence of minor bleeding was low (0.9%) and comparable between the two groups. These results are shown in Table 3 and S-Table 4.

Discussion

Preliminary data from this multicentre study suggest that use of NOACs appears to be effective and safe in HCM patient undergoing catheter ablation of AF. The incidence of thromboembolic events was low with both VKA and NOAC. A non-significant but numerically higher rate of major bleeding and cardiac tamponade in patients on VKA versus NOAC was observed.

Several landmark trials have demonstrated that NOACs are at least as effective as VKA for prevention of thromboembolic events of AF [10-13]. However, no randomised data are available on the effectiveness of NOAC in the HCM population. Similar to our findings, four observational studies have suggested that NOACs, compared to VKA, are associated with a similar or lower rate of thromboembolic and bleeding events in subjects with HCM and AF [14-17]. Current HCM guidelines from the European Society of Cardiology suggest the use of NOACs as a second-line drugs in patient with concomitant AF [2]. According to the *European Heart Rhythm Association 2018 Practical Guide on Oral Anticoagulants*, HCM patients might be eligible for NOACs [4]. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for AF (confirmed in 2019) state that NOAC “might represent another option to reduce the risk of thromboembolic events, but data for patients with HCM are not available” [3, 18].

Catheter ablation represents an effective treatment for symptomatic drug-refractory AF [19-20]. However, the intra- and post-procedural thromboembolic risk is not negligible and requires effective anticoagulation. In fact, both manipulation of the catheters and creation of lesions inside the left atrium can lead to local thrombus formation [6]. There is a significant body of evidence showing that NOACs can be safely used in patients undergoing catheter ablation of AF, with a similar or lower rate of bleeding and thromboembolic complications compared to VKA [6, 21]. The RE-CIRCUIT [22], VENTURE-AF [23] and AXAFA [24] trials have respectively demonstrated the safety and efficacy of uninterrupted dabigatran, rivaroxaban, and apixaban during catheter ablation of AF. However, patients with HCM were not represented in these trials. Data on catheter ablation of AF in HCM patients are still sparse, and only arising from small observational studies [1]. A systematic review and metanalysis from our group has shown that catheter ablation of AF appears to be safe in the HCM population, and might represent a valuable option despite a higher arrhythmia relapse rate compared to the general population [1].

To the best of our knowledge, we present the largest published series of HCM patients undergoing catheter ablation of AF, and this is the first study to investigate the effectiveness of NOACs in this high-risk setting. We are not aware of other studies where NOACs have been used at the time of AF ablation in individuals with HCM.

Our findings are reassuring and add to the body of evidence suggesting that use of NOACs appears to be safe and effective in HCM patients with AF, with a risk profile which appears at least similar to VKAs. Of note, no intracardiac thrombus was identified in the 40 pre-procedural TOEs in the NOAC group. Similarly, there were no embolic events in the NOAC group and major bleeding and cardiac tamponade were numerically lower compared to VKA. We believe our findings might have relevant clinical implications in HCM patients with AF elected for an ablative strategy as they ease some of the concerns regarding NOACs and the absence of data in this high-risk setting.

Limitations

Several limitations should be acknowledged. This was an observational and non-randomised study, however it is unlikely that a randomised trial will ever be performed of NOAC versus VKA in HCM patients undergoing AF ablation. Whilst our data are non-randomised it is hoped that they will be a useful point of reference for others considering this approach. Given the small sample size, this study was underpowered to demonstrate non-inferiority of NOAC vs. VKA for most of the study comparisons (which referred to events with a rate <10%). However, our multicentre data constitute the largest cohort of HCM patients undergoing AF ablation, and this is the first study to investigate the use of NOAC in this setting. An interrupted oral anticoagulation strategy with heparin bridging is no longer the standard of care and was used in a few patients in this series. However, the observed numerical differences were maintained even in sub-analyses excluding such patients.

We could not provide data on silent cerebral infarction, as patients did not routinely undergo brain magnetic resonance imaging post-ablation. Only a limited number of patients were on edoxaban or dabigatran.

Conclusion

These preliminary data suggest that NOACs are as safe and effective compared to VKA in patients with HCM undergoing catheter ablation for AF.

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Tables

Table 1. Baseline characteristics of the study population

Table 2. Type of oral anticoagulant

Table 3. Efficacy and Safety Endpoints

Supplementary materials

Supplementary Table 4 . Subgroup analysis

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Table 1 . Demographics

	Global Sample n=137 % (n)	VKA n=82 % (n)	NOAC n=55* % (n)	P
Age	55.0±13.4	53.3±13.3	57.2±13.2	0.27
Female Sex	29.1% (39)	25.6% (21)	32.7% (18)	0.36
AF type at index procedure				0.013
Paroxysmal	57.5% (77)	40.2% (33)	61.8% (34)	
Persistent	41.0% (55)	59.8% (49)	38.2% (21)	
Longstanding	1.5% (2)	2.4% (2)	0%	
Persistent				
Baseline ECG in Sinus Rhythm – Index Procedure	58.2% (78)	51.2% (42)	65.4% (36)	0.1
Previous Non-AF ablation	9.8% (13)	9.8% (8)	9.0% (5)	0.71

	Global Sample n=137 % (n)	VKA n=82 % (n)	NOAC n=55* % (n)	P
Previous Alcohol Septal Ablation	4.5% (6)	2.4% (2)	7.3% (4)	0.17
Previous Surgical Myectomy	10.4% (14)	15.8% (13)	1.8% (1)	0.008
LV Apical Aneurysm	1.5% (2)	2.4% (2)	0%	0.51
Congestive HF	15.7% (21)	15.8% (13)	14.5% (8)	0.83
Hypertension	25.4% (34)	19.5% (16)	32.7% (18)	0.79
Diabetes	14.2% (19)	14.6% (12)	12.7% (7)	0.54
Stroke or TIA	10.4% (14)	12.2% (10)	7.3% (4)	0.35
Vascular Disease	9.7% (13)	8.5% (7)	10.9% (6)	0.64
Chronic Kidney Disease	3.8% (5)	3.6% (3)	5.4% (3)	0.61
Obstructive Sleep Apnoea	6.7% (9)	11% (6)	5.4% (3)	0.67
NYHA Class	1.8±0.7	1.8±0.7	1.7±0.7	0.91
CHA ₂ DS ₂ VASc	1.5±1.5	1.3±1.4	1.6±1.6	0.21
HAS-BLED	0.8±0.9	0.8±0.9	0.8±0.9	0.39
Single antiplatelet therapy	3.6% (5)	6.1% (5)	0%	0.08
Dual antiplatelet therapy	0	0%	0%	-
Apical Hypertrophy	10.9% (14)	7.3% (8)	10.9% (6)	0.79
Moderate to Severe MR	12.2% (14)	7.3% (6)	14.5% (8)	0.17
Restrictive pattern	21.6% (29)	23.2% (19)	18.2% (10)	0.48
Max LVOT gradient (mm Hg)	14±24	9±13	21±32	0.02
Max LV Thickness (mm)	17±4	17±4	18±3	0.009
LA diameter (mm)	47±7	49±7	45±6	0.5
LVEF	58±9	57±10	59±9	0.017

Abbreviations. VKA: vitamin-K antagonist. NOAC: non-vitamin K anticoagulant. AF: atrial fibrillation. LV: left ventricle. HF: heart failure. MR: mitral regurgitation. LVOT: left ventricular outflow tract. LA: left atrium. LVEF: left ventricular ejection fraction.

Table 2. Type of oral anticoagulant

	VKA n=82 % (n)	NOAC n=55 % (n)
Warfarin	97.6% (80)	-
Flunidione	2.4% (2)	-
Apixaban	-	32.7% (18)
Dabigatran	-	7.3% (4)
Edoxaban	-	3.6% (2)
Rivaroxaban	-	56.4% (31)

Table 3 . Outcomes

	Global Sample n=230 procedures % (n)	VKA n=160 procedures % (n)	NOAC n=70 procedures % (n)	P
Thromboembolism	0.4% (1)	0.6% (1)	0%	1.0
Stroke	0.4% (1)	0.6% (1)	0%	1.0
TIA	0%	0%	0%	-
Pulmonary embolism	0%	0%	0%	-
Systemic embolism	0%	0%	0%	-
Major bleeding	5.2% (12)	6.9% (11)	1.4% (1)	0.09
Cardiac tamponade	3.9% (9)	4.8% (7)	1.4% (1)	0.26
Vascular-access related	1.3% (3)	1.8% (3)	0%	0.55
Minor bleeding	0.9% (2)	0.6% (1)	1.4% (1)	0.54
Haematoma	0.4% (1)	0.6% (1)	0%	1.0
Pericardial effusion not requiring drain	0.4% (1)	0%	1.4% (1)	0.30
Other complications	3.5% (8)	3.1% (5)	4.3% (3)	0.65
Pneumonia	0.4% (1)	0.6% (1)	0%	1.0
PV stenosis	0.4% (1)	0.6% (1)	0%	1.0
Acute pulmonary oedema	1.3% (3)	1.2% (2)	1.4% (1)	0.91
Complete AV block	0.4% (1)	0%	1.4% (1)	0.30
Phrenic nerve palsy	0.9% (2)	0.6% (1)	1.4% (1)	0.54

Abbreviations. VKA: vitamin-K antagonist. NOAC: non-vitamin K anticoagulant. PV: pulmonary vein. AV: atrio-ventricular.

Supplementary Table 4 . Sub-analysis of outcomes in patients on uninterrupted oral anticoagulant regimen

	Uninterrupted oral anticoagulant n=172 procedures % (n)	Uninterrupted VKA n=104 procedures % (n)	Uninterrupted NOAC n=69 procedures % (n)	P
Thromboembolism	0%	0%	0%	-
Stroke	0%	0%	0%	-
TIA	0%	0%	0%	-
Pulmonary embolism	0%	0%	0%	-
Systemic embolism	0%	0%	0%	-
Major bleeding	4% (7)	5.8% (6)	1.4% (1)	0.16
Cardiac	3.5% (6)	4.8% (5)	1.4% (1)	0.24
tamponade				
Vascular-access related	0.6% (1)	1.0% (1)	0%	1.0
Minor bleeding	1.2% (2)	1.0% (1)	1.4% (1)	0.77
Haematoma	0.6% (1)	1.0% (1)	0%	1.0
Pericardial effusion not requiring drain	0.6% (1)	0%	1.4% (1)	0.40
Other complications	4.6% (8)	4.8% (5)	4.3% (3)	0.88
Pneumonia	0.6% (1)	1.0% (1)	0%	1.0
PV stenosis	0.6% (1)	1.0% (1)	0%	1.0
Acute pulmonary oedema	1.7% (3)	1.9% (2)	1.4% (1)	0.81
Complete AV block	0.6% (1)	0%	1.4% (1)	0.40
Phrenic nerve palsy	1.2% (2)	1.0% (1)	1.4% (1)	0.77

Abbreviations. VKA: vitamin-K antagonist. NOAC: non-vitamin K anticoagulant. PV: pulmonary vein. AV: atrio-ventricular.