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Safety of Continuous Periprocedural Rivaroxaban versus Phenprocoumon for Patients Undergoing Left Atrial Catheter Ablation Procedures

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Content

ABBREVIATIONS

AAD	Antiarrhythmic drugs
ACT	Activated clotting time
AF	Atrial fibrillation
AT	Atrial tachycardia
b.i.d	bis in die (twice daily)
CFAE	Complex fractionated atrial electrograms
CI	Confidence interval
CL	Cycle length
CrCl	Creatinine clearance
CS	Coronary sinus
CT	Computer tomography
DCC	Direct current cardioversion
ESC	European Society of Cardiology
GI	Gastro-intestinal.
H2B	H2-blocker
ICH	Intracranial hemorrhage
IQR	Interquartile range
INR	International normalized ratio
ITT	Intention to treat
i.v	Intravenous
LA	Left atrium
LAA	Left atrial appendage
LIPV	Left inferior pulmonary vein

LSPV	Left superior pulmonary vein
LV	left ventricle
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NOAC	Novel oral anticoagulants
OAC	Oral anticoagulation
o.d.	once per day
OR	odds ratio
PCC	Prothrombin complex concentrate
P-gp	P-glycoprotein
PPI	Proton-pump inhibitor
PV	Pulmonary vein
PVI	Pulmonary vein isolation
RA	Right atrium
RF	Radiofrequency
RFA	Radiofrequency catheter ablation
TEE	Transesophageal echocardiography
SE	Systemic embolism
SR	Sinus rhythm
VKA	Vitamin K antagonist

I- Background

1) Atrial fibrillation: general aspects

Atrial fibrillation (AF) is the most common cardiac arrhythmia[1, 2]. It affects 1-2% of the general population, with an incidence increasing with age to up to 5-15% at 80 years [3]. AF is associated with an increased risk of mortality [4], thromboembolic-events [5, 6], heart failure and hospitalization [7]. These aspects make AF a major health problem in the general population and its optimal management of high importance [8].

According to the ESC guidelines 2010 [9], 5 types of AF can be distinguished based on the presentation and duration of the arrhythmia:

1) First diagnosed AF: Every patient who presents with AF for the first time, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.

2) Paroxysmal AF is self-terminating, usually within 48 h and up to 7 days.

3) Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC).

4) Long-standing persistent AF has lasted for ≥1 year when it is decided to adopt a rhythm control strategy.

5) Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician).

The principal therapeutic goals in AF patients include reduction of symptoms and prevention of severe complications associated with AF [9]. The two important parts in the AF management are:

- The antithrombotic therapy which is the only therapy with proven impact on mortality (see Paragraph 2).

- The rate and rhythm management: Several studies have compared the two strategies of rate control or rhythm control (AFFIRM, RACE, PIAF, STAF) [10]. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) found no difference in all-cause mortality or stroke rate between rate control and rhythm control [11, 12]. However, only 62.6% of patients in the rhythm control arm effectively were in sinus rhythm and the presence of sinus rhythm was associated with a decreased risk of death [13]. Moreover, the use of antiarrhythmic drugs (AAD) was associated with an increased risk of death due to a proarrhythmic effect [14]. This supports the hypothesis that a rhythm control strategy without use of AAD (for example by catheter ablation) might have a greater benefit compared to a rate control strategy.

2) Antithrombotic management in atrial fibrillation patients

Stroke prevention by an adequate antithrombotic therapy has become the key in the management of AF patients. Patients with AF are at a higher risk of clot formation due to the disorganization of regional atrial mechanical function, which favors thrombus formation in zones of blood stasis, especially in the left atrial appendage (LAA) [15, 16].

The Framingham study data showed that AF exerts a significant impact on the stroke risk, independently of the often associated cardiovascular abnormalities. There was a fivefold excess of stroke associated with AF. Moreover, the impact of AF on stroke risk increased with age and with the presence of cardiac conditions such as coronary artery disease (CAD), hypertension and cardiac failure [17].

2-1) Risk stratification for stroke and thrombo-embolism

The 2010 ESC Guidelines [9] focused on the necessity of using a risk factor-based approach to stratify stroke risk and on the importance of identifying 'truly low-risk' patients who do not need any antithrombotic therapy. Limitations of the risk assessment scheme represented by the CHADS2 score [cardiac failure, hypertension, age, diabetes, stroke (doubled)] were highlighted and a more accurate risk factor-based approach for patients with non-valvular AF expressed by the CHA2DS2-VASc score was introduced. This score includes: congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age 65–74 and sex category (female) (table 1). Patients with AF who have stroke risk factor(s) ≥1 are recommended to receive effective oral anticoagulation (OAC).

Table 1: Risk factor-based approach expressed as a point based scoring system: CHA2DS2-VASc. From Guidelines for the management of atrial fibrillation (European heart journal. 2010;31(19):2369-429).[9]

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2

Vascular disease	1
Age 65–74	1
Sex category (i.e. female sex)	1

2-2) Risk stratification for bleeding

Decision-making for thromboprophylaxis needs to balance the risk of stroke against the risk of major bleeding.

A simple bleeding risk score using a cohort of AF patients from the EuroHeart Survey was introduced in the last guidelines [18]. The HAS-BLED score includes: hypertension, abnormal renal or liver function, prior stroke, bleeding history or predisposition, labile INR, older age (>65) and drugs or alcohol use (table 2). A score ≥ 3 indicates a high risk of bleeding and requires a regular review of the indication for anticoagulation therapy.

Table 2: Clinical characteristics comprising the HAS-BLED bleeding risk score From Guidelines for the management of atrial fibrillation (European heart journal. 2010;31(19):2369-429).[9]

Letter	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1

L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2

2-3) Anticoagulation therapy with vitamin K antagonists

Several studies demonstrated the superiority of vitamin K antagonists (VKA) to aspirin. The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study showed that VKA with a target INR of 2–3 was superior to aspirin 75 mg daily in reducing the primary endpoint of fatal or disabling stroke, intracranial hemorrhage, or arterial embolism by 52%, with no difference in the risk of major hemorrhage [19]. Moreover, a study in octogenarians showed that dose-adjusted VKA was significantly better tolerated with fewer adverse events and serious bleeding than aspirin 300 mg [20].

In the ACTIVE W trial, VKA therapy was superior to the combination of clopidogrel plus aspirin for prevention of vascular events (RR reduction of 40%), with a lower risk of major bleedings [21].

Despite this clear benefit, VKA remain often under-used [22, 23]. This is in part due to the difficulty of VKA management. An optimal INR range of 2-3 is necessary for prevention of stroke and systemic embolism in patients with non-valvular AF. This narrow range allows maintaining a balance between stroke risk with lower INRs and bleeding risk with higher INRs. However, this goal can be difficult to achieve because of a high interindividual and intraindividual variation in INRs. Moreover, VKAs also have significant drug, food, and alcohol interactions. On average, patients may stay within the intended INR range of 2.0–3.0 for about 50-60% of the time [24].

2-4) Novel oral anticoagulants

2-4-1) Characteristics of novel oral anticoagulants

Novel oral anticoagulants (NOAC) have emerged as an alternative for VKA for stroke prevention in patients with non valvular AF. They are classified into 2 categories:

- Oral direct thrombin inhibitors: dabigatran.

- Direct factor Xa inhibitors: rivaroxaban, apixaban.

In contrast to VKAs, which block the formation of multiple active vitamin K-dependent coagulation factors (II, VII, IX, and X), NOAC specifically block the activity of a single step of the coagulation cascade [25] (Figure 1).

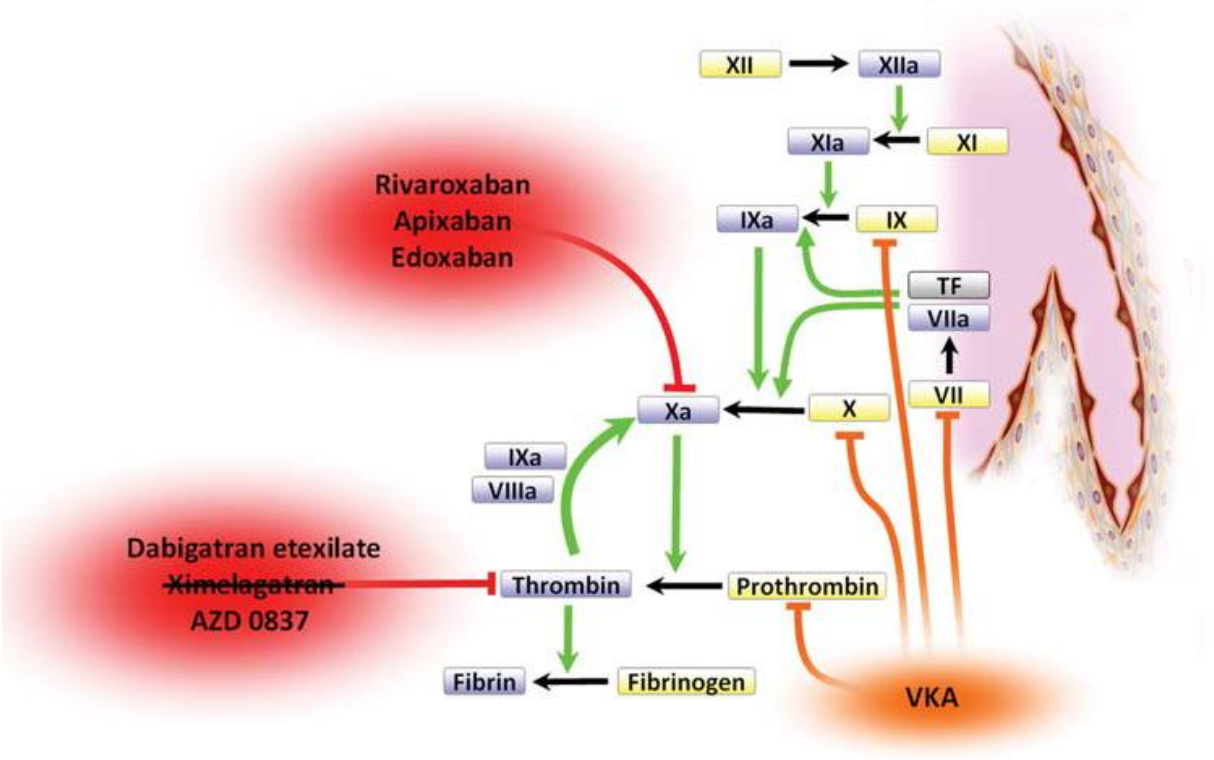

Figure 1: Point of action of novel oral anticoagulants in the coagulation cascade. From J. Steffel and E. Braunwald. Novel oral anticoagulants: focus on stroke prevention and treatment of venous thrombo-embolism (Eur Heart J. 2011;32:1968-76, 1976a).[26]

The pharmacokinetics of the different NOACs are shown in figure 2 and table 3. An important interaction mechanism for dabigatran and apixaban consists of significant re-secretion over a P-glycoprotein (P-gp) transporter after absorption in the gut. Moreover, in all the 3 NOAC, P-gp transporter may be involved in renal clearance, so that a competitive inhibition results in increased plasma levels. Many drugs used in AF patients are P-gp substrates (e.g. verapamil, dronedarone, amiodarone) [27]. CYP3A4 type cytochrome P450-dependent elimination is involved in rivaroxaban and apixaban hepatic clearance. Strong CYP3A4 inhibition or induction may affect rivaroxaban plasma concentrations and effect [28].

Most of the hepatic clearance of apixaban is as unchanged molecule, with only a minority being metabolized, which makes CYP3A4 interactions of less importance [29]. The bio-availability of dabigatran is markedly lower than that of the other drugs [30] However, food interaction is relevant neither for dabigatran nor for apixaban. For rivaroxaban, food intake has an impact on the absorption and bioavailability. The recommendation is therefore to take rivaroxaban with food (enhancing the bioavailability from 66% to almost 100%) [31].

Table 3: Absorption and metabolism of the different NOACs: adapted from Heidbuchel et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. (Europace 2013;15: 625-51).[31]

	Dabigatran	Apixaban	Rivaroxaban
Bio-availability	3–7%	50%	66% without food

			Almost 100% with food
Prodrug	Yes	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination; minor CYP3A4 contribution)	Yes (elimination)
Absorption with food	No effect	No effect	+39% more
Absorption with H2B/PPI	-12-30%	No effect	No effect
Elimination half-life	12–17 h	12 h	5–9 h (young) 11–13 h (elderly)

H2B, H2-blocker; PPI, proton-pump inhibitor; GI, gastro-intestinal.

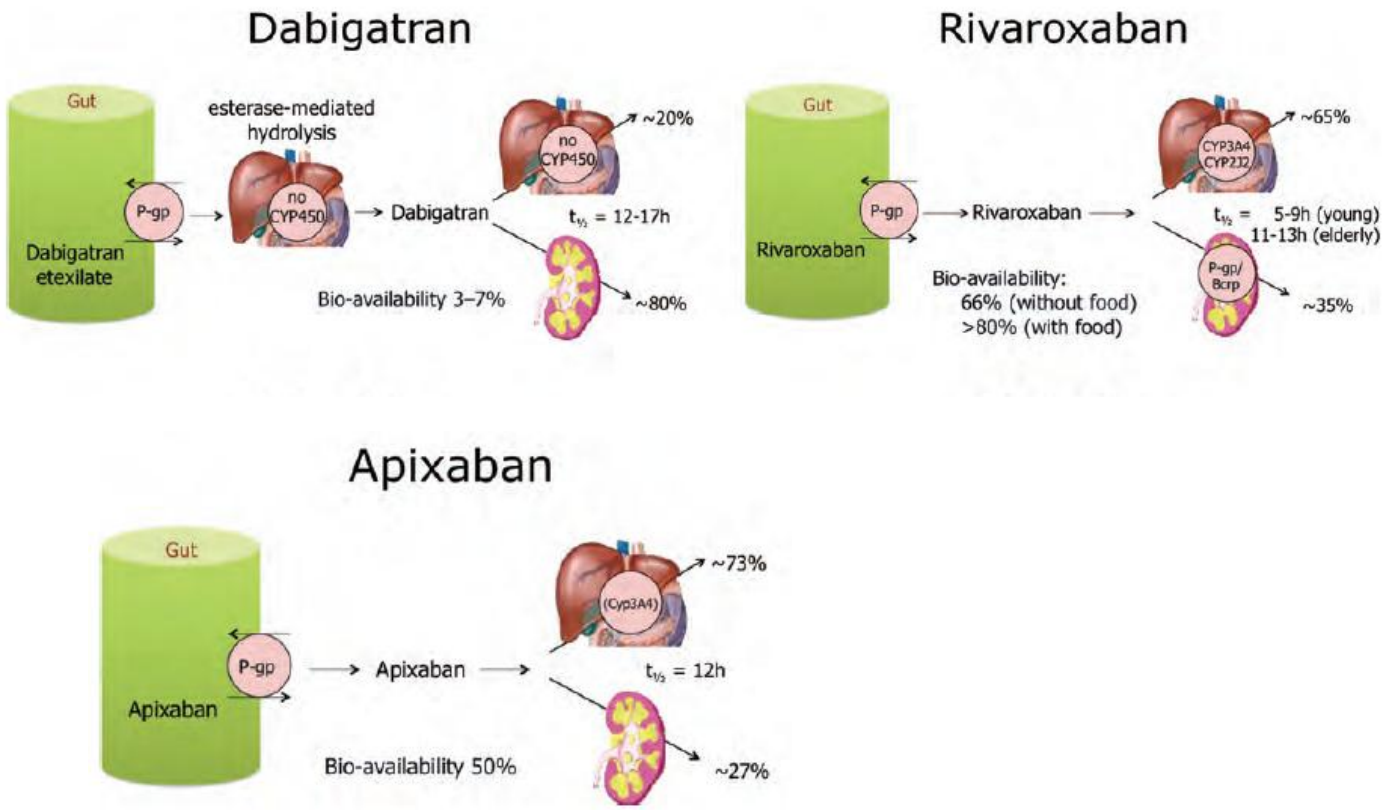

Figure 2: Absorption and metabolism of the different NOACs: from Heidbuchel et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. (Europace 2013;15: 625-51).[31]

2-4-2) Clinical trials with novel oral anticoagulants

In clinical trials, NOACs have all shown at least non-inferiority compared with VKAs and better safety. On this basis, a focused update of the ESC guidelines was published in 2012, recommending them as broadly preferable to VKA in the vast majority of patients with non-valvular AF [32].

Clinical trials involving NOACs are represented in Table 4. The RE-LY trial was a prospective randomized open-label trial comparing two blinded doses of dabigatran etexilate (110mg b.i.d or 150 mg b.i.d) to warfarin with a target INR of 2-3. Dabigatran

given at a dose of 110 mg b.i.d was non inferior to warfarin regarding rates of stroke and systemic embolism and was associated with lower rates of major hemorrhage [33]. Administered at a dose of 150 mg, dabigatran was superior to warfarin regarding the efficacy endpoint but showed similar rates of major hemorrhage. Rates of haemorrhagic stroke and intracranial hemorrhage (ICH) were lower with both doses of dabigatran, but gastrointestinal (GI) bleeding was significantly increased with a dose of 150mg b.i.d.

The ROCKET-AF study was a double-blind trial which randomized patients with nonvalvular AF to receive either rivaroxaban (at a daily dose of 20 mg or 15 mg daily for those with estimated CrCl of 30–49 mL/min) or dose-adjusted warfarin. Rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group [34].

The ARISTOTLE trial was a randomized, double-blind trial comparing apixaban (5 mg b.i.d., with a dose adjustment to 2.5 mg b.i.d. in patients ≥80 years, weight ≤60kg or with a serum creatinine ≥1.5 mg/dL) with warfarin (target INR 2.0–3.0) in patients with non-valvular AF. Compared to warfarin, apixaban was associated with a significant reduction in the primary efficacy outcome of stroke or systemic embolism, with a significant reduction in major bleeding and a significant reduction in all-cause mortality. Rates of hemorrhagic stroke and ICH were significantly lower in patients treated with apixaban than with warfarin, whereas gastrointestinal bleeding was similar between treatment arms [35].

Table 4: Summary of the clinical trials involving novel anticoagulants vs. warfarin for stroke prevention in non-valvular AF: adapted from 2012 focused update of the ESC Guidelines for the management of atrial fibrillation (Eur Heart J. 2012;33:2719-47).[36]

	Dabigatran (RE-LY)	**Rivaroxaban (ROCKET-AF)**	**Apixaban (ARISTOTLE)**
Study characteristics			
Study design	Randomized, open-label	Randomized, double-blind	Randomized, double-blind
Number of patients	18 111	14 264	18 201
Follow-up period, years	2	1.9	1.8
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg b.i.d., 110 mg b.i.d.)	Dose-adjusted warfarin vs. rivaroxaban 20 mg o.d.	Dose-adjusted warfarin vs. apixaban 5 mg b.i.d.
Baseline patient characteristics			
Age, years	71.5 ± 8.7 (mean ± SD)	73 (65–78) [median (IQR)]	70 (63–76) [median (IQR)]
Male sex, %	63.6	61.3	64.5

CHADS2 (mean)	2.1	3.5	2.1
Outcomes			

	Dabigatran 150 (RR, 95% CI; P value)	***Dabigatran 110*** (RR, 95% CI; P value)	***Rivaroxaban*** (HR, 95% CI; P value)	***Apixaban*** (HR, 95% CI; P value)
Stroke/ systemic embolism	0.66, 0.53–0.82; **P** for superiority ***<0.001***	0.91, 0.74–1.11; ***P*** for non-inferiority ***<0.001***	0.88, 0.75–1.03; ***P*** for non-inferiority ***<0.001***, P for superiority = 0.12 (ITT)	0.79, 0.66–0.95; ***P <0.001*** for non-inferiority, ***P = 0.01*** for superiority
Major bleeding	0.93, 0.81–1.07; P = 0.31	0.80, 0.69–0.93; ***P = 0.003***	1.04 (0.90–1.20); P = 0.58	0.69 (0.60–0.80); ***P <0.001***
Intracranial bleeding	0.40, 0.27–0.60; ***P <0.001***	0.31, 0.20–0.47; ***P <0.001***	0.67; 0.47–0.93; ***P = 0.02***	0.42, 0.30–0.58; ***P <0.001***
Gastrointestinal bleeding	1.50, 1.19–1.89; ***P <0.001***	1.10, 0.86–1.41; P = 0.43	1.60; 1.29-1.98; ***P<0.001***	0.88, 0.66–1.17; P = 0.37
Myocardial infarction	1.27, 0.94-1.71; *P* = 0.12	1.29, 096-1.75; *P* = 0.09	0.81; 0.63–1.06; P = 0.12	0.88, 0.66–1.17; P = 0.37
Death from	0.88, 0.77–	0.91, 0.80–	0.85; 0.70–	0.89, 0.80–

any cause	1.00; P = 0.051	1.03; P = 0.13	1.02; P = 0.07	0.99; ***P = 0.047***

AF = atrial fibrillation; b.i.d. = bis in die (twice daily); CHADS2 = congestive heart failure, hypertension, age ≥75, diabetes, stroke/TIA [doubled]; CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio; ITT= intention-to-treat; o.d. = once daily; RR = relative risk; SD = standard deviation; IQR: interquartile range TIA = transient ischaemic attack; VKA = vitamin K antagonist:

In summary, dabigatran 150 mg and apixaban, but not rivaroxaban or dabigatran 110 mg, significantly reduced all-cause stroke/systemic embolism (SE) compared with adjusted-dose warfarin. The absolute difference in all-cause stroke/SE for the NOACs versus warfarin ranged from two to six fewer events per 1,000 patients treated each year. Except for apixaban (1 less death per 1,000 patients), none of the NOACs significantly reduced all-cause mortality. None of the NOACs reduced the risk of myocardial infarction (MI) relative to adjusted-dose warfarin [37, 38].

Concerning bleeding risk, apixaban and dabigatran 110 mg significantly reduced the risk of major bleeding relative to warfarin. All of the NOACs significantly reduced the risk of intracranial bleeding relative to warfarin. By contrast, none of the NOACs significantly reduced the risk of major GI bleeding, and dabigatran 150 mg and rivaroxaban were associated with a significant increase in the risk of a major GI bleeding versus warfarin [37, 38]. Subgroup analysis showed that when the time in therapeutic range (TTR) was ≥ 66%, none of the NOACs reduced the risk of stroke/SE versus warfarin, and apixaban was the only NOAC that reduced the risk of major bleeding. In contrast, when the TTR was < 66%, 150 mg dabigatran reduced the risk of stroke/SE versus warfarin, and 110 mg dabigatran, 150 mg dabigatran, and apixaban reduced the risk of major bleeding versus warfarin [39].

3) Catheter ablation of atrial fibrillation

3-1) Catheter ablation techniques

One of the greatest discoveries in cardiac electrophysiology has been the recognition of the important role of pulmonary vein (PV) myocardial sleeves in AF initiation [40]. In the last years, many ablation strategies have been developed and pulmonary vein isolation (PVI) has now become a routine approach for AF ablation [41, 42].

Electrical isolation of PVs is the cornerstone of all AF ablation procedures [43]. An initial segmental PVI technique described by Haisaguerre and colleagues consisted of the identification and ablation of the PV ostium at the earliest sites of activation of the PV musculature [44]. An ablation strategy of encircling the PVs with RF lesions guided by 3D electroanatomical mapping was developed by Pappone and colleagues [45]. The segmental approach showed significantly better results than the anatomical approach in 2 randomized studies [46, 47]. This was mostly caused by the occurrence of subsequent atrial tachycardias due to electrically incomplete lesions with residual LA-PV conduction in the anatomical approach [48].

The recognition that the atrial myocardium surrounding the PVs is involved in the pathophysiology of AF contributed to a further development of the ablation strategy [49]. Beside the arrhythmogenic foci, the proximal PVs serve as substrate for microreentry with slow and decremental conduction [50]. Parasympathetic innervation and sustained rotors related to stretch have also been observed in the area around the PVs as possible mechanisms for the initiation and perpetuation of AF [51]. As a result, the most commonly used ablation strategy is now to target the atrial tissue with a circumferential ablation around both ipsilateral PVs with verification of LA-PV conduction block [52, 53]. Two randomized studies showed that this strategy is a more effective treatment than a segmental PVI, particularly in persistent AF [54, 55].

For substrate modification the two most commonly used strategies are the linear ablation and the ablation of complex fractionated atrial electrograms (CFAE) [52]. Linear lesions deployed in the atria serve as conduction barriers preventing the development and perpetuation of re-entrant circuits [56]. In contrast, CFAE ablation targets critical areas of slow conduction which are thought to perpetuate micro-reentries sustaining the arrhythmia [57]. The endpoint of the first strategy is the demonstration of bidirectional block [58-60]. Using CFAE ablation, we can reach AF cycle length (AFCL) prolongation, organization into atrial tachycardia (AT) or termination to sinus rhythm [61, 62]. This last result has been shown to be the preferable endpoint regarding outcome [63]. In a randomized study comparing the linear and the CFAE ablation, no significant difference in outcome could be demonstrated. The 2 groups differed only with the type of recurrent atrial arrhythmia during follow-up: AF was predominant after linear lesions, whereas AT was most common after CFAE ablation [64].

A combination of ablation techniques has been proposed. In the stepwise approach[65], PVI is followed by a CFAE ablation. If AF persists, linear lesions are deployed. In a modified approach (sequential approach)[63, 66], linear lesions are only deployed if AF is organized to AT during CFAE ablation. In a compilation of patients treated by stepwise approach, O'Neill et al. found that linear lesions contributed to 21% of AF termination [67]. Using either the sequential or the stepwise approach, termination to sinus rhythm could be reached in 32-86% of patients [62, 63, 67, 68].

3.2) Catheter ablation results

AF ablation has been shown to be superior to AAD in maintaining sinus rhythm [69-71] and was associated with an improved quality of life [72] and an improved left ventricular systolic function [73]. Several large clinical trials are now investigating whether aggressive early ablation therapy can reduce cardiovascular morbidity and mortality. One of the largest ongoing trial is the Catheter Ablation versus Anti-arrhythmic drug therapy for Atrial fibrillation trial (CABANA, Clinical Trials.gov number NCT00911508). This study randomizes patients to catheter ablation versus current state-of-the art therapy with either rate or rhythm control drugs with the endpoint of mortality reduction.

In paroxysmal AF, success rates reach 75% with repeat ablation procedures [70, 74]. Since the publication of the MANTRA-PAF and the RAAFT II trial, AF ablation has been accepted as a first-line therapy in selected patients with paroxysmal AF [36, 75, 76]. In persistent and long-standing persistent AF, success rates are lower and require often multiple procedures [77]. Several data support the fact that additional substrate modification is necessary to improve ablation results. In a randomized study by Willems et al., PVI alone was insufficient in the treatment of persistent AF with only 20% of patients remaining in sinus rhythm during follow-up [78]. Additional linear lesions significantly increased the success rate to 69% (p=0.0001) [79]. In a meta-analysis of 5 trials, addition of CFAE ablation resulted in a statistically significant increase in freedom from atrial arrhythmias (62% for PVI+CFAE vs. 47% for PVI alone; RR 1.32, P = .02) [80]. With a stepwise ablation approach reported single-procedure, drug-free clinical success ranged from 38% to 62% at approximately 18 months. The integration of repeat procedures, mostly for atrial tachycardia, increased the drug-free clinical success rate to 70-88% [67, 68, 81].

3.3) Anticoagulation management during left atrial catheter ablation

Since RFA has become an established therapy for treating patients with AF and AT, the numbers of left atrial RFA procedures increased rapidly over the last years [74]. Nevertheless, it is a technically demanding procedure with an overall periprocedural major complication rate of 4.5% reported by Cappato et al. [74]. The risk of thromboembolic as well as bleeding complications during or after RFA procedures remains a significant concern. Whereas the incidence of periprocedural thromboembolic events is reported in the range of 0.1 - 1.1% [74, 82, 83], the incidence of major and minor bleeding complications after left atrial RFA is significantly higher with 12.2 to 20% [83-85].

At present, the optimal anticoagulation management that minimizes thromboembolism while not increasing hemorrhagic complications is not well established. Discontinuation of VKA 3 to 5 days before RFA and use of heparin as a bridging strategy is currently the most frequently used anticoagulation protocol in left atrial RFA [52]. Recently, it has been shown that uninterrupted therapeutic warfarin administration during the periprocedural RFA period is associated with a significant reduction of embolic events without an increased bleeding risk [86, 87]. Continuation of oral anticoagulation therapy with VKA is also recommended in the recent HRS/EHRA/APHRS consensus statement [52] on AF ablation, as an alternative to a bridging approach with heparin, for patients on oral anticoagulation with VKA prior to catheter ablation.

4) Aim of the study:

The introduction of NOACs for patients with non-valvular AF several years ago has changed the anticoagulation landscape and created new challenges for managing patients undergoing left atrial RFA. However, the safety and efficacy of rivaroxaban as a periprocedural anticoagulant for RFA procedures are unknown.

The purpose of this study was to evaluate the safety and efficacy of periprocedural rivaroxaban in comparison with the more established uninterrupted phenprocoumon during left atrial RFA procedures for AF and atrial flutter.

II- Methods

1) Patients population

We retrospectively analyzed our data base for all left atrial RFA procedures performed between February 2012 and May 2013. We defined two groups of patients:

- Rivaroxaban group (RivG): This group included 272 consecutive patients who underwent a left atrial RFA procedure under continuous rivaroxaban therapy. Rivaroxaban (Xarelto®) was administered at a dose of 20 mg or 15 mg (in case of renal impairment with a creatinine clearance <50 ml/min) orally o.d.. The morning or evening administration according to patients´ habit was continued. 57% of patients received rivaroxaban 2- 6 hours prior to the procedure and 43% of patients 6-12 hours prior to the procedure.

- Phenprocoumon group (PhenG): An equal number of patients matched for age, sex, and type of rhythm disorder was included who received therapeutic (INR 2.0 - 3.0) anticoagulation with the VKA phenprocoumon (Marcumar®).

In both groups, oral anticoagulation therapy was started ≥4 weeks before RFA and was administered periprocedurally without interruption.

2) Ablation procedure

In all patients, transesophageal echocardiography (TEE) or dual source computer tomography (CT) scan was performed before the procedure to rule out left atrial appendage (LAA) thrombus. There was no LAA thrombus detected on TEE or dual source CT scan in any of the patients in either group.

All patients provided written informed consent. Ablation procedures were performed in the fasting state under conscious analgo-sedation (fentanyl sodium and midazolam or propofol) using a 3D mapping system for anatomy and catheter visualization (NavX, St. Jude Medical, St. Paul, MN, USA or Carto, Biosense Webster, Diamond Bar, CA, USA). Vascular access was obtained through the right and exceptionally left femoral vein. A 4-F femoral arterial sheath for invasive blood pressure monitoring was placed at the discretion of the operator. A steerable 8-polar catheter was placed in the coronary sinus (CS; EP-XT, C.R. Bard, Lowell, MA; USA). The left atrium (LA) was accessed by single transseptal puncture or via a patent foramen ovale. In both groups, after access to the LA, an i.v. bolus of unfractionated heparin (50 IU /kg body weight if baseline activated clotting time (ACT) was >170 sec or 60 IU /kg body weight if baseline ACT was ≤170 sec) was given. While catheters remained in the LA, the ACT was checked 15 min after the bolus and every 30 min thereafter to maintain an ACT between 270 and 300 sec with a continuous infusion of unfractionated heparin.

In paroxysmal AF, a circumferential pulmonary vein (PV) isolation was performed two by two [88]**.** Electrical isolation of the PV had to be demonstrated on a circular mapping catheter (Orbiter PV™, C.R, Bard, Lowell, MA, USA or Lasso™, Biosense Webster, Diamond Bar, CA, USA) by achieving entry block.

In persistent AF, a sequential ablation approach was used [63]. After PV isolation, the circular mapping catheter was placed in the LAA to monitor AF cycle length. An electrogram-guided (CFAE) substrate ablation was performed. The LA, right atrium and the CS were searched for CFAE as described by Nademanee et al. [57, 61] and, if found, ablated.

Atrial tachycardias as presenting rhythm for ablation or arising after CFAE ablation were mapped using entrainment maneuvers and activation sequence [89, 90]. A roof line between both superior PVs was performed for roof-dependent re-entries. An anterior line between the anterolateral mitral annulus and the ostium of the left superior PV was deployed for perimitral reentries. Alternatively, a mitral isthmus line deployed between the lateral mitral annulus and the left inferior PV could be performed. Localized reentries and foci were ablated focally.

For all ablations, irrigated radiofrequency (RF) energy using a 3.5-mm open irrigated tip ablation catheter (Therapy Cool Path Duo™ or Cool Flex™, St. Jude Medical, St. Paul, MN, USA or Thermocool® SmartTouch™ or SF Catheter, Biosense Webster, Diamond Bar, CA, USA) with a flow rate of 30 ml/min (15 ml/min for Cool Flex™ and Biosense SF Catheter) was delivered with a maximum temperature of 43°C and a maximum power of 30-40 W.

In absence of sinus rhythm after mapping and ablation, a DCC was performed at the end of the procedure.

The same operators performed the ablation procedures in both groups. Vascular access, ablation strategy and ablation techniques were similar between the two groups.

3) Postprocedural management

The sheaths were removed once the activated partial thromboplastin time was below 150 sec. Rivaroxaban 15 or 20 mg per os o.d. or phenprocoumon were given 24 hours after the last intake preprocedurally. Each oral anticoagulant was continued for ≥3 months. After RFA, all patients had a physical examination, an electrocardiographic monitoring, a transthoracic echocardiography and a duplex sonography of the vascular access site.

4) Safety endpoint

The safety endpoint was a composite of bleeding, thromboembolic events and death. The bleedings were classified according to the REPLACE-2 bleeding definition [91] with the inclusion of pericardial effusion.

Major bleeding complications included:

- Any bleeding requiring blood transfusion
- Retroperitoneal bleedings and hematomas requiring surgical intervention
- Pericardial effusions requiring drainage or surgical intervention (tamponade).
- Intracranial hemorrhage

Minor bleeding complications included:

- Hematomas (>5 cm) not requiring blood transfusion or surgical intervention

- Pericardial effusions (>5 mm) not requiring an intervention (non-tamponade).

Thromboembolic events included:

- Cerebrovascular accidents and transient ischemic attacks. In case of a suspected cerebrovascular event, a cranial CT scan or MRI of the brain had to be performed and the diagnosis had to be confirmed by a neurologist.

- Deep vein thrombosis and pulmonary embolism

- Peripheral arterial embolism

5) Statistical analysis

Data are presented as mean values and standard deviations for continuous variables with normal Gaussian distribution, non-normally distributed continuous variables are presented as median (interquartile range), categorical data are presented as exact numbers and percentages. Both groups were compared using the independent student t-test for continuous variables, non-parametric Wilcoxon tests for non-normally distributed traits, and the chi-square test or Fisher exact test where appropriate for categorical variables. A multivariable logistic regression analysis was performed to determine predictors of complications. All potential confounders were included in a stepwise regression analysis based on clinical significance or observed univariable association. The odds ratio (OR) and 95% confidence interval (CI) of composite bleeding and thromboembolic complications were computed. A two-tailed p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 21 for Windows (SPSS, Inc., Chicago, Illinois, USA).

III- Results

1) Baseline characteristics

1.1) Clinical characteristics

The patients' characteristics of both groups are shown in table 5. The mean age of the patients was similar in both groups (62.5 ± 10.6 years in the RivG and 63.7 ± 9.6 years in the PhenG, p = 0.18) with 68 % being male in each group. The treated arrhythmia was atrial fibrillation in 77 % of patients of each group and was classified as paroxysmal in 133 of 209 patients (64 %) in the RivG and in 126 of 209 (60 %) in the PhenG (p = 0.61). There were no significant differences in the individual components of the CHA2DS2-VASc score, the mean CHADS2 score, left atrial size, and the presenting rhythm on arrival at the electrophysiology laboratory between both groups.

There were more redo procedures in the PhenG than in the RivG (128 (47%) vs. 64 (24%), p <0.001). The duration of the ablated rhythm disorder before RFA was longer in the PhenG compared to the RivG (37 ± 41 months vs. 26 ± 38 months, p<0.01). The use of antiplatelet agents, aspirin and clopidogrel, and other clinical characteristics were similar between the two groups except for the use of beta-blockers and calcium-channel-blockers, which was higher in the PhenG (257 (94%) vs. 221 (81%), p<0.001, and 30 (11%) vs. 5 (2%), p<0.001), respectively).

Table 5: Baseline demographics, clinical parameters and medication of patients presenting for RFA on rivaroxaban (Xarelto®) or phenprocoumon (Marcumar®)

Baseline characteristics	**Rivaroxaban group (RivG) (n = 272)**	**Phenprocoumon group (PhenG) (n = 272)**	**p Value**
Demographics			
Age, yrs	62.5 ± 10.6	63.7 ± 9.6	0.18
Age ≥75 yrs	26 (10)	31 (11)	0.71
Male	185 (68)	185 (68)	>0.99
Body mass index, kg/m^2	27.3 ± 4.5	27.5 ± 4.4	0.64
Medical history			
AF type			
Paroxysmal	133 (49)	126 (46)	0.61
Persistent	76 (28)	83 (31)	0.57
Atrial tachycardia	63 (23)	63 (23)	>0.99
Redo procedure	64 (24)	128 (47)	<0.001
Duration of AF/AT, months (mean)	26 ± 38	37 ± 41	<0.01
Heart failure (LVEF <40%)	9 (3)	13 (5)	0.52
Hypertension	173 (64)	162 (60)	0.86
Diabetes mellitus	26 (10)	32 (12)	0.49
Prior TIA or stroke	16 (6)	19 (7)	0.73
Coronary artery disease	35 (13)	32 (12)	0.70

Chronic renal insufficiency	17 (6)	9 (3)	0.23
$CHADS_2$ score, mean	0.9 ± 0.8	1.0 ± 0.9	0.25
CHA_2DS_2-VASc score, mean	1.8 ± 1.4	2.0 ± 1.5	0.22
0	50 (18)	50 (18)	>0.99
1	73 (27)	67 (25)	0.62
≥2	149 (55)	155 (57)	0.67
Mean left atrial size, mm	44 ± 6	45 ± 7	0.09
Mean LVEF, %	60 ± 37	56 ± 7	0.05
Medication use			
Aspirin	41 (15)	39 (14)	0.90
Clopidogrel	6 (2)	5 (2)	>0.99
Aspirin and Clopidogrel	4 (1)	3 (1)	>0.99
ACE inhibitor / ARB	121 (44)	142 (52)	0.09
Beta-blocker	221 (81)	257 (94)	<0.001
Calcium-channel blocker	5 (2)	30 (11)	<0.001
Digoxin	9 (3)	18 (7)	0.11
Statins	75 (28)	73 (27)	0.85
Diuretic	61 (22)	85 (31)	0.03

Values are mean ± SD or n (%); ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AT, atrial tachycardia; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack

1.2) Procedural and anticoagulative data

1.2.1) Procedural data

Procedural data are shown in table 6. The median procedure time was longer in RivG (151 vs. 141 min., p=0.03). There were no differences in the median radiofrequency ablation time (42 vs. 45 min., p=0.15) and fluoroscopy time (22 vs. 20 min., p=0.35) between both groups. PV isolation was performed in 235 of 272 (86%) and 231 of 272 (85%) in the rivaroxaban and phenprocoumon group, respectively (p = 0.62). Additional ablation including ablation of CFAE and linear ablation was similarly performed in both groups (76 (28%) vs. 76 (28%), p >0.99 and 110 (40%) vs. 105 (39%), p = 0.86, respectively).

Table 6: Comparison of procedural data between patients on rivaroxaban (Xarelto®) and phenprocoumon (Marcumar®).

Procedural Variables	**Rivaroxaban group (RivG) (n = 272)**	**Phenprocoumon group (PhenG) (n = 272)**	**p Value**
Presenting rhythm			
- Sinus rhythm	147 (54)	129 (47)	0.07
- AF / AT	125 (46)	143 (53)	0.15
Procedural time, min median (25th and 75th perc.)	151 (116, 200)	141 (98, 185)	0.03

Fluoroscopy time, min median (25th and 75th perc.)	22 (14, 33)	20 (12, 31)	0.35
RF time, min median (25th and 75th perc.)	42 (24, 67)	45 (30, 70)	0.15
Intraprocedural cardioversion	70 (26)	66 (24)	0.84
PV isolation	235 (86)	231 (85)	0.62
Lines	110 (40)	105 (39)	0.86
CFAE	76 (28)	76 (28)	>0.99

Values are mean ± SD, median (25th and 75th perc.) or n (%); AF = atrial fibrillation; AT = atrial tachycardia; RF = radiofrequency; PV = pulmonary vein; CFAE = complex fractionated atrial electrogram

1.2.2) Anticoagulative data:

The mean INR on the day of the procedure was 1.2±0.2 (RivG) and 2.1±0.4 (PhenG) ($p<0.001$). The baseline ACT was significantly higher in the RivG (156±37 seconds) than in the PhenG (142±20 seconds, $p<0.001$). The mean ACT during the procedure was significantly lower in the RivG than in the PhenG (278±32 seconds vs. 289±35 seconds, $p<0.001$). There was no difference in the mean of maximum ACT during the procedure between the two groups (307±47 seconds vs. 311±44 seconds, $p=0.31$). The median of total unfractionated heparin required to maintain a therapeutic ACT during RFA was significantly higher in the RivG (9550 IU/kg) than in the PhenG (8075 IU/kg, $p <0.001$), however this difference was abolished after accounting for body

weight and procedure duration (total heparin dosage/body weight/hour: 45 vs. 44 IU/kg/h, p=0.19) (Table 7).

Table 7: Comparison of intraprocedural anticoagulative data between patients on rivaroxaban (Xarelto®) and phenprocoumon (Marcumar®).

Intraprocedural anticoagulative data	**Rivaroxaban group (RivG) (n = 272)**	**Phenprocoumon group (PhenG) (n = 272)**	**p Value**
INR	1.2 ± 0.2	2.1 ± 0.4	<0.001
Baseline ACT (sec)	156 ± 37	142 ± 20	<0.001
Maximum ACT (sec)	307 ± 47	311 ± 44	0.31
Mean ACT (sec)	278 ± 32	289 ± 35	<0.001
Any ACT value >300 sec (%)	139 (51)	157 (58)	0.12
Total heparin dosage (IU) median (25th and 75th perc.)	9550 (7375, 12225)	8075 (6250, 10600)	<0.001
Total heparin dosage/body weight (IU/Kg) median (25th and 75th perc.)	116 (90, 141)	99 (78, 124)	<0.001
Total heparin dosage/body weight/hour (IU/kg/h)	45 (36, 60)	44 (33, 59)	0.19

median (25th and 75th perc.)			

Values are mean ± SD; or median (25th and 75th perc.), INR, international normalized ratio; ACT, activated clotting time

2) Safety endpoint (Table 8)

No deaths and no thromboembolic complications occurred in either group. Periprocedural complications consisted of bleeding complications occurring in 55 of 544 (10%) patients.

The prevalence of total bleeding complications between the RivG (8%) and the PhenG (13%) (p = 0.09), as well as the composite endpoint of bleeding and embolic complications (8% vs. 13%, p = 0.09) did not differ significantly. In the RivG, the timing of drug administration relative to the procedure did not result in a significant difference in the safety endpoint (<6 hrs vs. ≥6 hrs, p=0.37).

Major bleeding complications occurred in 1 of 272 (0.4%) patients in the RivG (cardiac tamponade requiring surgery of a disruption of the posterior LA) and 1 of 272 (0.4%) patients in the PhenG (groin hematoma requiring two units of packed red blood cells transfusion) (p >0.99). Both patients had uneventful recovery after intervention. None of the patients with major bleeding complications received coagulation factor complexes.

Minor bleeding complications occurred in a similar proportion of patients in the RivG (20 of 272, 7%) and PhenG (33 of 272, 12%), respectively (p = 0.08).

Pericardial effusion without tamponade occurred more often in the PhenG (22 of 272; 8%) than in the RivG (9 of 272, 3%), p = 0.03). Groin hematomas requiring no

intervention occurred in a similar proportion of patients in both groups (12 (4%) vs. 11 (4%), p > 0.99, respectively).

Table 8: Comparison of complications between patients on rivaroxaban (Xarelto®) and phenprocoumon (Marcumar®)

	Rivaroxaban group (RivG) (n = 272)	**Phenprocoumon group (PhenG) (n = 272)**	**Total *(n = 544)***	***p Value***
Major bleeding complications (%)	1 (0.4)	1 (0.4)	2 (0.7)	>0.99
Cardiac tamponade (%)	1 (0.4)	0 (0)	1 (0.2)	>0.99
Groin hematomas requiring vascular surgery (%)	0 (0)	0 (0)	0 (0)	>0.99
Groin hematomas requiring blood transfusion (%)	0 (0)	1 (0.4)	1 (0.2)	>0.99
Retroperitoneal bleeding (%)	0 (0)	0 (0)	0 (0)	>0.99
Minor bleeding complications (%)	20 (7)	33 (12)	53 (10)	0.08
Pericardial effusion without tamponade >5mm (%)	9 (3)	22 (8)	31 (6)	0.03

Groin hematomas >5cm (%)	11 (4)	12 (4)	23 (4)	>0.99
Total bleeding complications (%)	21 (8)	34 (13)	55 (10)	0.09
Embolic complications (CVA/TIA) (%)	0 (0)	0 (0)	0 (0)	>0.99
Death (%)	0 (0)	0 (0)	0 (0)	>0.99
Composite of bleeding and embolic complications and death (%)	21 (8)	34 (13)	55 (10)	0.09

Values are mean ± SD or n (%); CVA, cerebrovascular accident; TIA, transient ischemic attack

3) Predictors of bleeding complications (table 9)

On univariate analysis, a higher CHA_2DS_2-VASc score (2.3 ± 1.3 vs. 1.8 ± 1.4, p = 0.03), a larger left atrial size (47 ± 6 mm vs. 44 ± 7 mm, p = 0.04), arterial hypertension (75% vs. 60%, p = 0.03), persistent AF ablation (71% vs. 50%, p < 0.01), intraprocedural cardioversion (42% vs. 23%, p < 0.01), CFAE ablation (45% vs. 26%, p < 0.01) and persistent AF or AT as presenting rhythm (73% vs. 47%, p < 0.001) were associated with bleeding complications.

On multivariate regression analysis including age, sex, CHA_2DS_2-VASc score, type of presenting rhythm disorder, aspirin use, and rivaroxaban use, the independent predictors of the safety endpoint were female gender (OR 1.96, 95% CI 1.10 - 3.49) and persistent AF or AT as presenting rhythm disorder (OR 3.25, 95% CI 1.74 - 6.08). Rivaroxaban was not an independent predictor of the safety endpoint (OR 1.652, 95% CI 0.92-2.96).

Table 9: Univariate and multivariate predictors of complications (composite of bleeding and thromboembolic complications and death)

	Univariate analysis			**Multivariate analysis**		
	No complications	**Complications**				
	(n = 489)	(n = 55)	*p Value*	*Odds ratio*	*95% CI*	*p Value*
Age, yrs	62.8 ± 10.2	65.6 ± 8.9	0.05	-	-	0.37
Female	150 (31)	24 (44)	0.05	1.96	1.10 - 3.49	**0.02**
Body mass index,	27.3 ± 4.3	28.3 ± 5.4	0.09			

kg/m^2						
CHA_2DS_2-Vasc score, mean	1.8 ± 1.4	**2.3 ± 1.3**	**0.03**	-	-	0.37
0	**96 (20)**	4 (7)	**0.03**			
1	128 (26)	12 (22)	0.48			
≥ 2	265 (54)	**39 (71)**	**0.02**			
Mean left atrial size, mm	44 ± 7	**47 ± 6**	**0.04**			
Mean LVEF, %	58 ± 27	56 ± 8	0.64			
Hypertension	294 (60)	**41 (75)**	**0.03**			
Chronic renal insufficiency	25 (5)	1 (2)	0.30			
AF or AT as presenting rhythm	228 (47)	**40 (73)**	**<0.001**	3.25	1.74 - 6.08	**<0.001**
Persistent AF ablation	246 (50)	**39 (71)**	**<0.01**			
Redo procedure	166 (34)	26 (47)	0.08			
RF time, min	44 [28, 68]	40 [26,67]	0.46			
Procedure duration, min	147 [105, 191]	140 [112,200]	0.73			
Intraprocedural cardioversion	113 (23)	**23 (42)**	**<0.01**			
PV isolation	420 (86)	46 (84)	0.62			
Lines	194 (40)	21 (38)	0.87			
CFAE ablation	127 (26)	**25 (45)**	**<0.01**			
Aspirin	70 (14)	10 (18)	0.44	-	-	0.41
Rivaroxaban	251 (51)	21 (38)	0.06	1.652	0.92-2.96	0.09
Maximal ACT (sec)	310 ± 46	304 ± 44	0.37			
Mean ACT (sec)	284 ± 34	279 ± 32	0.28			

Total heparin dosage (IU)	8850 [6650, 11600]	9425 [7162, 11975]	0.59			
Total heparin dosage/body weight (IU/kg)	107 [82, 131]	109 [83, 139]	0.43			

Values are mean ± SD; or median (25th and 75th perc.); ACT, activated clotting time; AF = atrial fibrillation; AT = atrial tachycardia; RF = radiofrequency; PV = pulmonary vein; CFAE = complex fractionated atrial electrogram

IV- Discussion

The main finding of the study is that uninterrupted rivaroxaban is not associated with thromboembolic events or with an increased bleeding risk compared to uninterrupted vitamin K antagonist (phenprocoumon) administration.

1) Catheter ablation under uninterrupted novel oral anticoagulants

Up to now, there are only limited and conflicting data about the periprocedural use of dabigatran during left atrial RFA [92, 93]. Regarding rivaroxaban, one prospective observational study from Eitel et al. [94] showed that anticoagulation with NOACs including rivaroxaban after AF catheter ablation is safe and effective. A recently published post-hoc analysis of a ROCKET AF substudy [95] showed that rivaroxaban (n=36) could be continued periprocedurally for RFA with no differences in long-term stroke rates or survival compared to periprocedural warfarin therapy (n=43). There are no randomized data to support the use of rivaroxaban as the periprocedural anticoagulant for RFA [31]. Our study systematically evaluated the safety of uninterrupted periprocedural rivaroxaban during left atrial RFA compared to the more accepted uninterrupted phenprocoumon therapy in a large group of patients. In this

study, no deaths or thromboembolic complications occurred with rivaroxaban. The overall bleeding rate of 10% corresponds to previously published studies dealing only with phenprocoumon [82, 84] Total bleeding complications were not significantly different between both groups. There was a tendency toward less minor bleeding complications with rivaroxaban (7%) compared to VKA (12%), this was due to a higher rate of non-tamponade pericardial effusions in the phenprocoumon group. These small pericardial effusions are frequent after extensive LA ablation and a differentiation between an inflammatory reaction and a bleeding complication is in most cases impossible [96].

Our results are in line with the recently published multicenter registry study of Lakkireddy et al.[97]. In this study, 321 patients undergoing AF ablation on uninterrupted rivaroxaban were matched with an equal number of patients on uninterrupted warfarin. The two groups showed similar rates for major (1.6% vs. 1.9%; p=0.772) and minor (5% vs. 5.9%; p=0.6) bleeding complications. One transient ischemic attack occurred in each group.

In the multivariate regression analysis, female gender was associated with complications and this has been shown in other studies [98-100]. Persistent AF and AT as presenting rhythm represented a risk factor for complications, probably because of a more extensive ablation strategy and a more fibrotic LA[99].

2) Advantages and disadvantages of rivaroxaban therapy

Rivaroxaban has several advantageous pharmacologic properties. In addition to having a favorable anticoagulation profile [34], the drug has a relatively short half-life (5

- 9 hours) and rapid onset of action (2 - 4 hours) with shorter time to therapeutic anticoagulation than a VKA like phenprocoumon. It has a predictable pharmacokinetic profile with lower inter- and intraindividual variability that permits fixed dose administration without the need for coagulation monitoring [101].

For left atrial RFA procedures, the pharmacologic properties favor the periprocedural use of rivaroxaban. It can be immediately restarted with fully anticoagulatory effect once a hemostatic state is established after sheath removal. On the other hand, the most concerning disadvantage is the lack of a specific antidote to acutely reverse the anticoagulatory effect. Prothrombin complex concentrate (PCC) and activated PCC have been used and completely reverse the anticoagulant effect of rivaroxaban [102, 103]. In our study, there was one periprocedural cardiac tamponade in the rivaroxaban group which had to be managed surgically. Using continuous periprocedural rivaroxaban in RFA-procedures may therefore necessitate PCC administration or surgical intervention to manage bleeding complications. In this context, it has to be said, that there is also no specific, rapidly acting antidote for VKA.

The question remains, if the bleeding risk outweighs the advantages of using rivaroxaban for left atrial RFA procedures. In our study, consistent with the findings by Piccini et al. [95] and Lakkireddy et al. [97], we neither found evidence for an increased risk of stroke or systemic embolism nor for an increased bleeding risk in patients treated periprocedurally with rivaroxaban compared with continued VKA. Therefore, and knowing the overall safety profile and predictable pharmacokinetics, rivaroxaban could represent an optimal anticoagulant strategy during left atrial RFA.

3) Intraprocedural ACT measurement and heparin administration during continuous rivaroxaban therapy

For intraprocedural heparinization we choose to target an ACT of 270-300 sec. In the recent consensus statement [52], it was recommended to maintain a target ACT of at least 300-350 sec. This recommendation is based on studies that showed that thrombi can form on the transseptal sheath and/or electrode catheter almost immediately after crossing the septum and that early heparinization substantially decreases this risk. However, these studies were conducted with discontinued warfarin and periprocedural bridging with heparin [104-106].

A recent meta-analysis [87] showed variable ACT target values and the individual use of protamine. There is no clear recommendation regarding the target ACT in patients under continuous oral anticoagulation [107].

In a multicenter registry evaluating the safety of continuous dabigatran with a target ACT of 300-400 sec, the incidence of major bleeding was as high as 6% [92]. In another large study in which dabigatran was stopped on the evening before the procedure and ACT targeted at 300–350 sec, major bleeding occurred in 2% of patients without thromboembolic complications [93]. This shows that a slightly lower ACT could decrease bleeding complications without increasing thromboembolic events. In our experience, intraprocedural heparin infusion with a target ACT of 270-300 sec in patients under continuous oral anticoagulation represents a safe and effective protocol [108].

Patients who were treated with rivaroxaban received a 15% increased heparin dose compared to patients receiving phenprocoumon, however this difference was no longer significant after accounting for body weight and procedure duration.

Nevertheless, despite comparable heparin dose, the mean ACTs achieved during the RFA procedure were significantly lower in the rivaroxaban group. ACT measurement does not seem to appropriately reflect the true anticoagulative status of the patient under continuous rivaroxaban therapy. Similar findings were described using periprocedural dabigatran [93]. Further investigation is needed to understand this mechanism. Upcoming alternative anticoagulation assays such as drug-specific anti-factor Xa activity measurements may prove useful for assessing anticoagulatory activity and potentially helpful to guide intraprocedural heparin administration.

4) Study limitations

The present study was not randomized but accomplished with a retrospective data collection of patients treated with rivaroxaban or phenprocoumon in a single center. However, the patient groups were well matched for age, sex and type of rhythm disorder. The difference regarding redo procedures and duration of the rhythm disorder before RFA seem to reflect the recent introduction of NOACs. Patients with new AF onset are more likely to be anticoagulated with rivaroxaban, whereas patients with previously well-adjusted INR values continue taking phenprocoumon.

Given the size of the study and the low event rate for thromboembolic complications, we are limited in drawing clinical conclusions about the efficacy in the prevention of thromboembolic events. Additionally, in view of our intraprocedural ACT and heparin measurements, the optimal heparin dosage seems to require further investigation.

V- Summary

Data about the use of novel oral anticoagulants in the setting of left atrial radiofrequency catheter ablation (RFA) procedures are lacking. This study aimed to evaluate the safety of continuous periprocedural rivaroxaban administration during left atrial RFA in comparison with the more established uninterrupted oral vitamin K antagonist (VKA) administration.

The study cohort included 544 patients who underwent left atrial RFA procedures between February 2012 and May 2013. All patients (n=272) receiving uninterrupted periprocedural rivaroxaban 15 or 20 mg/day before the procedure (RivG) were matched by age, sex, and type of rhythm disorder with an equal number of patients with the uninterrupted VKA phenprocoumon (PhenG) (INR: 2-3). During RFA, heparin i.v. was given to maintain an activated clotting time (ACT) at 270-300 seconds. The safety endpoint was a composite of bleeding, thromboembolic events and death.

There were no thromboembolic complications and no deaths in either group. The prevalence of major bleeding complications was similar in both groups (one tamponade in RivG and one groin hematoma requiring transfusion in PhenG). Minor bleeding complications occurred equally in both groups (20 of 272, 7% in the RivG vs. 33 of 272, 12% in the PhenG, p=0.08).

On multivariable regression analysis, female gender (OR 1.96, 95% CI 1.10-3.49, p=0.02) and atrial fibrillation or atrial tachycardia as presenting rhythm disorder (OR 3.25, 95% CI 1.74 - 6.08, p<0.001), but not rivaroxaban (OR 1.652, 95% CI 0.92-2.96, p=0.09) were found as independent predictors of the safety endpoint.

Thus, continuous rivaroxaban appears to be as safe as the uninterrupted therapeutic use of VKA (phenprocoumon). Large, randomized controlled studies are required to confirm our results and to identify the optimal periprocedural

anticoagulation protocol for left atrial ablation procedures.

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