Oct - Nov 2018

Volume 11 - Issue 3

JAFIB

Journal of Atrial Fibrillation

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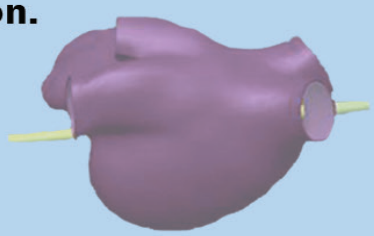

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Oct-Nov 2018
Volume 11, Issue 3

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From the Editor's Desk

Journal of Atrial Fibrillation (JAFIB)

Oct - Nov 2018

Issue 3

Volume 11

Dhanunjaya (DJ)Lakkireddy
MD, FACC, FHRS
Editor-in-Chief, JAFIB

Dear Colleagues

On behalf of JAFIB we welcome you to 2019. Hope you had a productive and fruitful 2018 on the personal and professional fronts.

We want to thank all the contributors whose efforts enhanced the value of JAFIB in its mission of quality education for healthcare professionals and patients alike. Several exciting inventions, discoveries, theories and hypothesis have marked 2018 in the AF world. Clearly the focus shifted from target specific therapies to a comprehensive systemic approach. The importance of risk factor modification in arresting the evolution of the disease processes is the evolving mantra.

The Journal had a tremendous patronage and viewership this year. We will continue to build on the gains we made over the years. In this issue we have some excellent manuscripts covering a wide range of topics – from implantable loop recorder- based diagnostics in stroke evaluation to understanding the impact of various types of ablation technologies on AF therapy outcomes. In the New Year we aim to give a little make over to our website and manuscript submission process. For those that are interested in being reviewers and contributors please check the main website for details.

This edition of JAFIB has some exceptionally good original articles and reviews that we are sure you will enjoy.

We wish you a happy New Year and a blessed 2019 in all your endeavors.

Best wishes

DJ Lakkireddy

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Original Research
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Predictors of Successful Ultrasound Guided Femoral Vein Cannulation in Electrophysiological Procedures

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Abstract

Background: Vascular complications are frequently reported after electrophysiological (EP) procedures. Ultrasound (US) guidance during femoral vein cannulation has shown to reduce vascular damage related to unsuccessful attempts.The aim of our study is to define, under ultrasound guidance,anatomical and technical predictors of successful femoral vein cannulation in a cohort of patients undergoing EP.

Material and Methods: From December 2015 to January 2018, 192 patients (mean age 63,1±15,9 years, M:F=118:74) undergoing EP were enrolled in the study. US-guided approach to femoral vessels cannulation was used in all subjects by four untrained operators. Femoral vein and artery depths and diameters were measured in all patients. Unsuccessful attempts (UA) and time to successful cannulation (TSC) were also calculated.

Results: Vein and artery depths correlated with body weight (r=0.38 and 0.39, p=0.00), body mass index (r=0.53 and 0.50, p=0.00), and body surface area (r=0.25 and 0.28, p=0.00). Interestingly, the number of UA)positively correlated with vein depth (r=0.23, p=0.01 for the right side and r=0.33, p=0.00 for the left side). Linear regression analysis showed that both vein depth (ß=0.42, p=0.001) andoperator training(ß= -0.75,p=0.00)were independently associated with UA.

Conclusions: Anthropometric features, namely BMI and BSA, may provide information about femoral vein/artery anatomy in patients undergoing EP procedures. Patients with high BMI have deeper and larger veins, however only vein depth is a determinant of successful cannulation. Numbers of UA and TSC significantly decrease with operators training.

Introduction

Vascular damages are frequent but underestimated complications in patients undergoing electrophysiological (EP) procedures[1]. In the recent FIRE and ICE trial patients undergoing ablation for atrial fibrillationhad a high rate (4.3% in the radiofrequency group and 1.9% in the cryoablation group) of groin-site vascular complications, namelyvascular pseudoaneurysm, arteriovenous fistulas, hematomas,puncture-site hemorrhages, and groin pain[2]. Many factors concur to the increased risk of vascular complications in patients undergoing EP. These include - but are not limited to - the increasing use of peri-procedural anticoagulant therapy[3], introduction of several wide sheaths within the same vein as well as vein cannulation techniqueused[4].The procedure of vein cannulation usually fore sees the palpation of the laterally positioned common femoral artery to guide the insertion of the needle into the vessel ("so called"blinded approach). However,this procedure is highly dependent both on patient anatomyand operator skills. These variables significantly reduce the chances of first pass success, leading in many cases to undesirable arterial or nerve punctures. Ultrasound (US) guidance during EP procedures has shown to be a valuable tool for the visualization of femoral vessels trajectory,and its use has shown to dramatically decrease vascular complications[5-7].

The aim of the present study is toidentify clinical predictors of femoral vessel anatomy and unsuccessful vein cannulationin patients undergoing EP procedures withUS-guided cannulation. We also investigatehow operator performance and training may impact on successful vein cannulation.

Key Words

Ultrasound Guided Cannulation, Femoral Vein Puncture, Vascular Complications, Electrophysiological Procedures

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Material and Methods

Patient population

From December 2015 to January 2018 all patients undergoing EP procedures among the Electrophysiology Laboratory of Misericordia Hospital, Grosse to, Italy, were consecutively enrolled in the study. Clinical history and laboratory parameters were collected for each subject. At the time of the procedure, all patients provided written informed consent to data storage and analysis. After the procedure patients were evaluated on daily basis until discharge,and underwent a follow-up visit at 30-days.

Ultrasound guided femoral cannulation and anatomical measures

An US-guided approach was used by four untrained electrophysiologists in all patients. Right and/or left femoral veins were selective cannulated based onprocedural needs.

An ultrasound system (MyLabTMSevenHD CrystalLine, ESAOTE s.p.a., Genoa, Italy) equipped with a 7.5 MHz AL2442 linear probe was used for all the exams. Briefly,the probewas inserted in a sterilesleeve and positioned on the groins. Basal frames were recorded at the level of desired puncture site (about 1-1,5 cm under the inguinal ligament)in the short axis view. Femoral vein and artery depths and diameters were measured, as shown in [Figure 1]. Duringreal time visualization of the femoral vasculature (both artery and vein) in short axis scanning, local anesthetic was injected into the subcutaneous tissue. Thereafter,an 18-gauge, 7-cm length needle was advancedbelow the US probe toward the vein while watching for needle tip or tissue movement on the US screen. Once the vein was entered(Seldinger technique),a metallic guide was introduced into the needle that was removed. An unsuccessful attempt (UA) was defined in case of failure to reach the vessel leading to remove the needle from the skin; inability to introduce the wire once the vessel was tip with needto move away the needle, or in case of arterial or nerve puncture.A maximum of two sheaths (from 5F to 15F) were placed into each femoral vein. Instead of using fluoroscopy, the operator checked the effective route of the guidewire inside the vein using US short and long axis view. When a retrograde approach was desired the right or left femoral artery was also cannulated in the same manner. Time to successful cannulation (TSC) was considered the time to complete insertion of the needed sheats "per side" and not "per single vein" including: visualization of the vessels, needle advancing with vessel puncture, insertion of the wires, check of the wires in long axis view, insertion of the sheats.

Electrophysiological study and ablation

Procedures were performed following the standard of care for each indication using appropriate tools and systems.Traditional fluoroscopy-guided simple electrophysiological studies and ablations such asintra-nodal reentry tachycardias, cavo-tricuspid isthmus dependent atrial flutters, accessory pathways-related tachycardias were performed. CARTO®3 mapping system (Biosense Webster, Johnson and Johnson, Diamond Bar, USA) was used for complex ablations like Pulmonary Veins Isolation (PVI), atypical atrial flutters, ventricular tachycardias, premature ventricular contractions (PVCs) ablation and for redo procedures. Almost half of PVI procedures (21/49) were performed using Crioballoon technology (Artic FrontAdvanceTM, Medtronic, Minneapolis, USA).Warfarin was uninterrupted during the procedures. During the first year direct oral anticoagulants(DOACs)were suspended according to international guidelines[8,9]whereas DOACs were left uninterrupted during the second year based on recent evidence[3,10,11,12]. During catheterization of left side chambers intravenous nonfractionated heparin was administered reaching target ACT values of 300 to 400 sec[13]. Protamine Solphate was administered at the end of the procedure to reverse anticoagulation.

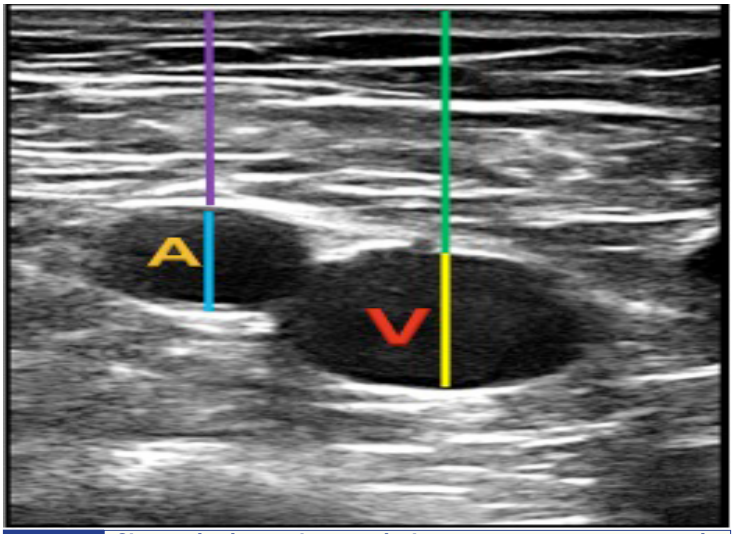

Figure 1: Short axis view and anatomical measurements at puncture site. To be noted femoral vein lying below and medial to the ipsilateral artery. V=vein, A=artery, green bar=vein depth, yellow bar=vein diameter, violet bar=artery depth, light blue bar=artery diameter.

Postprocedural follow up

Patients were discharged the next day of the procedure in case of simple electrophysiological studies and ablation or the second day after in case of complex ablations. If the patient needed therapy other than ablation hospitalization was prolonged according to the specific treatment. We routinely checked groins with inspection, palpation and auscultation the evening of the procedure, the next morning, and the day of discharging. In case of presence of any complication we checked the groin every day until discharge. If indicated a groin ultrasound was performed. Patients were reevaluated at 30 days after the procedure with clinical examination and were carefully asked for any complication during the time spent at home.

Statystical Analysis

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages. Pearson correlation was employed to evaluate a possible relationship between femoral vein depth and anthropometric and clinical characteristics. Several multivariate linear regression model (with a stepwise forward procedure) adjusted for relevant confounders were built to identify predictors of unsuccessful attempts. The statistical package SPSS 17.0 was used for the analysis. A $p < 0.05$ was considered as significant.

Results

Baseline Population characteristics

From December 2015 to January 2018, 192 consecutive Caucasian patients (mean age 63,1±15,9 years, M:F=118:74) were consecutively enrolled. [Table 1]resumes baselineanthropometric and laboratory characteristics of the study population. [Table 2] depicts clinical information (i.e. underlying heart disease, antithrombotic therapy, indication to the EP procedure). 61.5% of patients were males while 54.7% displayed overt heart disease. Half of patients underwent procedures under antiplatelet or anticoagulant therapy (up to 55,7% including DOACs, vitamin K antagonists, aspirin, clopidogrel, low molecular weight heparins). Only 15 out of 34 (44,1%) patients, assuming warfarin uninterruptedly, had INR 2<3 on the day of the procedure.The high rate of prescribed antithrombotic therapy reflects the fact that half of the indications to the EP procedure were

represented by atrial flutter/atrial fibrillations (46,4%, [Table 2]).

Table 1: Anthropometric and laboratory characteristics of study population

Number of patients	192
Age (years)	63.1±15.1
M:F (%)	61.5:38.5
Weight (Kg)	77.1±14.6
Height (m)	1.7±0.1
BMI (Kg/m2)	26.4±4.1
BSA (m2)	1.9±0.2
Creatinine (mg/dl)	1.1±0.5
Haemoglobin (gr/dl)	13.6±1.6
Platelets (x 10 3 /mL)	217.5± 8.5

BMI: Body mass index, BSA: Body surface area

Table 2: Clinical characteristics of study population.

		N (%)
Cardiomyopathy	Hypertensive	60 (31.3)
	Ischaemic	15 (7.8)
	Valvular	14 (7.3)
	Idiopathic	11 (5.7)
	Other (i.e. congenital, tachycardiomiopathy)	5 (2.6)
Antithrombotic Therapy	None	85 (44.3)
	DOACs	41 (21.3)
	Vitamin K antagonists	34 (17.7)
	Antiplatelets	29 (15.1)
	LMWH	3 (1.6)
Indications to EP procedure	PSVT	54 (28.1)
	AF/Atypical AFL	52 (27.1)
	Typical AFL	37 (19.3)
	Syncope	30 (15.6)
	VAs	19 (9.9)

DOACs=Direct Oral Anticoagulants; LMWH=Low Molecular Weight Heparin, EP=Electrophysiological, PSVT=Paroxysmal SupraVentricular Tachycardia, AF=Atrial Fibrillation, AFL=Atrial Flutter, VAs = Ventricular Arrhythmias

Anatomical features of femoral vessels

Mean femoral vein depth was 2.2±0.6 cm,higher than artery depth (1.8±0.6 cm). Vein and artery diameters were respectively 0.9±0.3 cm and 0.8±0.2 cm. Interestingly enough,we observed that both vein and artery depths significantly and positively correlated with body weight (r=0.38 and 0.39, p=0.00), BMI (r=0.53 and 0.50, p=0.00) and BSA (r=0.25 and 0.28, p=0.00). The same anthropometric factors also correlated with veins (r=0.44, p=0.00 for weight; r=0.32, p=0.00 for BMI; r=0.44, p=0.00 for BSA) and arteries diameter (r=0.33, p=0.00 for weight; r=0.16, p=0.02 for BMI; r=0.36, p=0.00 for BSA). [Figure 2] shows linear correlation between right femoral vein depth and BMI.

Unsuccessful attempts (UA) and time to successful cannulation (TSC)

Among 192 procedures, 62 were performed by operator 1 (27 during the first year and 35 during the second year), 57 were performed by operator 4 (22 in the first year and 35 in the second year). Operator 2 and operator 3 performed respectively 38 (15 and 23) and 35 (10 and 25) cases. The four operators showed comparable rates of unsuccessful attempts (UA ≥ 1), ranging between 21,3% to 38% on the right side and from 20.7 to 27.8% on the left side([Figure 3], upper panels). Interestingly, the number of UAfor each operator positively correlated with vein depth (r=0.23, p=0.01 for the right side and r=0.33, p=0.00 for the left side).

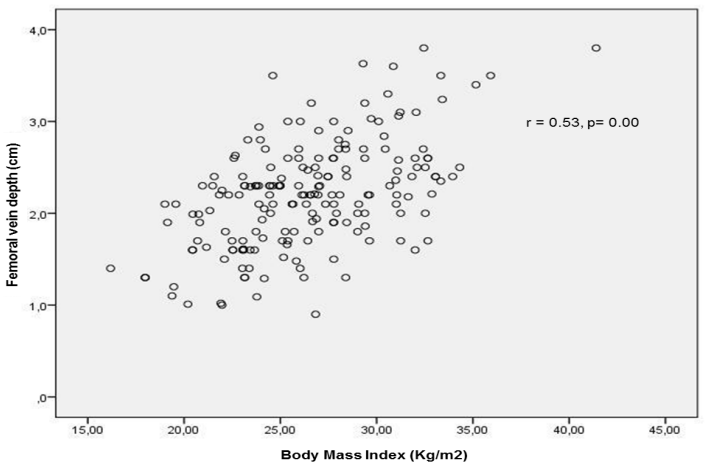

Figure 2: Linear correlation between femoral vein depth andbody mass index.

Unsuccessful attempts (UA) and time to successful cannulation (TSC)

Among 192 procedures, 62 were performed by operator 1 (27 during the first year and 35 during the second year), 57 were performed by operator 4 (22 in the first year and 35 in the second year). Operator 2 and operator 3 performed respectively 38 (15 and 23) and 35 (10 and 25) cases. The four operators showed comparable rates of unsuccessful attempts (UA ≥ 1), ranging between 21,3% to 38% on the right side and from 20.7 to 27.8% on the left side([Figure 3], upper panels). Interestingly, the number of UAfor each operator positively correlated with vein depth (r=0.23, p=0.01 for the right side and r=0.33, p=0.00 for the left side).

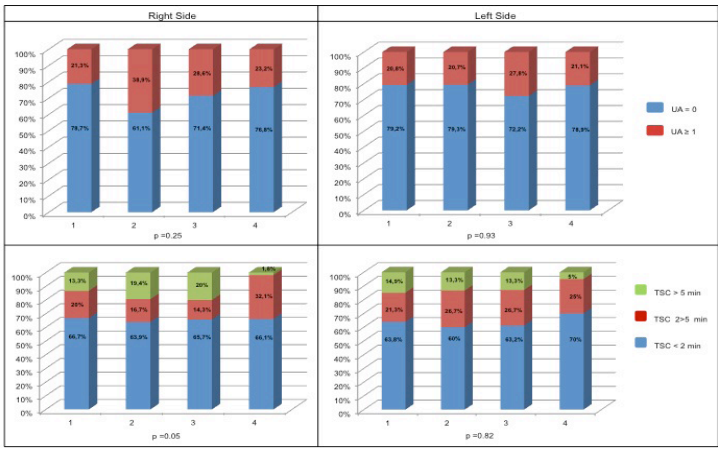

Figure 3: Upper Panels: global rate of unsuccessful attempts (UA) for cannulation divided across operators (1,2,3,4). Lower Panels: global time to successful cannulation (TSC) divided among operators (1,2,3,4).

Rates of accidental artery puncture varied among operators in a range of 0-11.1% on the right side and in 2.1-11.1% on the left side. The mean time to successful cannulation (TSC) was <2 minutes in 65,8% of cases on the right side and 64.7% on the left side with no significant differences between operators ([Figure 3], lower panels).

When analyzing the number of UAand TSC along the study period, they significantly decreased during the second year as compared to the first one[Figure 4]. Time-dependent reduction of UA and TSC was comparable among the 4 operators [Figure 5].

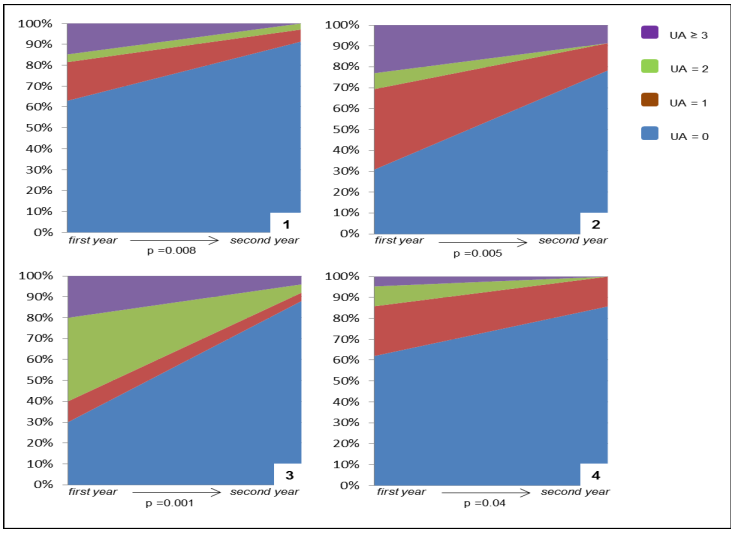

Figure 4: Rate of unsuccessful attempts (UA) for cannulation counted for each operator (1,2,3,4) during the first and during the second year of the study.

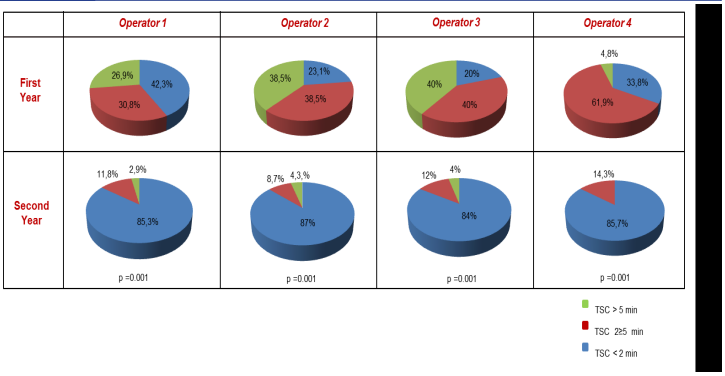

Figure 5: Time to successful cannulation (TSC) counted for each operator during the first and during the second year of the study.

Linear regression analysis found an independent correlation between vein depth(ß=0.42, p=0.001), operators training time during the study (second year vs first year)(ß= -0.75, p=0.00), and unsuccessful attempts after adjusting for all variables (Table 3).

Table 3: Linear Regression Analysis showing the association between unsuccessful attempts (UA) and anatomical or technical variables.

	Linear Regression Analysis	
Variables	**Unstandardized Coefficients**	**P-value**
M:F (%)	**B**	**61.5:38.5**
Vein depth (cm)	0.43	0.001
Operators training time (second year vs first year)	-0.75	0.000

Dependent variable: unsuccessful attempts during cannulation. The model is created after adjusting for age, gender, BMI, BSA, height, weight, vein and artery depths, vein and artery diameters, operators training time: defined as difference inoperators performance between the second (2017) and the first (2016) year of the study.

Vascular complications

Over a 30-day follow-up we observed 4(2,08%) superficial groin ecchymosis, but no clinical hematoma, arterio-venous fistulas or pseudoaneurysms necessitating interruption of anticoagulant therapy, surgery or blood transfusion. All the ecchymosis spontaneously regressed in a few days, in the absence of symptoms.Interestingly only anticoagulated patients (2 on warfarin, 1 on rivaroxaban, 1 on apixaban) developed complications.

Discussion

Ultrasound-guided vascular access has been shown to shorten time of the procedure, reduce the number of failed puncture attempts, and minimize complications during central venous catheterization [14]. In the setting of EPprocedures an US guidance to femoral cannulation is related to a 60% reduction in the likelihood of major vascular complications and a 66% reduction in the likelihood of major vascular complications[6]. This is probably due tothe visualization of the exact course of the vessels along the femoral triangle of the anterior thigh. In fact, there is a clinical relevant percentage of patients in whom the femoral artery overlaps the vein, making the perforation of the artery a real possibility. Reviewing the inguinal region of 100 computed tomographic scans of the pelvis (200 vessel pairs), Baum et al. found a portion of the common femoral artery overlapping the vein on the anterior-posterior plane in 65% of cases. In addition, more than 25% of the arteryoverlapped the vein in 8% of the vessel pairs [15]. In the pediatric population this percentage drops to 17% [16]. But the femoral vein can also split or double, encircling the femoral artery or be separated from the artery in its course [17].

We investigated with ultrasound the principal anatomical parameters of the femoral vessels (i.e. depth and diameter). Moreover, we investigated independent predictors of unsuccessful vein cannulation in patients undergoing US-guided EP procedures. In our study a complete (100%) of overlapping between artery and vein was present only in 3 cases (1,5%) and it did not rise the rate of unsuccessful attempts, probably for the help of the ultrasound guidance.

Our first result was that femoral vein depth is linearly correlated with anthropometric variables, especially BMI. Namely the higher the BMI the deeper is the vein. Consistently, vein diameter was also larger in patients with higher body weight, BMI and BSA values. Univariate analysis showed that only vein depth (and not diameter) was related to unsuccessful attempts. This is confirmed by linear regression models (ß=0.42, p=0.001) showingthat for every 2 cm increase in veindepthanew UA was observed. Our results can be explained by the fact thatthe deeper is thevein the more difficult is to visualize the needle tip advancing under the probe. However, in obese patients an US-guided approach would certainly prevent a large number of UA and accidental arterial punctures and it should be always used.The impact of reducing major vascular complications in overweight patients is outlined by the recent estimates from the international diabetes federation stating that more than 600 million people are expected to develop obesity by the year 2040[18].

An important finding of our study is that, despite slight differences

among the four operators, therates of unsuccessful attempts, arterial puncture and time to cannulation using the US-guided approach are rather low. Errhamouni and coauthors published their preliminary experience in 2014 showing an extremely low complications rates and setting the learning curve of the technique on six cases, after which the puncture time reaches a plateau [19]. As compared with the latter study, we observed a significantly lower rate of unsuccessful attempt during the second year of training after a least of 11 procedures. Globally the medium time to cannulation was reasonably low for all the operators (< 5 min in most of cases) since the beginning of the study, although none of them had been previously trained. It confirms that the technique, even as self-taught, can be easily learned and performed. Furthermore, in a previous elegant study, Rodriguez Munoz et al, using US-guided technique during EP procedures, calculated their average time to successful cannulation (87,3±94,3 sec), medium number of unsuccessful attempts (0,26±0,8 attempts per cannulation) and rate of accidental arterial puncture (0,02±0,1 arterial punctures per cannulation)[20]. We performed in a very similar manner collecting a medium of 0,51±1,05 UA and an average of 0,07±0,32 accidental artery punctures. TSC was < 120 sec in 65,8% of cases and totally <320 sec in almost 86,3% of cases. This homogeneity of results confirms the technique is highly reproducible.

Finally, the very low rate of vascular complications, exclusively minor in terms of clinical relevance (i.e. modest ecchymosis not requiring any diagnostic or therapeutic approach) confirms the technique is safe.

Limitations

This is a single center, not randomized, study aimed to characterize femoral vessels anatomy and clinical predictors of successful cannulation in a cohort of consecutive patients undergoing EP procedures. Thus, our results cannot be extrapolated to the general population. Although the retrospective nature of the study, we attempted to minimize selection bias by collecting data on consecutive patients who underwent EP procedures in our lab. Finally, according to our cannulation protocol we inserted no more than two sheats per vein when needed. Thus it's possible the results could be different when three sheats are inserted in the same vessel.

Conclusion

Anthropometric features may provide information about femoral vein and artery anatomyas assessed with US-guided femoral cannulation, in patients undergoing EP procedures. Patients with high BMI have deeper and larger veins but only vein depth seems to berelated to unsuccessful cannulation. In US-guided femoral vein cannulation numbers of unsuccessful attempts and time to successful cannulation significantly decrease with operator training.

Disclosures

All the authors report they have no relationships relevant to the contents of this paper to disclose.

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Additional Diagnosticvalue of Mini Electrodes in an 8-mm Tip in Cavotricuspid Isthmus Ablation

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Abstract

Background: Eight-mm ablation catheters are widely used in cavotricuspid isthmus ablation (CTI) for treatment of right sided atrial flutter. However a high success rate, these large ablation tips comes with adisadvantage of lower resolution of fractionated signals.

Purpose: The aim of this study was to evaluate the additional diagnostic value of the electrograms recordedfrom mini electrodes (MEs) in an 8-mm ablation catheter tip during CTI.

Methods: CTI-ablation procedures were compared retrospectively in two groups, namely, group A: the Abbott Safire 8-mm tip with a 3D mapping system (n =37) and group B: the Boston Scientific MiFi IntellaTip XP 8-mm tip without a 3D mapping system (n=13). We analyzedacute procedural success, ablation characteristics and recurrence rate at one-year follow-up. Electrograms from MEs were analyzedright before the onset of the critical ablation application that resulted in acute CTI-block. We determined whether these ME electrograms had additional diagnostic value in addition to of the 8-mm tip derivedelectrogram.

Results: At the onset of the critical ablation application, the MEs had an important additional value in 3 out of 13 cases as local signals were sensed on the MEs that were not recorded by the 8-mm tip electrode. In 2cases the ME did not show local electrogramsalthough the ablationwas still effective. Acute procedural and long-term success wereobserved in all patients. No differences were found in time to bidirectional block, procedure time or fluoroscopic exposure.

Conclusions: Our data show that signals recorded from the MEs had additional diagnostic value, but only in asmall percentage of the patients. We did not observe, although omitting 3D-mapping in the ME group, any differencebetween groups with regard to procedural or ablation characteristicsduring CTI-ablation.

Introduction

Right isthmus-dependent atrial flutter (AFL) is one of the most common supra-ventricular arrhythmias. The activation front during tachycardia travels through a macro-reentrant circuit in the right atrium, encompassing the isthmus located between the tricuspid annulus and inferior vena cava (cavotricuspid isthmus, CTI)[1,2].Consequently, typical counter-clockwise AFL is characterized by a negative p-wave with a saw-tooth pattern in the inferior leads of the 12-lead ECG[3]. Due to the stability of the circuit, rate control can be challenging. Rhythm control strategies consist of pharmacologicaltreatment, electrocardioversion or radiofrequency (RF) ablation[4].

CTI-ablation is widely used and effective at restoring and maintaining sinus rhythm. The first reports describe the use of a 4-mm non-irrigated catheter to create anablation line of conduction block along the CTI[1].Anatomical variance among CTI patients in combination with a small ablation electrode size can cause lack of convective cooling. This may result in a temperature rise of the ablation tip and decreased power delivery. This, in turn, will result in a smaller lesion size and an increased risk of steam-pops. By using a larger ablation electrode size, more electrode surface is available for convective cooling, resulting in increased power deliveryand greater lesion size[5-8].Indeed, several investigators have described the superiority of an 8-mm ablation catheter compared to a 4-mm non-irrigated ablation catheter[9-11].However, this advantage comes at the cost of lower resolution of local fractionated electrograms. To overcome this issue,a new 8-mm tip ablation catheter was recently developed, equipped with mini electrodes (MEs) to optimize sensing of local electrograms. In this ablation catheter, three 1-mm electrodes are located within 2-mm of the ablation catheter tipwith a 2,5-mm spacing (Figure1). A small studyof Iwasawa et al[12]. and a case seriesof Tzeis et al[13]. showed conflicting outcomesin efficacy using MEs in an 8-mm catheter.Furthermore, it has not been established in for what percentage of patients MEs detect local electrograms, when electrograms on the conventional bipolar electrodes are absent. Therefore, the question remains as to whether the use of MEs results in increased procedural efficacy, and whether the use of MEs allowsa 3D navigation system to be omitted.

Key Words

Catheter Ablation, Atrial Flutter, Cavotricuspid Isthmus, Mini Electrodes

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Methods

Population and study design

Fifty consecutive patients who underwent a CTI-ablation between 2013 and 2016 in the OLVG hospital in Amsterdam, the Netherlands were included in this analysis. The local ethics committee approved this retrospective study and issued a waiver for informed consent.Our patient did not demonstrate a high risk accessory pathway ERP on or off isoproterenol. However, AV conduction over the accessory pathway improved on isoproterenol from 230ms to 200ms, suggesting a very high risk accessory pathway.

We compared two groups: group A consisted of patients undergoing CTI-ablation using the Safire F 8-mm (Abbott, Abbott Park, IL, USA) ablation catheter in combination with a 3D mapping system (n = 37); group B consisted of patients undergoing CTI-ablation using the MiFi IntellaTip XP 8-mm (Boston Scientific, Boston, MA, USA) ablation catheter without a 3D mapping system to attain an electrogram based ablation (n = 13). Patients with a prior CTI-ablation or atrial tachycardias not dependent on the CTI were excluded. Atrial size was qualitatively assessed by transthoracic echocardiogram. Ablation was performed either by using a point-by-point or focal application of about 30 seconds before dragging forward, with a maximum application duration of 240 seconds. The RF strategy was chosen as per the operator preference. The final RF application that resulted in CTI-block was defined as the critical application. We compared the presence of interpretable intracardiac electrograms from the MEs to those intracardiac electrograms recorded from the conventional electrodes at the onset of the critical application. An interpretable cardiac recording (non-zero) was defined as a peak-peak amplitude of the bipolar electrogram>0.2mV at the steepest dv/dt for the conventional 8-mm tip and >0.1mVfor recordings retrieved from the MEs. Electrograms with lower amplitudes were supposed to represent a zero potential. In both groups we recorded procedure time, time to bidirectional block, fluoroscopic exposure, total ablation time,total number of ablation applications and the need to use a steerable sheath.

Procedural characteristics

All procedures were performed with an opioid analgesic (fentanyl) and without sedation.The femoral vein was punctured for access. A duo decapolar diagnostic catheter was placed in the right atrium around the tricuspid annulus; a quadripolar diagnostic catheter was placed in the coronary sinus. Surface ECG and intracardiac recordings were acquired with a Bard EP recording system (Boston Scientific, Boston, MA, USA).Filter settings on the ablation channel were similar for both conventional 8-mm and ME recordings. We used 30-250Hz band-pass filter and a notch filter. The Ensite 3D mapping system (Abbott, Abbott Park, IL, USA) was only used in group A. RF-energy was delivered using IBI-1500T11 (Abbott, Abbott Park, IL, USA); ablation generator settings were 70W and 55 degrees Celsius.Bidirectional block was assessed with bidirectional differential pacingmanoeuvres[14]and by measuring the widthof the local double potentials. Procedural success was achieved when bidirectional block was still present after a waiting period of 20 minutes after the last RF application.

Follow-up

Follow-up data was collectedfrom electronic patient records at one-year and by investigating all rhythm recordings performed by the referring hospitals. Recurrence was defined as registration of AFL on a 12-channel ECG, regular atrial tachycardia with a cycle length between 200-260ms in a cardiac implantable electronic device, or Holter registration. Recurrence of symptoms without documentation of arrhythmias was documented as well.

Statistical Analysis

Statistical package for social science (SPSS) was used for statistical analyzes(SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables are presented with a mean and a standard deviation, non-normally distributed with a median and an interquartile range, categorical variables in numbers and percentages. The parametric independent T-test and non-parametric Mann-Whitney U-test were used for statistical analysis of continuous variables, while X2 and Fisher's exact test were used to compare numbers between groups.

Results

We included 50 patients with a typical AFL (n=37 in group A vs.n=13 in group B) of whom 84% were male. Mean age was 63.3 ±8.6 years. Right atrium dilatation was present in 41.5% of the patients (n=11 vs.n=6 patients p=0.678). Counter-clockwise activation was observed in 46 patients (n=35 vs.n=11 p=0.069) whereas clockwise activation was also observed in 7 of these patients (n=5 in group A and n=2 in group B). Baseline patient characteristics are summarized in [Table 1]. Twenty-one patients (56.8%) in group A and 5 patients (38.5%) in group B had a history of atrial fibrillation (p=0.265).In group A 3 patients (8.1%) used flecaïnide compared to 5 (38.5%) in group B (p=0.010). [Figure 1A] shows a graphic of the localization of MEs on the ablation catheter and [Figure 1B] shows the conventional ablation catheter.

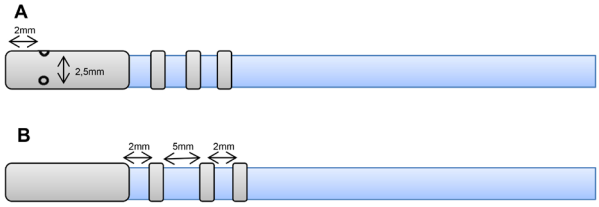

Figure 1: 8-mm ablation catheter with 1-mm mini electrodes within a 2-mm distance from the ablation tip and a 2,5-mm spacing. B, conventional 8-mm ablation catheter with a 2-5-2 electrode spacing.

CTI ablation was associated with acute procedural success of100% inboth groups. There was no difference in any of the predefined ablation or procedural characteristics, as summarized in [Table 2]. In particular, there was no difference with respect to the total procedure duration, fluoroscopic time or time to bidirectional block. A steerable sheath was used in 2 patients in each group

(p=0.275).Long-term outcomes arepresented in [Table 2].There was no recurrence of documented atrial flutter in any patient at one-year follow-up.Seventeen patients (34%) had symptoms of palpitations after CTI-ablation (n=13 (35%) vs.n=4 (31%)p=0.775). Whereas, 19 patients (39%) had documentation of a different atrial arrhythmia (n=14(38%) vs.n=5 (38%)p=0.968). [Figure 2] shows a typical example of local electrograms from the MEs versus those derived from the conventional electrode at the onset of the critical RF application. Interpretable local electrograms were present on the MEs, but absent on the ablation catheter in 3 out of 13 patients. Local electrograms were detectable with both modalities in 8 out of 13 patients. Finally, there were no local electrograms detectable with the MEs in 2 out of 13 patients. Hence, an additional diagnostic advantage was demonstrated in only 3 out of 13 (23%) of the patients. Notably, there was no difference in any of the ablation characteristics in these patients with detectable electrograms on the MEs and the absence of the electrograms on the conventional electrode, also not with respect to the more frequent use of flecainide in the ME group. The recording in [Figure 3A] demonstrates a case where double potentials across the ablation line were recorded on the MEs but not on the conventional catheter tip. [Figure 3B] presents an example of a site of re-conduction after multiple ablation applications. Here also, small local electrograms were only observed in the MEs (box). In these cases, we were able to identify these electrograms recordedfrom the MEs but not from the conventional catheter tip.

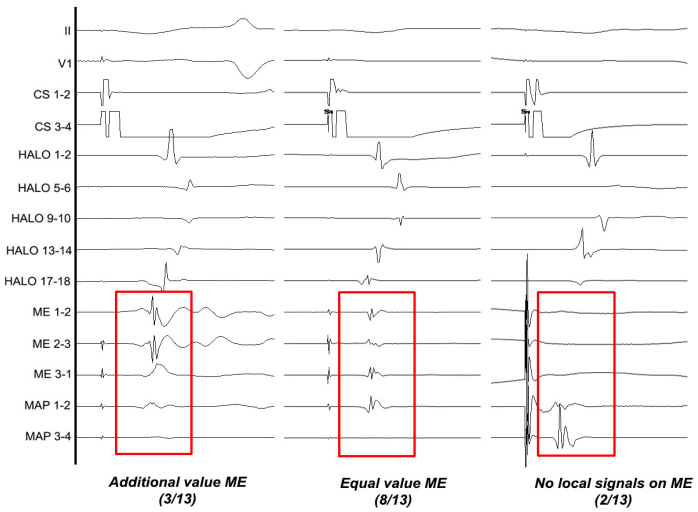

Figure 2: Intra cardiac electrogram before critical ablation point measured on mini electrodes (ME 1-2,2-3,3-4) and between the 8-mm electrode and the second electrode (MAP 1-2, boxes).

Table 1: Baseline characteristics

Baseline characteristics	Abbott Safire N=37	Boston Scientific MiFi N=13	P value
Male	31 (83.8)	11 (84.6)	0.944
Age	63.3 ±8	64 ±11.7	0.924
Body mass index	25.7 [22.2-30.3]	28.4 [24.2- 32.9]	0.201
Structural heart disease	20 (54.1)	10 (76.9)	0.148
Ejection fraction	53.7 ±12.4	51.4 ±10.2	0.639
Right atrium dilatation	11 (39.3)	6 (46.2)	0.678
Left atrium dilatation	17 (60.7)	7 (66.7)	0.722
Counterclockwise flutter	35 (100)	11 (84.6)	0.069
Clockwise flutter	5 (14.3)	2 (15.4)	0.622
Paroxysmal atrial flutter (<7days)	21 (65.6)	8 (61.5)	0.948
Persistent atrial flutter	11 (34.4)	4 (33.3)	0.948
Atrial fibrillation	21 (56.8)	5 (38.5)	0.256
CHA2DS2 VASc	2 (1-2)	3 (0.5-3)	0.482
Congestive heart failure	4 (10.8)	2 (15.4)	0.497
Hypertension	17 (45.9)	8 (61.5)	0.333
Diabetes	8 (21.6)	2 (15.4)	0.629
Stroke	2 (5.4)	1 (7.7)	0.604
Vascular disease	8 (21.6)	3 (23.1)	0.913
Beta blockers	27 (73)	8 (61.5)	0.439
Flecainide	3 (8.1)	5 (38.5)	0.010

Congestive heart failure, hypertension, age (75), diabetes, stroke, vascular disease, age (65), sex (CHA2DS2 VASc). Mean ±SD, numbers (%), median [25-75 percentiles].

Table 2: Procedural characteristics and follow-up

Procedural characteristics and follow-up	Abbott Safire N=37	Boston Scientific MiFi N=13	P value
Ablation:			
Number of RF-applications	6 [3.5-10]	8 [2.5-14]	0.838
Average duration per application (sec)	70.2 Â±33.7	60.5 Â±22.6	0.343
Average temperature (Celsius)	49.5 Â±1.9	52.53 Â±3.5	0.059
Average impedance (ohm)	74.5 Â±5.6	74.2 Â±6.1	0.912
Average power (Watts)	46.4 Â±11.6	45.24 Â±12.9	0.365
Total ablation time (sec)	456 [263-661.8]	364 [181-821]	0.550
Procedure:			
Concomitant PVI	0	1(7.7)	0.260
Cross-over	0 (0)	0 (0)	-
Steerable sheath	2 (5.4)	2 (15.4)	0.275
Time to bi-directional block (min)	23 [12.5-37.5]	16 [3-23]	0.217
Fluoroscopic time (min)	13 [8-17]	18 [7-22]	0.631
Procedure time (min)	65 [53-80.5]	50 [34.75-73.25]	0.133
Follow-up:			
Recurrence of atrial flutter at one-year	0 (0)	0 (0)	
Recurrence of symptoms	13 (35.1)	4 (30.8)	0.774
Occurrence of other atrial arrhythmia	14 (37.8)	5 (38.5)	0.960

Pulmonary veins isolation (PVI). Mean Â±SD, numbers (%), median [25-75 percentiles].

Discussion

Major findings

This study is the first reporting follow-up data on atrial flutter ablation using an 8-mm ablation catheter with MEs. MEs detected local electrograms more accurately than the conventional large ablation electrodes in 3 out of 13 (23%) patients. Using MEs without a 3D mapping system resulted in similar procedure time, fluoroscopic exposure and RF time to achieve bidirectional block.

Previous studies

MEs in a conventional ablation catheter is a relatively novel catheter design and evidence supporting the efficacy of MEs in an 8-mm ablation catheter during CTI-ablation is lacking.In a small case series

published byTzeis et al., which included 6 patients,bi-directional block was achieved in allpatients, and procedural characteristics were comparable with the conventional 8-mm ablation catheter[13]. Iwasawa et al. performed a small prospective studyin which they compared an 8-mmcatheter with MEswith the conventional 8-mm and cryo ablation catheter. A high cross-overrate was observed in the MEs group (14 out of 25 patients, 56%),whereasno cross-overs occurred in the conventional group (0 out of 30, 0%). Also, there were 3(out of 30)cross-over patients (10%) in whoma cryo ablation catheter was used. Thehigh cross-over rate was explained by a decreased power delivery during temperature-controlled ablation due to an isolated temperature sensor[12]. In our study,we observed a 100% procedural success rate in 13 patients treated with the ablation catheter with MEs. However, the additional diagnostic value of the MEs was seen in 23%, equal value in 62% and absence of ME electrograms in 15% of the patients in group B. We speculate that the lackof additional diagnostic valueresults is partly due to theoblique positioning of the large electrode,resulting in floating MEswithout tissue contact

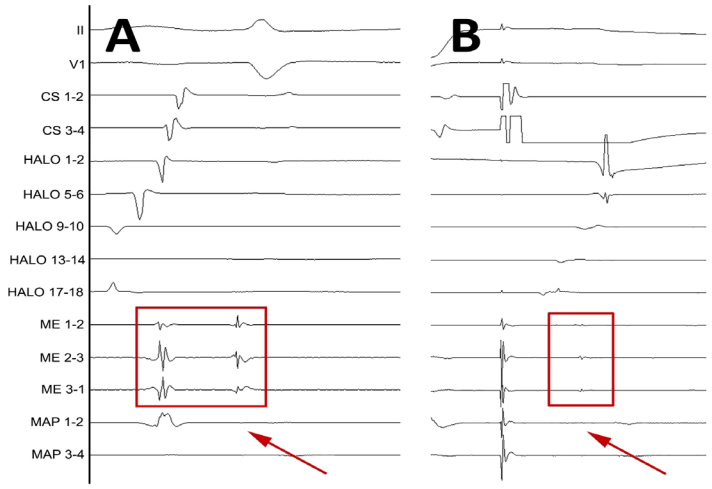

Figure 3: **A, double potentials measured across the ablation line. Note, local signals were only observed on the ME (box). Whereas, no signals were observed on the conventional electrogram (MAP 1-2, arrow). B, intra cardiac electrogram of an area of re-conduction after multiple ablation applications. Small fractionated signals were only observed on the ME (box). Whereas, no signals were observed in de conventional electrogram (MAP 1-2, arrow).**

while the large ablation tip had sufficient tissue contact. Of note, one could argue that a point-by-point ablation strategy would be most appropriate when investigating MEs. However, our study describes the use of MEs in a real-world clinical setting rather than in a randomized trial environment. The finding of a higher temperature in the MEs group in a previous study is in contrast with our findings[12]. However, there was a trend towards higher ablation temperature in our MEs group (49.5 ±1.9 vs. 52.5 ±3.5p=.059),but this did not influence the power delivery (46.4 ±11.6 vs. 45.2 ±12.9p=.365) or the ability to create bidirectional block.

Clinical implications

In our experience, a small learning curve exists when using the MiFi Intellatip XP 8-mm ablation catheter. Reduction of ME electrogram amplitude can be misinterpreted asa marker of ablation lesion completion. Once ablation was started, ME electrograms rapidly disappeared. These findings are in concert with a previous study which described a rapid decrease of ME amplitude within 7.3 ±3.9s[15]. Meanwhile, based on maximum ME amplitude attenuation, a transmural lesion was formed after 25.9 ±8.1s in canine atria[16]. Dragging the ablation catheter further after reduction of amplitude in the ME electrograms tended to create superficial transient lesions that needed additional ablation.

Multi-electrode diagnostic catheters with small electrode sizes and spacing are being employed for high and ultra-high resolution 3D maps of scar and densescar, revealing areas of slow conduction[17]. Voltage maps are more accurate when 1-mm electrodes with small inter-electrode spacing are used. Due to better sensing abilities, a 64% increase in amplitude was observed. This may result in a reduction inthe total amount of dense scar in a 3D mapping system of one-third at a cut-off value of <0.05mV and even two-thirds at a cut-off value of <0.25mV. Remarkably, this difference was not found in healthy atria where the electrogram amplitude is generally high[18]. Furthermore, smaller electrodes allow better annotation of fragmented electrograms during tachycardia and are associated with lower pacing thresholds during entrainment pacing[18,19]. A lower pacing output reduces the amount of saturation of the amplifier, making electrograms during entrainment pacing better interpretable[20]. Regarding the voltage cut-off values, decreasing these values will improve the visualization of channels within the scar. For these reasons it appears rational to use closely space electrodes , such as MEs, when searching for small channels of conduction. Also, the closer spacing and dimensions of the MEs allowed us to use stricter cut-off criteria for interpretable electrograms than in the conventional 8-mm tip recordings. Which value we should use to define scar is asubject of on-going discussion, and it remains unclear whether consensus voltage cut-off values are relevant to the CTI-ablation. Taken together, mapping techniques for visualization of small local electrograms are improving.Recording and localizing these specific electrograms using an 8- or 4-mm ablation catheter can be challenging, and MEs couldbe helpful in these cases.As displayed in two examples in Figures 3, electrograms may be present on MEswhile not discernible on the conventional catheter tip, and can indeed be helpful in the assessment of the width of double potentialsand the detection of reconnection. Indeed, also other manufacturers are now introducing similar technology to better identify small or fractionated local electrograms[21].

Study limitations

This study is a single-centre retrospective study with a small sample size. The study is underpoweredfor outcome analysis, mainly because an optimal success rate was achieved in both arms. Either point-by-point ablation or dragging with intermittent focal ablation was used depending on the preference of the operator and not systematically applied. Indeed, point-by-point ablation should have preference when searching for conduction gaps. However, our study describes the use of ME technology in a real-world clinical setting, and the proportion detectable and non-detectable MEs should be interpreted in that setting.Follow-up data was collected retrospectively, but all available rhythm recordings from referring hospitals were included in the analysis. However, despite these limitations, we were able to assess the absence of increased procedural or long-term efficacy of the CTI-ablation procedure.

Conclusion

In conclusion, the data show that MEs have added value to detect local electrograms in a fraction of patients. Our data did not show a trend towards reduced effectiveness but suggest that MEs may allow omitting a 3D mapping system. Identifying local electrograms with MEs can potentially be helpful in specific cases where one is searching for small, local fractionated electrograms.

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Incidence and Predictive Factors of Hidden Atrial Fibrillation Detected by Implantable Loop Recorder after an Embolic Stroke of Undetermined Source

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Abstract

Background: The term embolic stroke of undetermined source (ESUS) has been defined for patients with ischemic strokes, where neither a cardioembolic nor a non-cardiac source can be detected. These patients may have asymptomatic episodes of atrial fibrillation (AF). Prolonged monitoring with implantable loop recorder (ILR) and daily remote interrogation in patients after an ESUS has shown an incidence of AF of about 25%.

Aims: The main objective of this study was to analyze the incidence and predictive factors of atrial fibrillation in patients with ESUS who underwent an ILR implantation.

Methods: It was a single center study. From June 2013 to January 2017 all consecutive patients with an ESUS, who underwent an ILR implantation searching for hidden AF, were included. Possible predictive factors of AF were also analyzed.

Results: 65 patients were included (mean age 65.4±13.8 years, 55.4% males, mean CHA2DS2VASc score 2.3± 1.5). After a median follow-up of 17.1±10.7 months, AF was detected in 19 (29.2%) of patients. Variables associated with AF were:

age > 65 years (HR 9.45 (CI 95% 1.25-71.34); p= 0.02), CHA2DS2VASC score≥2 (HR 4.09 (CI 95% 0.93-17.87); p=0,06), left atrial enlargement (HR 2.29 (CI 95% 0.89-5.91); p=0.08) and presence of SVC on 24-hour Holter (HR 4.05 (CI 95% 1.55-10.57); p = 0.004) A cut-point of 0.15% for SVC was identified to predict AF with a sensitivity and specificity of 88.9 and 90%, respectively. A CHA2DS2VASc score<2 and age<65 years showed a negative predictive value to exclude AF of 91.3% and 96%, respectively.

Conclusion: A high incidence of AF was detected in this population. Age >65 years, LA enlargement, CHA2DS2VASC score≥2 and presence of SVC on 24-hour Holter are predictive factors of AF in patients with ESUS.

Introduction

Ischemic stroke is one of the leading causes of death and disability[1]. It is known as cryptogenic stroke when its origin is unknown, what happens in 20-40% of cases after an extensive diagnostic workup[2-6]. One of the most frequent causes is hidden atrial fibrillation (AF)[7], and risk of stroke recurrence is drastically reduced with anticoagulant therapy[7-8].

In patients with cryptogenic stroke, prolonged monitoring (for up to 36 months) with implantable loop recorder(ILR)[9], has shown and incidence of previously undiagnosed AF of about 30%, much higher than the one got by conventional follow-up. Similarly, incidence of AF was 16.1% in the subgroup of patients who were followed with an event recorder for a period of 30 days after a cryptogenic stroke[10].

The CHA2DS2VASc score is clearly validated to predict risk of stroke in patients with non-valvular AF[11]. Risk is estimated by the presence or absence of some clinical variables such as: heart failure, hypertension, age, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease or sex.

Recently, embolic stroke of undetermined source (ESUS), and complementary tests needed for its diagnosis, has been described as a new clinical entity[12]. The clinical construct ESUS was introduced to identify patients with non lacunar cryptogenic ischemic strokes in whom embolism was the likely stroke mechanism.

This new definition allows a more homogeneous comparison between studies of what was previously defined as cryptogenic stroke.

Key Words

Atrial Fibrillation, Embolic Stroke of Undetermined Source, CHA2DS2-VASC, Supraventricular Premature Complex, Left Atrial Enlargement, Implantable Loop Recorder

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Figure 1: Reveal LINQ and Reveal XT. Reveal LINQ size is noticeably smaller.

Materials and Methods

From June 2013 to January 2017, all consecutive patients that had suffered an ESUS and who, according to the opinion of the Cardiology and Neurology departments, were candidates for an ILR were included. The diagnosis of stroke was made by a neurologist, based on symptoms and radiological (Magnetic resonance imaging, MRI; or computed tomography, CT) findings. The diagnosis of ESUS was made after an extensive study that included: blood test with complete blood count, coagulation, biochemistry with lipid profile, chest X-ray, supra-aortic vessels echo-Doppler, transcranial Doppler, and CT angiography or angio-MRI, if needed. A 12 lead Electrocardiogram (ECG) was also performed, 24-hour Holter monitoring, transthoracic or transesophageal echocardiogram or thrombophilia screening (in subjects under 55 years). Complementary tests did not show a clear cause for the stroke. Patients with a patent foramen ovale (diagnosed by transesophageal echocardiography) were included.

All patients signed an informed consent form before entering the study. They underwent implantation of an ILR Reveal XT (@ Medtronic) or Reveal LINQ (@Medtronic) [Figure 1] by the Arrhythmia Unit of the participant center. It was an ambulatory procedure and the device was implanted subcutaneously in the prepectoral left area with local anesthesia. These devices can detect and store automatically episodes of AF, independently of symptoms or heart rate[14].

Follow-up was performed through remote monitoring with the Care-Link (@Medtronic) system. A monthly report from each patient was obtained. With the Reveal LINQ device, transmission of data was done automatically whilst the Reveal XT system needed patient interaction to send the information.

Episodes of AF were defined as presence of an irregular rhythm, without P waves and with a duration of at least 30 seconds in Reveal XT and 2 minutes in Reveal Linq. All episodes were analyzed and reviewed by a technician and 2 electrophysiologists who were blinded to the clinical information of the patient whose records were analyzing [Figure 2].

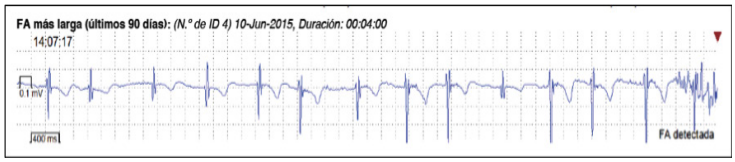

Figure 2: Atrial fibrillation episode in patient with a Reveal LINQ.

The following variables were evaluated as possible predictors of AF: age, sex, arterial hypertension, diabetes mellitus, presence of cardiomyopathy, prior stroke, peripheral artery disease, ischemic heart disease, atrial tachycardia, supraventricular premature complexes (SVC), percentage of SVC on 24-hour Holter monitoring, smoking habits, CHA2DS2-VASC score and left atrial volume measured with transthoracic or transesophageal echocardiography. Atrial tachycardia was defined as presence of a tachyarrhythmia of at least 4 beats, at a rate faster than 100 beats per minute with a P wave that looked different from the one in sinus rhythm. Presence of SVC was defined as at least 1% of SVC during the 24-hour Holter monitoring. All these tests were performed using a Holter "210 Plus with Zymed Algorithm, Philips Medical, Andover, MA, USA", with simultaneous 3-channel recording capacity and 12 lead ECG estimation. The stroke that triggered loop recorder implantation was not taken into account for the calculation of CHA2DS2-VASC score, what means that subjects with CHA2DS2-VASC< 2 could be included in the study. Left atrial enlargement was defined as a left atrial volume corrected per body surface area > 34 ml/m2, calculated by biplane disc summation method in apical 2 and 4-chamber apical view. All echocardiographic studies were performed with a Philips Echocardiogram IE33 from Philips Medical, Andover, MA, USA.

Main endpoint of the study was detection of AF through the use of an ILR.

Statistical analysis

The Categorical variables are expressed as number of observations (frequency) and percentage. Exact Fischer test was used to compare this type of variables. Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range, if not normally distributed. Kolmogorov-Smirnoff or Shapiro- Wilk tests were used to check if variables had a normal distribution.

T Student or U Mann-Whitney tests were used to analyze differences between groups.

The Kaplan-Meier method was performed to analyze survival free

Table 1: Baseline characteristics of study population.

Variable	
Age (years)	65.43±13.8
Males (%)	36 (55.4)
HTA (%)	37 (56.9)
DM (%)	10 (15.4)
Dyslipidemia (%)	17 (26.2)
Current smoker (%)	22 (28.2)
Ex-smoker (%)	4 (5.1)
Valvulopathy (%)	0 (0)
Normal LVEF (%)	65 (100)
Ischemic cardiomiopathy (%)	4 (6.2)
Peripheral vascular disease (%)	6 (8%)
CHA2DS2VASc score	2.26 ± 1.5

DM: Diabetes mellitus, LVEF: Left ventricular ejection fraction, HTA: arterial hypertension

of AF. Kaplan-Meier curves and log Rank tests were applied to check differences in survival free of AF between subgroups according to: CHA2DS2VASc score, age, presence of SVC and left atrial size. Fischer test was used to analyze predictive variables of AF. A ROC (Receiver Operating Characteristic) analysis was performed to find out a cut off point for % SVC on 24h Holter monitoring to predict AF. All statistical analysis was performed using software SPSS 20 Statistics of IBM Corp., Armonk, NY, USA

Results:

An ILR was implanted in 65 patients. Reveal XT was implanted in 13,8%. Reveal Linq was implanted in 86,2%. Baseline characteristics of study population are shown in [Table 1]. Mean age was 65.4 ±13.8 years. 55.4% were males. All patients had normal left ventricular ejection fraction and none of them had a severe valvular heart disease. Mean CHA2DS2VASc score was 2.3±1.5. 64.6% of patients had a CHA2DS2VASc score ≥2. The ILR was implanted after a median time of 56 days [Q1-Q3; 28-109] from the diagnosis of ESUS.

[Table 2] shows imaging tests and Holter results. 21.5% of patients had left atrial enlargement, defined by volume parameters. 13.8% of patients had SVC and 21.5% atrial tachycardia as defined per protocol.

After a mean follow-up of 17.1 ± 10.7 months, AF was detected in 19 (29.2%.) of patients. [Figure 3] shows survival free of AF curves. The incidence of AF at 1, 2 and 3 years is showed in [Table 3]. Mean episode duration was 12,3 hours (SD 15,52).

The first episode of AF was diagnosed at a median time of 31 days [Q1-Q3; 11-59] from ILR implantation. Anticoagulant therapy was started in every patient with AF diagnosis as soon as the physician was aware of it. Median time to detection was not different according to device type (28 days (Q1-Q3 20,5-117) vs 31 days (Q1-Q3 11-56) p=0,84) with XT compared to Linq respectively.

Patients who had AF were significantly older (75.8±7.9 vs. 61.1±13.4 years; p=0.005), had more frequently SVC (44.4% vs 2.5%; p<0.001) and a higher left atrial volume (31.5±6.9 vs 26.1±6.1 ml/m2; p=0.003). Percentage of patients with a CHA2DS2VASc score ≥2 was also higher in the AF group (89.5% vs 54.3%; p=0.009) compared with those patients in which AF was not detected [Table 4]. Anticoagulant therapy was started in all patients with newly detected AF.

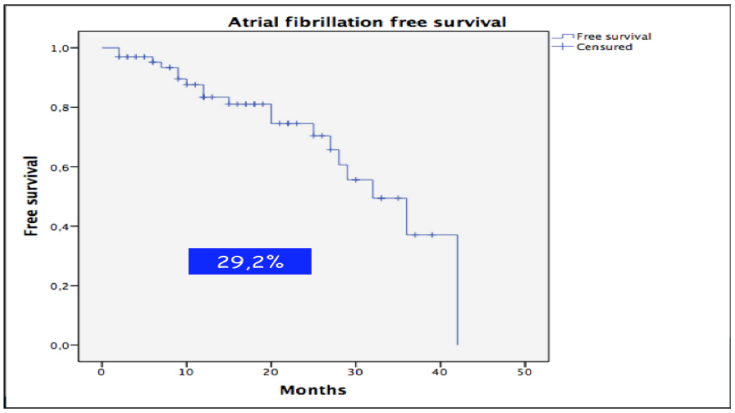

Figure 3: Atrial fibrillation-free survival curve. AF: atrial fibrillation.

Table 2: Complementary data from Holter and echocardiogram.

Variable	
PFO (%)	9 (13.8)
Left atrial diameter (mm)	35.27±5.13
Left atrial volume (ml/m2)	27.74±8
Enlarged left atrium (%)	14 (21.5)
AT on Holter (%)	14 (21.5)
SVC on Holter (%)	9 (13,8)

PFO: patent foramen ovale; SVC: supraventricular premature complex; AT. Atrial tachycardia;

In the univariate analysis, the following variables were predictive of AF: age > 65 years (HR 9.45 (CI 95% 1.25-71.34); p= 0.02), age as a continuous variable (HR for a 10-year increase in age 1.83 (CI 95% 1.15-2.92); p=0.01), CHA2DS2VASC score≥2 (HR 4.09 (CI 95% 0.93-17.87); p=0,06), left atrial enlargement (HR 2.29 (CI 95% 0.89-5.91); p=0.08) and presence of SVC on 24-hour Holter (HR 4.05 (CI 95% 1.55-10.57); p = 0.004), [Table 5].

Table 3: AF incidence according to year of FU.

Variable	PORCENTAGE
AF incidence at 1 year FU	13 (95% CI, 5-22)
AF incidence at 2 year FU	18 (95% CI, 8,7-28)
AF incidence at 2 year FU	27 (95% CI, 16-38)

AF: Atrial fibrillation. FU: Follow up

A CHA2DS2VASC score < 2 and age < 65 years showed a high negative predictive value (91.3% and 96%, respectively) to exclude the development of AF. Only 8.7% of patients with a CHA2DS2VASC score < 2 and 4% of patients under 65 years developed AF during the follow-up. On the other hand, presence of SVC on 24-hour Holter monitoring showed a high positive predictive value, detecting AF in 88.9% of these patients during the study period [Figure 4].

A ROC curve analysis was performed to find the optimal cut-point value of percentage of SVC, showing that figures over 0.15% on Holter monitoring had a sensitivity of 88.9% and a specificity of 90% to predict the development of AF [Figure 5].

Discussion

In Active search for AF in patients with ESUS is of vital importance, due to its clinical implications. American Heart Association and American Stroke Association guidelines for the prevention of stroke in patients with stroke and transient ischemic attack considers prolonged rhythm monitorin as reasonable (IIa) after acute ischaemic stroke or TIA with no other apparent cause[15]

If AF is detected, oral anticoagulation with acenocumarol or novel anticoagulants is highly recommended. Patients with paroxysmal, persistent or permanent AF exhibit a similar risk of stroke[14] and benefit from anticoagulation[16].

The main variable of the study was incidence of AF lasting at

Table 4: Differences between patients with/without atrial fibrillation during follow-up.

	Atrial fibrillation (19)	No Atrial fibrillation (46)	P value
Age (years)	75.8±7.9	61.1±13,4	0.005
Males (%)	9 (47.4)	27 (58.7)	0.4
HTA (%)	14 (73.7)	23 (50)	0.08
DM (%)	2(10.5)	8 (17.4)	0.71
Dyslipidemia (%)	3 (15.8)	14 (30.4)	0,.5
CHA2DSVASC≥2 (%)	17 (89.5)	25 (54.3)	0.009
IC (%)	0 (0)	4 (8.7)	0.31
PVD (%)	1 (5.3)	1 (2.1)	0.5
AT on Holter (%)	8 (44.4)	6 (15)	0.31
SVC on Holter (%)	8 (44.4)	1 (2.5)	< 0.001
LA diameter (mm)	34.7±4.9	31..¬5±6.9	0.15
LA volume (ml/m2)	31.5±6.9	36.1±6.1	0.003

LA: left atrium, DM: Diabetes Mellitus, SVC: supraventricular premature complex; HTA: hypertension ; AT: atrial tachycardia. IC: ischemic cardiomyopathy; PVD: peripheral vascular disease.

least 30 seconds. This definition is in accordance with guidelines[17] and although this is an arbitrary figure, it is a fundamental finding to assess the need for anticoagulation. New generation ILR are equipped with remote monitoring technology. Devices are able to transmit daily diagnostic data and arrhythmic episode snapshots through a wireless receiver without any active patient or physician interaction. These transmission are reviewed by hospital staff and the time needed to adopt therapeutic measures is shortened.

In our study, AF was detected in 29.2% of patients which is in line with the results of the CRYSTAL AF study[9] (30%), though that study had a longer period of follow-up (36 months). In the CRYSTAL AF study, after an 18-month follow-up AF was detected in 17% of patients, a lower figure than the one found in our study where the mean follow-up was 17.1 ± 10.7 months. Baseline characteristics of both study populations were similar, with regard to hypertension (65.2% vs. 56.9%) and diabetes (15.4% vs. 15.4%). However, our patients were a bit older (65.4 ±13.8 vs. 61.6 ±11.4 years) compared to the ones included in the CRYSTAL AF study.

In the EMBRACE[10]study, AF was diagnosed in 16.1% of patients after a 90-day follow-up period. This high incidence of AF in a short period of time could be explained by the inclusion of an older population (mean age 72.5 ±8.5 years) and a higher rate of hypertensive (71.3%) and diabetic (19.2%) patients compared with our study and the CRYSTAL AF.

According to the results of our study, occurrence of AF in patients with ESUS is clearly determined by the presence of SVC and left atrial enlargement. Presence of SVC, defined as a quantity of SVC >1% of all heart beats analyzed during a 24-h Holter monitoring, was related to new-onset AF. This finding has been previously reported in the Cardiovascular Health Study[18] and in the Copenhagen holter study[19], where patients with a frequency of SVC over 30/hour or with 20 or more consecutive SVC had a higher incidence of AF, stroke or death. The findings of Johnson´s study[20], in which presence of SVC preceded AF, corroborate previous results. A cut-point of 0.15% for SVC showed high sensitivity and specificity values in our

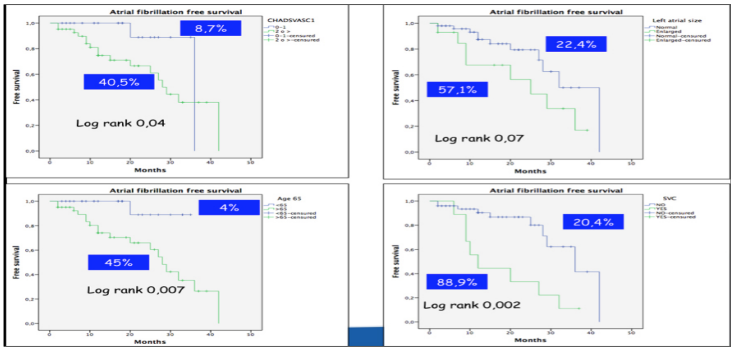

Figure 4: Atrial fibrillation-free survival curves according to CHA2DS2VASc score, age, left atrial size and presence of supraventricular premature complex (SVC). AF: atrial fibrillation

study, so that this figure could be taken into account to evaluate the risk of new-onset AF in that population.

Left atrial enlargement was also an independent predictor of AF, though with a lower impact than SVC. This factor is not only related with incidence of AF but also with risk of recurrence of AF after a rhythm control strategy using antiarrhythmic drugs, electrical cardioversion or pulmonary vein ablation[21]. In a study of hospitalized patients with AF, those with left atrial enlargement showed higher values of CHADS2 or CHA2DS2VASc scores than those with a normal left atrial size[22].

Two variables (CHA2DS2VASc score< 2 and age< 65 years) showed a very high negative predictive value for the absence of AF during follow-up. CHA2DS2VASc score includes the main risk factors for developing AF. In the study performed by Mitchell et al[23], where risk of stroke in a population naive of AF was analyzed according to CHADS2 and CHA2DS2VASc scores, incidence of new-onset AF was related to both scores and reached 3.85% in subjects with a CHADS2 score≥3 and 2.52% in those with a CHA2DS2VASc score ≥ 4. Therefore, high values of these scores identify a higher risk population for new onset AF, which in most cases may be asymptomatic. Similarly, the study by Chao et al[24] also reported that incidence of AF progressively increased with number

Table 5: Univariate analysis.

	HR (IC 95%)	P value
Age> 65 years	9.45 (1.25-71.34)	0.002
Age (10 years)	1.83 (1.15-2.92)	0.01
Male sex	0.49 (0.18-1.31)	0.21
HTA	1.37 (0.47-3.92)	0.54
DM	0.27 (0.03-2.07)	0.12
FOP	0.33 (0.04-2.53)	0.29
Dyslipidemia	0.69 (0.20-2.41)	0.69
CHA2DS2VASC≥2	4.09 (0.93-17.87)	0.06
LA enlargement	2.29 (0.89-5.91)	0.08
AT on Holter	2.01 (0.75-5.35)	0.16
SVC on Holter	4.05 (1.55-10.57)	0.004

LA: left atrium; DM: Diabetes mellitus; SVC: supraventricular premature complex; HTA: Hypertension; AT: atrial tachycardia.

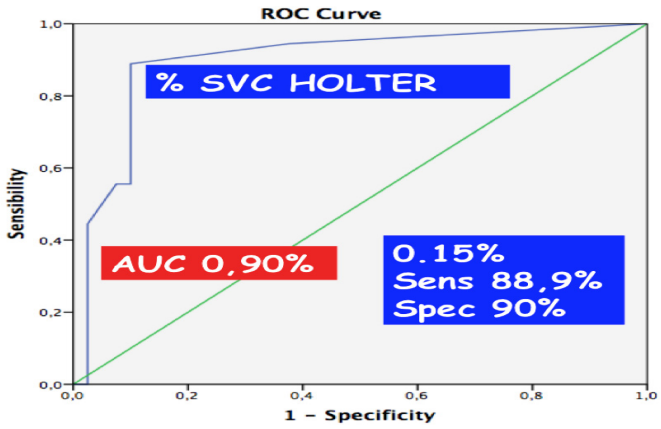

Figure 5: ROC curve for the percentage of SVC on Holter monitoring. SVC: supraventricular premature complexes.

of patients' comorbidities, which are represented by the CHADS2 score. In our study, only 8.7% of patients with a CHA2DS2VASc score 0-1 showed AF during the follow-up. The combination of a CHA2DS2VASc score < 2 and age < 65 years could make the use of ILR less worthwhile in this low embolic risk population.

On the contrary, AF was detected in 40.5% of patients with a CHA2DS2VASc score ≥ 2, despite a relatively short follow-up period of 17 months, percentage that could be higher with longer periods of follow-up. This factor, in association with presence of SVC >1% (that showed a highly positive predictive value for AF), could create a point of controversy: the possibility of starting oral anticoagulant therapy in ESUS patients with a CHA2DS2VASc score ≥ 2 and with a certain burden of SVC on Holter monitoring, without the need of searching for hidden AF. In this sense, there are an ongoing clinical trials in patients with ESUS that analyze the routine use dabigatran - RE-SPECT ESUS, ClinicalTrials.gov Identifier: NCT02239120, trials.) and will probably give answers to this question.

Nonetheless, the evidence of a direct relationship between the detected episode of AF and embolic stroke is controverted. In fact, there are several monitoring studies, using pacemakers or defibrillators[25-26], in which risk of stroke is analyzed according to the presence or absence of AF. These studies show that there is not a temporal relationship between AF episodes and stroke, being arrhythmia episodes considered a risk marker more than a direct causative factor. In the study of Turakhia et al [27], only 13 over 187 acute ischemic stroke patients and continuous rhythm monitoring, had AF episodes longer than 5,5h in the 30 days before the event, compared to a period of 120-30 days before the stroke. However OR for stroke was highest in the five days immediately following and AF episode lasting at least 5,5h.

AF has been detected widely in patients with risk factors that were implanted with an ILR and had no previous AF documentation. AF was detected in 40% patients at 30 months[29], and at an incidence of 34,4% per person-year[30] in REVEAL AF trial and ASSERT II trial respectively. Almost 40% in REVEAL AF and 48% in ASSERT II had a previous history of stroke, TIA or embolism.

The main limitation of the present study is its small sample size. It was also a unicenter study and results may not be extrapolated to populations with other baseline characteristics.

AF episodes were documented by a Reveal registry that has only one derivation, and there is a remote possibility of having confused episodes of multifocal atrial tachycardia with AF.

AF algorithm of ILR are not the gold standard for heart rhythm monitoring as they are affected by false positive and false negative results[30].

We analyzed incidence of AF but not clinical response to initiation of anticoagulant therapy (reduction of recurrence after stroke). The small sample size and the absence of stroke recurrence in any patient during follow-up make this analysis undoable. However, that kind of study could be done in the future with a larger sample size.

Median time since stroke episode to ILR implantation was around 60 days. Incidence of new-onset AF may be higher during the first weeks after the ischemic event. An earlier (closer to ESUS episode) placement of the device could have provided a higher rate of AF.

Conclusion

Incidence of new-onset AF was 29.2% in our study population. Presence of SVC (>1% on 24-hour Holter monitoring) and left atrial enlargement were independent predictors of AF after an ESUS. SVC on Holter showed a high positive predictive value whereas age < 65 years and a CHA2DSVasC score < 2 showed a high negative predictive value for absence of AF.

Conflicts of Interest

The authors declare no conflicts of interest.

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Long Term Outcome and Pulmonary Vein Reconnection of Patients Undergoing Cryoablation and/or Radiofrequency Ablation: Results from the TheCryo Versus RF Trial.

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Abstract

Introduction: Long term prospective data comparing the efficacy of radiofrequency (RF) and cryoballoon ablation (CRYO) for paroxysmal atrial fibrillation (PAF) is lacking. We report the long-term outcomes of a randomized control trial comparing CRYO to RF ablation, or a novel COMBINED approach (RF followed by CRYO) for PAF. We studied the number and pattern of pulmonary vein (PV) reconnections in patients undergoing repeat procedure(s). The COMBINED approach had significantly higher single procedure success rate and is associated with the fewest reconnected PVs.

Methods: C203 patients who underwent first time PAF ablation in a randomized clinical trial comparing CRYO (67), RF (67) and COMBINED (69) approaches were followed up. All patients with symptomatic recurrence of AF were offered a repeat procedure(s). Reconnected PV(s) at repeat procedure(s) were recorded. In a subset, the PV reconnection sites during the first repeat procedure were prospectively assessed and categorised into one of 8 segments.

Results: At 5 years, 57% of COMBINED patients remained free of AF after a single procedure compared to 47% CRYO and 19% RF patients ($p<0.001$ COMBINED vs RF and CRYO vs RF, $p=0.043$ COMBINED vs CRYO). During the first repeat procedure, theCOMBINED group had less number of reconnected PVs (mean number of reconnected PVs in the COMBINED group 1.2 vs 2.3 CRYO and 2.4 RF, $p=0.034$). There was a different pattern of PV reconnection comparing the CRYO and RF groups.

Conclusion: The COMBINED approach had a significantly higher single procedure success rate with fewer reconnected PVs and fewer reconnection sites compared to either CRYO or RF alone. CRYO in turn was superior to RF. PV reconnection pattern differed between CRYO and RF and the synergistic effect of the COMBINED approach may explain the improved single procedure efficacy.

Introduction

Catheter ablation to isolate pulmonary veins (PVs) is an effective treatment for drug-refractory paroxysmal atrial fibrillation (PAF)[1,2]. PV isolation is conventionally achieved using radiofrequency (RF) energy to create contiguous and transmural point-to-point lesions encircling the veins[1]. This is however time consuming, technically challenging and PV reconnection causing AF recurrence remains a problem[2,3].

A balloon-based approach using cryothermal energy has emerged as a comparable alternative with the potential of isolating PVs with a 'single-shot' technique and associated with lower risk of thermal injury and PV stenosis compared to radiofrequency (RF) energy sources[4]. A recent systematic review has suggested good acute procedural safety and efficacy with a one year freedom from AF of 73%[5]. Our own randomised control trial (The Cryo Versus RF Trial) comparing segmental ostial isolation with cryoballoon to wide antral circumferential ablation (WACA) of PVs using RF energy and a novel approach combining both found that cryoballoon and the combined approach were both superior to the conventional RF approach at 1 year. There was no significant difference between using cryoballoon alone compared to the combined approach [6].

However, long term prospective data comparing the efficacy of cryoballoon and RF ablation is lacking. Furthermore, there are little data comparing ablation strategies with respect to the extent and pattern of PV reconnection. In this study, we sought to address this by following up the cohort of patient in the theCryo Versus RF trial, looking at the long-term outcome following ablation and studying the distribution and pattern of PV reconnection during the repeat procedure.

Key Words

Atrial Fibrillation, Catheter Ablation, Radio Frequency Catheter Ablation, Cryo Balloon Ablation, Pulmonary Vein Reconnection, Long Term Outcomes

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Material and Methods

Study population

234 patients undergoing first-time catheter ablation of PAF

were randomized to cryoballoon (CRYO, n=78), radiofrequency (RF, n=77), or a novel cryoballoon and radiofrequency combined procedure (COMBINED, n=79) at a single institution as part of a randomized controlled trial (CryoVs RFA trial), the results of which have been reported[6]. The study was approved by the local research ethics committee and was prospectively registered on NIH clinical trials. gov (NCT01038115). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Briefly, patients enrolled were aged over 18 years, had documented paroxysmal AF on at least two occasions and accepted for catheter ablation for AF. Patients were excluded from the trial if they had severe left atrial dilatation (greater than 50mm in diameter), severe valvular disease, or previous left atrial ablation.

Catheter ablation procedures

All patients underwent trans-oesophageal echocardiography pre-procedure and were anticoagulated without interruption. The procedures were performed under local anaesthetic (lidocaine), and conscious sedation (midazolam and diamorphine). A quadripolar catheter was inserted into the coronary sinus and a multipolar circular mapping catheter was used for mapping of the PVs. Double transseptal puncture was performed when dual transseptal access was required.

For CRYO, a 28mm and/or a 23mm first generation ArticFrontcryoballoonwere used. Retrograde PV angiography was used to demonstrate occlusion. Two freezes of up to 300s were performed initially in each PV with phrenic nerve pacing for the right-sided treatments. Further freezes were delivered if the veins were not isolated. If this approach failed, the operator could take the alternative cryoballoon size or complete PV isolation using focal ablation. Focal lesions were applied with an 8 mm cryoablation catheter (Freezor Max, Medtronic, USA), and if this failed a 3.5 mm RF ablation catheter (Thermocool Celsius, Biosense Webster, Diamond Bar, CA, USA) was used.

For RF, ablation energy was delivered using an irrigated F curve 3.5 mm non-contact force sensing ablation catheter (Navistar Thermocool, Biosense Webster, Diamond Bar, CA, USA) guided using CARTO 3 (Biosense Webster, Diamond Bar, CA, USA). Patients underwent WACA, with lesions placed 1–2 cm outside the PV ostia to isolate them in ipsilateral pairs. Power was limited to 30W and flow was adjusted from 2 mL/min up to 30 mL/min to achieve this without exceeding temperature limit of 48^{0}C.

For COMBINED, patients initially underwent WACA as in the RF group, with electrical isolation demonstrated using the circular mapping catheter followed by two further 5 min freezes using the cryoballoon, judged by good PV occlusion on venogram and temperatures of ≤ -40^{0}C.

In all cases, electrical isolation of all PVs was the end point for the procedures.

Follow-up

All antiarrhythmic drugs were stopped post procedure and patients were followed up at 3, 6 and 12 months with a 7 day Holter recording. There was open access to arrhythmia nurse specialists subsequently and further ambulatory monitoring prompted by symptoms. All patients with recurrence of symptoms and documented atrial arrhythmias lasting greater than 30s after the blanking period of 3 months were offered a repeat procedure. Attempts were made to contact all the patients for review between 1 April to 31 May 2017 to determine any adverse events, recurrences of AF/AT, current medications and symptoms. Patients with follow-up of less than 18 months were excluded from analysis.

Study endpoints

Success was defined as freedom from documented AF/AT lasting at least 30 seconds following a 3-month blanking period. The primary endpoint of the study was the success rate following a single procedure without antiarrhythmic drugs. Secondary endpoint was the success rate at last follow-up after one or more procedures off and on antiarrhythmic drugs.

PV reconnection sites at first repeat procedure

All repeat procedures were performed with RF ablation using an open irrigated-tip catheter in conjunction with an electroanatomic mapping system. Using the multipolar circular mapping catheter, PV potentials were sequentially mapped and ablated until PV isolation. The positions of all reconnected PVs were prospectively documented.

In a subset of patients during the first repeat procedure, the PV reconnection sites of each individual PV were prospectively documented. Each PV was categorized into eight individual segments as described by Valles et al[7] and was used to describe PV reconnection patterns. The site of the earliest PV potential was mapped and categorized into one of the eight segments. If antral ablation at that site eliminated all PV potentials, the respective PV

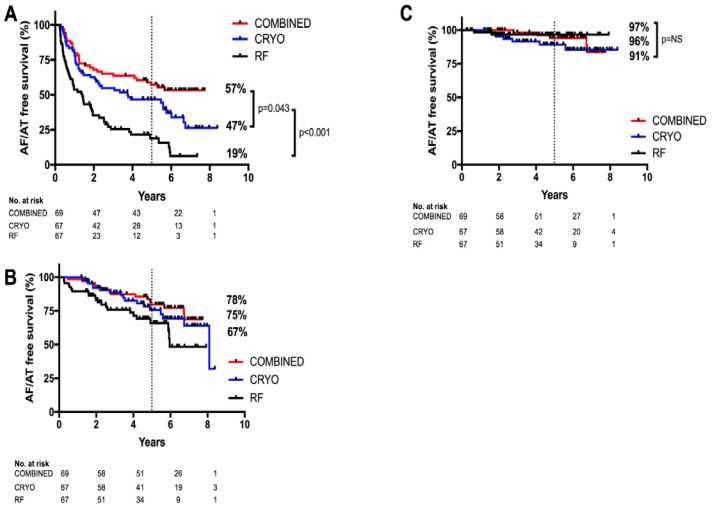

Figure 1: **Comparison of AF free survival. Kaplan–Meier analysis of survival free from AF following (A) index procedure, (B) final repeat procedure(s) off anti-arrhythmic drugs, and (C) final repeat procedure(s) on anti- arrhythmic drugs for RF, CRYO and COMBINED groups. AF free survival at 5 years shown by dotted lines.**

was found to have a single conduction gap. If ablation resulted in a change in activation sequence, the earliest PV potential was mapped and ablated until complete PVI was achieved. Hence, more than one reconnection sites were possible per PV.

Statistical analysis

Continuous data are presented as mean ± standard deviation if normally distributed or median ± inter quartile range if not. Categorical data are described as count (percentage). Continuous data were compared using Student's t-test. Categorical data were compared using a chi-squared test and further pair-wise comparisons used Fisher's exact test. Differences in survival on the Kaplan Meir curve was compared by log rank test. Univariate analysis was performed to assess for differences between groups and association of clinical characteristics with AF/AT recurrence. In all instances, a Pvalue of <0.05 was considered statistically significant. Analysis was performed using SPSS version 24 (IBM, NY, USA) and Prism 6 (GraphPad, CA, USA).

Results

Patients

Of the 234 patients in the original study, 203 patients (67 RF, 67 CRYO and 69 COMBINED) had follow-up of at least 18 months and were included in this analysis. The median follow-up duration was 5 years (IQR 3.6 to 6.4 years). [Table 1] compares the patient characteristics between the treatment groups, stratified by AF recurrence following a single procedure. There were no significant differences between the groups and no predictors of recurrence on univariate analysis.

Table 1: Patient characteristics

	RF (n=67)		CRYO (n=67)		COMBINED (n=69)		P-value
	No recurrence (n=11)	Recurrence (n=56)	No recurrence (n=25)	Recurrence (n=42)	No recurrence (n=38)	No recurrence (n=38)	
Age (years)	59±11	61±12	57±10	55±11	58±10	60±12	0.706
Male	8 (73%)	34 (61%)	16 (64%)	32 (76%)	24 (63%)	16 (52%)	0.968
AF duration (months)	60 (IQR 27-84)	60 (IQR 24-96)	36 (IQR 24-120)	61 (IQR 24-120)	60 (IQR 25-96)	84 (IQR 24-132)	0.063
LA diameter (mm)	43±5	43±5	43±4	42±5	43±4	42±4	0.736
Hypertension	2 (18%)	19 (34%)	12 (48%)	13 (31%)	10 (26%)	16 (52%)	0.506
DM	1 (9%)	4 (7%)	1 (4%)	3 (7%)	4 (11%)	1 (3%)	0.323
IHD	1 (9%)	5 (9%)	3 (12%)	3 (12%)	4 (11%)	1 (3%)	0.353
Cardiac failure	2 (18%)	2 (4%)	1 (8%)	6 (14%)	5 (14%)	3 (10%)	0.509
CVA/TIA	0 (0%)	6 (16%)	3 (12%)	2 (5%)	21 (11%)	5 (16%)	0.970
AADs failed	2±1	2±1	2±1	2±1	2±1	2±1	0.420

Patient characteristics in each group stratified by AF recurrence after a single procedure. Data shown as mean ± SD, median (IQR), or proportion (%) as appropriate. P-values shown are of univariate analysis assessing association of factors to recurrence of AF/AT.

Primary Endpoint: Freedom from AF/AT after a single procedure

Kaplan-Meier curves demonstrating freedom from AF/AT after a single procedure are shown in [Figure 1A]. At 5 years, 57% of COMBINED patients remained free of AF/AT after a single procedure compared to 47% CRYO and 19% RF patients (p<0.001 COMBINED vs RF and CRYO vs RF; p=0.043 COMBINED vs CRYO). At final follow-up, 38/69 (55%) COMBINED patients remained free of AF/AT compared to 25/67 (37%) CRYO and 11/67 (16%) RF patients. The COMBINED approach was superior to both RF (hazard ratio for AF recurrence, HR 0.33 95% CI 0.21-0.51) and CRYO (HR 0.63, 95%CI 0.39-0.99). CRYO in turn was superior to RF (HR 0.48, 95%CI 0.32-0.72).

Secondary Endpoint: Freedom from AF/AT after one or more procedures

36/67 (54%) RF and 33/67 (49%) CRYO patients underwent one or more repeat procedure(s) compared to only 16/69 (23%) in the COMBINED group (p<0.01 for COMBINED vs RF and COMBINED vs CRYO) [Figure 2]. First repeat procedure was performed at median of 382 days (IQR 199-718 days) from index procedure with no significant differences between groups.

After a mean of 1.7 procedures in the RF and CRYO groups, and 1.3 procedures in the COMBINED group, 45/67 (67%) RF, 50/67 (75%) CRYO and 54/69 (78%) COMBINED patients remained free of AF/AT off antiarrhythmic drugs (RF v COMBINED, p=0.02; RF v CRYO, p=0.10; CRYO v COMBINED, p=0.80). After repeat procedure(s) at a median of 5 years, the COMBINED group remained superior to RF (HR 0.48, 95%CI 0.25-0.92). There were no significant differences between COMBINED vs CRYO (HR 0.80, 95%CI 0.40-1.60) and CRYO vs RF (HR 0.60, 95% CI

0.32-1.13) [Figure 1B].

When patients who remain symptom free on antiarrhythmic medications are included, the efficacy after repeat procedure(s) rise to 65/67 (97%) for RF, 61/67 (91%) for CRYO and 66/69 (96%) for COMBINED (p=0.20 COMBINED vs RF; p=0.15 CRYO vs RF; p=0.75 COMBINED vs CRYO) [Figure 1C].

There were significantly more patients in the RF group on antiarrhythmic medications compared to patients in the CRYO and COMBINED group: RF 20/67 (30%) vs CRYO 9/67 (13%) and COMBINED 10/69(14%), p-0.04. There was 1 death in the RF group and 2 deaths each in the CRYO and COMBINED group. All deaths occurred more than 2 years after the index procedures.

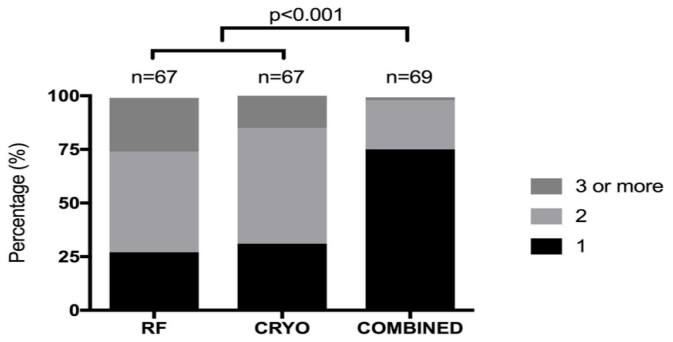

Figure 2: Number of AF ablation procedure(s). Number of AF ablation procedure(s) performed in each group.

Number and distribution of reconnected PVs during first repeat procedure

Among patients undergoing a first repeat procedure, 6/16 (38%) in the COMBINED group had no reconnected PVs compared to 2/33 (6%) in the CRYO group and 2/36 (6%) in the RF group (CRYO/RF versus COMBINED, p < 0.001). Patients in the COMBINED group also had fewer reconnected PVs (mean number of reconnected PVs in the COMBINED group 1.2 vs 2.3 CRYO and 2.4 RF, p=0.034). [Figure 3].

At the last procedure, 5/33 (15%) in the CRYO, 4/36 (11%) in the RF and 6/16 (38%) in the COMBINED group had no reconnected PVs.

Distribution of reconnected PVs and sites of PV reconnection during first repeat procedure

The distribution of reconnected PVs and sites of PV reconnections in each group is shown in [Figure 4].

There was a significant difference between the groups in the rate of reconnection among the superior veins between the groups. For RSPV, both CRYO and the COMBINED groups had significantly less reconnection compared to RF (CRYO vs RF, OR 0.28 CI 0.10 – 0.75, p=0.015; COMBINED vs RF, OR 0.13 CI 0.03-0.47, p=0.001). For LSPV, there was significantly less reconnection in the COMBINED group compared to both CRYO and RF (COMBINED vs CRYO,

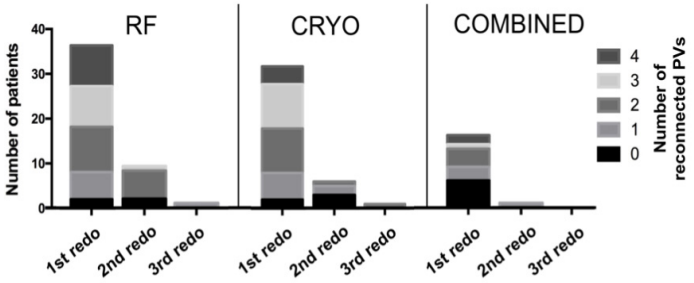

Figure 3: Number of reconnected PV(s) during repeat procedure(s).Number of reconnected PV(s) documented during first and subsequent repeat procedure(s).

OR 0.11 CI 0.03-0.48, p=0.002; COMBINED vs RF 0.16 CI 0.04-0.63, p=0.008). The frequency of PV reconnection in the inferior veins was similar between the groups.

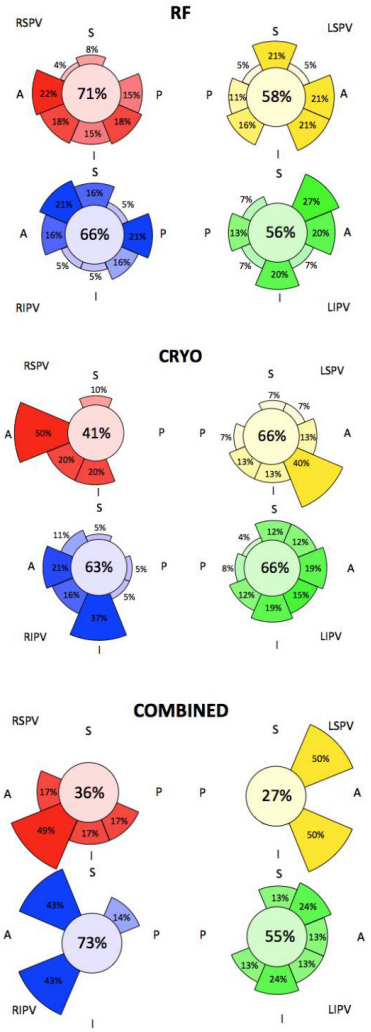

Figure 4: Pattern of PV reconnection during first repeat procedure. Distribution of PV reconnections during the first repeat procedure. Number in the centre circle of each vein represents the frequency of the vein being reconnected expressed as a percentage of the total number of patients in each group. Numbers in the periphery show the distribution of reconnection sites within each vein among the subset of patient for which this was prospectively evaluated. S- superior, A- anterior, I- inferior, P- posterior.

PV reconnection sites were prospectively studied in a subset of 20 consecutive cases each in the CRYO and RF groups, and 10 in the COMBINED groups. There were 72 reconnection sites in 51 PVs in the CRYO group, 80 reconnection sites in 58 PVs in the RF group, and 23 reconnection sites in 19 PVs in the COMBINED group.

For the CRYO group, the anterior-inferior region (anterior, anterior inferior and inferior segments) accounted for 43 out of 63 sites (68%) where reconnection was found, compared to only 33 out of 81 sites (41%) in the same region in the RF group (P= 0.001). This pattern is most pronounced in the RSPV where 90% of reconnection occurred and least so in the LIPV where only 53% was accounted for.

For the RF group, the superior and inferior regions on the right sided veins (anterior superior, superior and posterior superior segments of the RSPV and anterior inferior, inferior and posterior inferior segments of the RIPV) were least likely to be reconnected, accounting for only 9 out of 45 (20%) of reconnected right sided PVs. For the left sided veins, there were no reconnection sites on the inferior segment of LSPV and superior segment of LIPV. The sites of reconnections were otherwise evenly distributed when assessing segments within one clock face of each other.

For the COMBINED group, the pattern of reconnection in the RSPV appears similar to the CRYO group with 5 out of 6 (83%) of PV reconnections occurring in the anterior-inferior region. Otherwise, the inferior veins were more likely to be reconnected, accounting for 17 of the 26 segments (65%) with no clear pattern of distribution.

Discussion

Main findings

This study reports the 5-year outcome of three different PVI strategies for PAF: the cryoballoon, radiofrequency catheter ablation (RFCA) or a novel combined approach. We found that after a single procedure, the combined approach resulted in a significantly lower rate of AF recurrence in the long term compared to both cryoballoon and RFCA, and cryoballoon was in turn superior to RFCA. The combined approach was associated with significantly fewer reconnected PVs compared to the other two groups. The pattern of PV reconnection differed between those who underwent cryoballoon compared to those undergoing RFCA and may explain the synergistic effect of the combined approach. After repeat procedure(s), efficacy was similar between the groups with AF free survival of ~70-80% at 5 years off antiarrhythmic medications although the combined approach remained superior to RFCA. This combined with the proportion of patients with recurrence despite no PV reconnection suggest that even the perfect PVI strategy will have a long-term ceiling of ~80% success due to non-PV triggers.

Long term efficacy of the cryoballoon ablation

We have previously shown in a randomised controlled trial that the single procedure success rate off antiarrhythmic drugs at 1 year was 67% following ablation with the first generation cryoballoon[6], which was in keeping with other randomized studies and registry data[4,8,10]. The current study shows that at median follow-up of 5 years, AF free survival following cryoaballoon ablation drops to 47%.

There is limited long term (over 1 year of follow up) data for cryoballoon ablation in the literature. Vogt et al reported the outcomes of 605 patients who underwent cryoballoon ablation in a prospective registry [10]. Similar to our study, both 23 and 28mm Artic Front cryoballoons were used and Freezormax catheter was used when isolation was not achieved using the cryoballoon(s) alone. At 1 year follow-up, AF free survival after a 3-month blanking period was around 70%. At median follow-up of 30 months, follow-up data were available for 451 patients with 62% remaining free of AF. One other observational study involving 139 patients reported 49% freedom from AF at mean follow-up of 457 days [11]. Our findings are consistent with these data.

Comparison of long term single procedure efficacy to RF and Combined approach

The 1-year success rate obtained with conventional RF ablation was 47% and this dropped to 19% at median follow-up of 5 years. Recent multicenter trials and a large prospective registry have reported single-procedure success rates off antiarrhythmic drugs in the region of 43-50% at up to 2 years follow-up[2,12]. The results obtained with RF ablation in the current study therefore seem to be consistent with 'real world' practice. Cryoballoon ablation has a higher single-procedure AF free survival rate at 5 years, suggesting greater durability of PV isolation with this technology.

In contrast, AF-free survival for patients who had the combined approach was 57% during long-term follow-up. This suggests a lower rate of attrition compared to the other 2 groups and is comparable to other studies looking at rates of late recurrence[13].

We have previously suggested that the combined approach may be cost-effective over the long term by reducing the number of repeat procedures needed[14] but further study with appropriate economic modeling will be required to answer this question.

Patterns of PV reconnection comparing cryoballoon and RF ablation

We found a significantly different pattern of PV reconnection between the cryoballoon and RF group. Firstly, the RSPV appears to be less likely to be reconnected following cryoballoon ablation. Secondly, the anterior-inferior region appears more likely to be reconnected in patients undergoing cryoballoon ablation.

With the exception of Van Belle[11], other centers have also reported a lower incidence of PV reconnection of the RSPV following cryoballoon ablation with the left sided veins more likely to be reconnected than the right [4,15,16].

We are aware of only two studies which have characterized the pattern of PV reconnection sites within each vein following cryoballoon ablation. The first by Ghosh et al[17] studied 51 repeat procedures at a mean of 9 months following cryoballoon ablation. The study found that the anterior segments of the left-sided veins and the inferior segment of the RIPV was most likely to be reconnected.

Kuhne et al compared the pattern of PV reconnections between cryoballoon and RF ablation[18]. They reported the PV reconnection sites in a cohort of 25 patients with PAF undergoing cryoballoon ablation compared to 25 age and sex matched controls who underwent conventional RF ablation. After a 3-month blanking period, 5(20%) patients in the cryoballoon group and 7 (28%) patients in the RF group underwent a repeat procedure with a mean of 3 reconnected PVs per patient in each group. Similar to our findings, there were significantly fewer reconnected RSPVs and PV reconnections occurred most frequently in the inferior regions of the veins. It is important to note that in this study repeat procedures were performed within 1 year of the index procedure compared with the longer follow-up duration in our study. It remains uncertain whether PV reconnection and gaps become more or less apparent over time or simply remain unaltered.

PV reconnections in the Combined approach

The striking finding in our study is the low long-term recurrence rate and the low number of reconnected PVs in the patients in whom AF recurs in the combined group. This is the first long term report we are aware of for such an approach.

There are theoretical advantages to PV isolation by either segmental ostial isolation or WACA. The use of these two modalities in combination to create two rings of scar to insulate the PVs may therefore draw on the advantages of each strategy. In addition, the concomitant use of radiofrequency and cryothermal energy may itself be synergistic[19].

By studying the patterns of PV reconnection sites, we postulate another mechanism for the synergistic effect of the combined approach. Segmental ostial isolations using cryoballoon and WACA lines using RF appear to result in different patterns of PV reconnection. By combining the two approaches, the 'vulnerable' sites associated with each modality are covered by the other complementary technique.

Non-PV triggers in PAF

Finally, 18% of patients overall who underwent a repeat procedure were found to have all PVs isolated. Furthermore, 9% of the whole combined cohort (6/69) had recurrent AF but were found to have all four PVs isolated at the repeat procedure. This is therefore a minimum proportion of patients that have non-PV triggers[20]. It is probable that some patients (in all groups) had bystander PV reconnection, although this is not clear until patients have a repeat procedure with all PVs isolated. This leads us to conclude that 10-20% have non-PV triggers that may play a significant role in PAF and suggests a likely ceiling on the long-term success rate of a PVI alone strategy for PAF of 80-90%.

Limitations

Although this study was conducted at an experienced high-volume unit, the success rates in the conventional RF ablation group were seemingly average for the literature but comparable to real world outcomes[2,12,21]. In addition, follow-up was guided primarily by symptoms and hence asymptomatic recurrences of AF may have been missed. However, this again reflects real world practice[2], and equally affects all three groups of patients.

Contact force sensing technology is now available, as is the second generation cryoballoon with short to medium term outcomes comparing the two being reported [10]. It remains to be seen whether these advances or others will substantially impact long term success rates.

Although this study reports the outcomes of a previous generation technology, the results demonstrate that there appears to be a ceiling on long-term success with PVI alone strategy regardless of initial technique used and after repeated procedures.

Conclusion

We have shown that the 5-year outcome following a single catheter ablation procedure for PAF using a combined approach of RFCA followed by cryoballoon ablation is superior to that of either technique alone. Ablation with the cryoballoon was also superior to RFCA. The pattern of PV reconnection differs between cryoballoon and RFCA, which may explain the synergistic effect of the combined approach and low rates of PV reconnection at repeat procedures. These data suggest an excellent outcome at 5 years with an effective PVI strategy for PAF. However, the long-term success rate with such an approach is likely have a ceiling of 80-90% due to non-PV triggers.

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Effect of Non-fluoroscopic Catheter Tracking on Radiation Exposure during Pulmonary Vein Isolation: Comparison of 4 Ablation Systems.

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Abstract

Background: A novel non-fluoroscopic catheter tracking system (Mediguide) can be used in combination with a 3D mapping system for atrial fibrillation (AF) ablation. However, the benefit on radiation exposure of the Mediguide system compared to other ablation systems is unknown.

Methods: We retrospectively enrolled consecutive 73 patients (51 men; 59±11 years; 60 paroxysmal AF) undergoing pulmonary vein isolation by the same operator. Radiation time, radiation effective dose, procedure time, AF recurrence after ablation, and procedure-related complications were compared among 4 different ablation systems.

Results: Mediguide was used in 16 patients (group A), CARTO™ in 17 (group B), Cryoballoon in 30 (group C), and Multi-electrode Pulmonary Vein Ablation Catheter (PVAC) in 10 (group D). Although procedure time was shorter in patients with Cryoballoon (median 110 [interquartile range 99-120] min) and PVAC (123 [112–146] min) compared to those with Mediguide (181 [168–214] min) and CARTO (179 [160–195] min) (P<0.001), radiation exposure time and effective dose were decreased in patients with Mediguide compared to the other ablation systems (A: 5 [3–6] min; B: 14 [11–16] min; C: 14 [11–18] min; D: 20 [16–24] min, P<0.001 and A: 1.1 [0.8–2.0] mSv; B: 2.5 [1.3–3.8] mSv; C: 2.0 [1.4–2.5] mSv; D: 1.7 [1.4–3.6] mSv, P=0.015, respectively). AF recurrence rates and procedure-related complications were comparable among the 4 groups.

Conclusion: The Mediguide system reduces radiation exposure compared to other ablation systems without increasing AF recurrence or procedure-related complications.

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia with an increasing incidence related to the aging of the population[1]. Radiofrequency catheter ablation of AF has become a successful treatment option for patients with both paroxysmal and persistent AF and pulmonary vein isolation (PVI) is the cornerstone of AF ablation[2]. Although 3-dimensional electro-anatomical mapping systems (EAMS) are routinely used to facilitate catheter navigation, conventional fluoroscopy is still needed for intracardiac catheter manipulation throughout the procedure. Therefore, to minimize radiation exposure for both patients and physicians, alternative catheter tracking systems are needed.

A novel non-fluoroscopic catheter tracking system (Mediguide Technology, St Jude Medical, St Paul, MN) can be used in combination with an EAMS (NavX-Ensite Velocity, St Jude Medical, St Paul, MN) in PVI, which enables continuous visualization of multiple catheter positions in pre-recorded cine loops[3-5]. Although a recent study showed that the use of Mediguide in combination with Ensite Velocity during PVI reduces radiation exposure compared to Ensite Velocity only,3 no study has compared the radiation exposure during PVI using the Mediguide/Ensite Velocity versus single-shot devices. The aim of our study was to investigate whether radiation exposure can be reduced using Mediguide system during PVI as compared to other ablation systems including a conventional EAMS (CARTO3, Biosense Webster, Diamond Bar, CA), Cryoballoon catheter (Arctic Front Advance, Medtronic, Minneapolis, MN), and multi-electrode pulmonary vein ablation catheter (PVAC-GOLD, Medtronic, Minneapolis, MN)

Key Words

Radiation exposure, Atrial fibrillation, Ablation, Non-fluoroscopic Catheter Tracking System.

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Materials and Methods

Study Subjects

We retrospectively enrolled 524 patients who underwent radiofrequency catheter ablation of drug refractory AF in the Leiden University Medical Center between January 2014 and June 2016. Out of 524 patients, 189 patients with prior PVI, 99 patients who had additional ablation targets besides PVI and 163 patients treated by an electrophysiology fellow were excluded from this study to eliminate other factors influencing radiation time (e.g. complexity of the ablation, experience of the operator). The final study population comprised 73 patients[Figure 1].

The patients were classified in 4 groups according to the type of

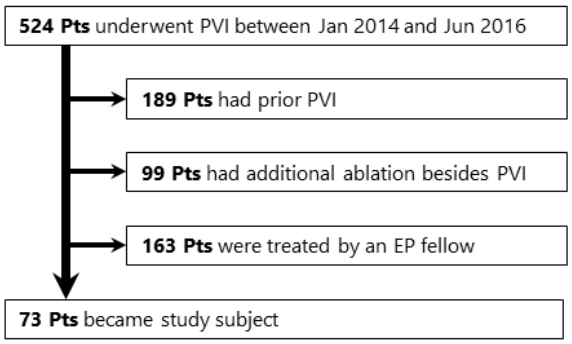

Figure 1: **Study design. Patients excluded from the analysis are indicated by arrows directed to the right. EP indicates electrophysiological; and PVI, pulmonary vein isolation..**

ablation system used during the procedure. The Mediguide system in combination with NavX-Ensite Velocity was used in 17 patients, CARTO 3 in 22, Cryoballoon in 48, and PVAC-GOLD in the remaining 10. The selection of the ablation system depended on the physician's decision. Primary endpoints were radiation exposure time, radiation effective dose and procedure time (from puncture to removal of sheaths) and secondary endpoints were AF recurrence after PVI and procedure-related complications. Data on age, sex, body mass index, cardiac risk factors and medication were collected. Transthoracic echocardiograms were reviewed for left atrium diameter, left ventricular ejection fraction, and valvular disease. All patients were treated according to our standard clinical protocol and provided informed consent. The Dutch Central Committee on Human-related Research (CCMO) permits use of anonymous data without prior approval of an Institutional Review Board, if the data are obtained for patient care and if the data do not contain identifiers that could be traced back to the individual patient.

Non-fluoroscopic Catheter Tracking System and Fluoroscopic Settings

The Mediguide technology has been described previously[6]. In brief, the Mediguide system is installed on a Siemens fluoroscopy system (Siemens Healthcare GmbH, Erlangen, Germany). The transmitter unit is integrated with the fluoroscopy detector of the X-ray imaging system and is able to create the electromagnetic field in alignment with the fluoroscopic field of view. The sensor-equipped catheter can be either visualized on conventional fluoroscopy or tracked non-fluoroscopically on pre-recorded fluoroscopy or cine loops.

For all four ablation systems, the pulse rate of the fluoroscopy system was set at 7.5 pulses per second for live X-ray (Dose of 10nGy/p, Pulse width of 8.0ms, copper filter of 0.6–0.9mm) and the frame rate was set at 10 frames per seconds for cine-angiocardiography (Dose of 0.17 microGy/p, pulse width of 6.4ms, copper filter of 0.1–0.2.mm).

Catheter Ablation

In all patients, a 320-slice Computer Tomography (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) was performed prior to the ablation to visualize the anatomy of the PVs and to guide the procedure[7]. All patients were on uninterrupted oral anticoagulation at the time of the ablation. Intravenous heparin was administered to maintain an activated clotting time of 300 to 400 seconds throughout the procedure.

Mediguide and CARTO procedures were performed using an EAMS (Navx-Ensite Velocity System and CARTO 3), an irrigated 3.5-mm ablation catheter (Coolpath Duo, St Jude Medical, St Paul, MN, or Thermocool [n=19] or Thermocool Smart Touch Surround Flow [n=3], Biosense Webster, Diamond Bar, CA), and a 10-polar circular mapping catheter (Lasso 2515, Biosense Webster, Diamond Bar, CA). Point-by-point ipsilateral PVI was performed. Radiofrequency power was delivered at 25W for a maximum duration of 30 seconds per application at the roof and the posterior left atrial wall and 30W at the anterior left atrium.

Cryoballoon ablation was performed with a 28-mm cryoballoon catheter (Arctic Front Advance, Medtronic, Minneapolis, MN) and an integrated circular mapping catheter (Achieve, Medtronic, Minneapolis, MN). The cryoballoon was advanced towards each PV to achieve occlusion verified by contrast injection. Cryoablation was performed with a single application of 240 sec in all PVs but the right superior PV (180 sec), resulting in PVI. To prevent phrenic nerve palsy, continuous phrenic nerve stimulation (cycle length of 2000ms and output of 20mA) was performed during ablation of the right PVs. A temperature probe was inserted in the esophagus to monitor the luminal esophageal temperature (Sensitherm, St Jude Medical, St Paul, MN). If loss of phrenic nerve capture or decrease in the luminal esophageal temperature below 18°C occurred, ablation was immediately interrupted by the "double stop" technique[8].

PVAC ablation was performed with the PVAC-GOLD catheter at a setting of 2:1 bipolar to unipolar energy. PVs were electrically isolated by targeted ablation of each PV antrum.

The endpoint of the ablation was PVI, defined as the presence of bidirectional conduction block from the atrium to the PVs and vice versa. Confirmation of bidirectional conduction block at least 30 minutes after successful PVI was routinely performed. Sinus rhythm was restored by cardioversion at the end of the procedure when needed.

Follow up and Definition of AF Recurrence

All patients were followed 3, 6 and 12 months after the procedure with a 12-lead ECG, 24 hour Holter monitoring and an exercise tests. Patients were encouraged to obtain ECG documentation in case of recurrent symptoms. Recurrence was defined as evidence of AF, atrial tachycardia or atypical flutter on a 12-lead ECG or lasting ≥30 seconds on Holter monitoring. A 3 month post-procedural blanking period was applied[9].

Statistical Analysis

Continuous variables were expressed as means ± standard deviation or medians (IQR). Differences among 4 groups for continuous variables were determined by analysis of variance or Kruskal-Wallis test according to the data distribution with or without normality, and post hoc analyses were performed with Bonferroni test. All categorical variables were presented as the number and percentage in

each group and were compared by a Fisher's exact test. A comparison of the probability of the freedom from AF among 4 groups was performed using Kaplan-Meier survival analysis with log rank test. "Time 0" for the survival analyses was the date of PVI. Multiple linear regression analysis was used to determine independent predictors of radiation effective dose. Variables that achieved statistical significance (P<0.05) or were close to significance (P<0.1) in the Spearman's rank correlation coefficient were included in the multiple linear regression analysis. A P value <0.05 was considered statistically significant. All analyses were performed with R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.1.1)

Results

Demographic and Clinical Characteristics among 4 groups

Demographic and clinical characteristics are summarized in [Table 1] The mean age of the patients was 59±11 years and 70% were male. Persistent AF was observed in 13 (18%) patients. The mean left atrial diameter was 41±5 mm. There was no significant difference in baseline clinical and echocardiographic characteristics among the 4 groups [Table 1].

Table 1: Demographic and Clinical Characteristics among 4 groups

Variable	All (n = 73)	Mediguide (n = 16)	CARTO (n = 17)	Cryoballoon (n = 30)	PVAC (n = 10)	P-value
Age, years	59 ± 11	61 ± 11	54 ± 15	61 ± 9	62 ± 9	0.142
Male gender, n (%)	51 (70%)	13 (81%)	13 (77%)	19 (63%)	6 (60%)	0.492
Body mass index, kg/m2	26 ± 3	26 ± 3	26 ± 3	27 ± 4	27 ± 3	0.768
Persistent AF, n (%)	13 (18%)	5 (31%)	4 (24%)	2 (7%)	2 (20%)	0.177
Risk factors						
Hypertension, n (%)	35 (48%)	9 (56%)	9 (56%)	12 (40%)	5 (50%)	0.708
Hyperlipidemia, n (%)	20 (27%)	3 (19%)	5 (29%)	8 (27%)	4 (40%)	0.696
Diabetes mellitus, n (%)	3 (4%)	1 (6%)	1 (6%)	1 (3%)	0 (0%)	0.850
Smoking, n (%)	26 (36%)	3 (19%)	8 (47%)	11 (37%)	4 (40%)	0.383
Chronic kidney disease, n (%)	7 (10%)	1 (6%)	2 (12%)	2 (7%)	2 (20%)	0.605
Ischemic heart disease, n (%)	6 (8%)	0 (0%)	3 (18%)	2 (7%)	1 (10%)	0.311
Echocardiographic findings						
LA diameter, mm	41 ± 5	42 ± 6	42 ± 7	40 ± 4	43 ± 5	0.335
LV ejection fraction, %	65 ± 11	60 ± 12	64 ± 14	66 ± 8	70 ± 9	0.096
Valvular disease, n (%)	2 (3%)	0 (0%)	1 (6%)	1 (3%)	0 (0%)	0.705
Medication						
Statin, n (%)	18 (25%)	3 (19%)	6 (35%)	7 (23%)	2 (20%)	0.687
ACE-I/ARB, n (%)	30 (41%)	8 (50%)	9 (53%)	10 (33%)	3 (30%)	0.429
B-blocker, n (%)	42 (58%)	10 (63%)	8 (47%)	17 (57%)	7 (70%)	0.666
Class I AAD, n (%)	30 (41%)	5 (31%)	7 (41%)	13 (43%)	5 (50%)	0.794
Sotalol, (%)	15 (21%)	5 (31%)	3 (18%)	6 (20%)	1 (10%)	0.594
Amiodarone, n (%)	8 (11%)	2 (13%)	1 (6%)	2 (7%)	3 (30%)	0.189
Warfarin, n (%)	59 (81%)	10 (63%)	15 (88%)	24 (80%)	10 (100%)	0.091
NOAC, n (%)	14 (19%)	6 (37%)	2 (12%)	6 (20%)	0 (0%)	0.091

Values are reported as the mean ± standard deviation or n (%). AAD indicates anti-arrhythmic drug; ACE-I, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; LA, left atrium; LV, left ventricle; and NOAC, new oral anticoagulant.

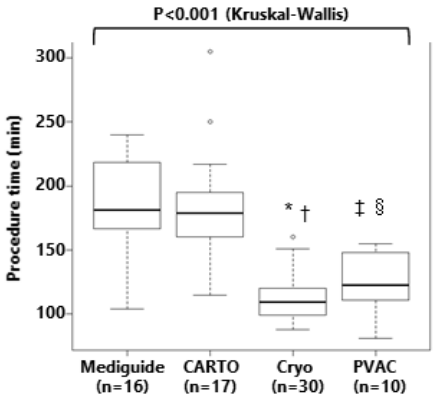

Figure 2: Radiation time among 4 groups.* P<0.001 vs. CARTO, † P<0.001 vs. Cryo, ‡P<0.001 vs. PVAC.

Primary and Secondary Endpoints

Procedure time was shorter for the Cryoballoon (median 110 [IQR 99–120] min) and PVAC groups (123 [112–146] min) compared to Mediguide (181 [168–214] min) and CARTO (179 [160–195] min, P<0.001 by Kruskal-Wallis test)[Figure 2]. However, of importance, patients in the Mediguide group experienced a shorter radiation time (5 [3–6] min) compared to CARTO (14 [11–16] min), Cryoballoon (14 [11–18] min), and PVAC (20 [16–24] min) groups (P<0.001)[Figure 3]. Furthermore, radiation effective dose differed significantly among the 4 groups (1.1 [0.8–2.0] mSv in Mediguide; 2.5 [1.3–3.8] mSv in CARTO; 2.0 [1.4–2.5] mSv in Cryoballoon; and 1.7 [1.4–3.6] mSv in PVAC, P=0.015) [Figure 4]. Multiple linear regression analysis identified a low body mass index (P=0.001), short left atrial diameter (P=0.004), and the use of the Mediguide

Table 2: Multiple Linear Regression Analysis of Variables Associated with Radiation Effective Dose.

Variable	Beta	Standard error	T value	P-value
(Constant)	-0.434	1.227	-3.535	<0.001
Left atrial diameter	0.074	0.025	2.968	0.004
Body mass index	0.139	0.041	3.366	0.001
Mediguide usage	-1.077	0.322	-3.341	0.001
R2 = 0.381 (P<0.001)				

ADR= Adverse Drug Reaction

Table 3: Procedural related complications among 4 groups.

Variable	All (n = 73)	Mediguide (n = 16)	CARTO (n = 17)	Cryoballoon (n = 30)	PVAC (n = 10)	P-value
Stroke/TIA, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0
Cardiac tamponade, n (%)	2 (3%)	1 (6%)	1 (6%)	0 (0%)	0 (0%)	0.476
Phrenic nerve palsy, n (%)	1 (1%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0.693
Permanent, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)	1.0
Transient, n (%)	1 (1%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0.693

Values are reported as n (%). TIA indicates transient ischemic attack.

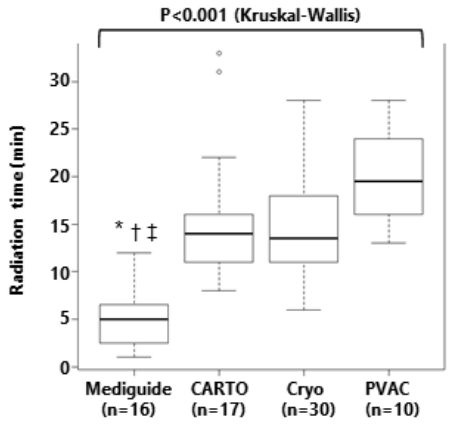

Figure 3: Illustration shows a receiver operator characteristics (ROC) curve analysis for left atrial dimension (LAD) in prediction of recurrence of atrial fibrillation (AF) in first three months post ablation. A left atrial size ≥ 37 mm had the highest accuracy (sensitivity 100%, specificity 26%, PPV 54, NPV 100) for predicting atrial fibrillation (AF) recurrence in the blanking period (P 0.036).

system (P=0.001) as independent factors associated with a decrease of radiation effective dose [Table 2].

Procedural related complications did not differ among the 4 groups [Table 3]. None of the study patients experienced a stroke or transient ischemic attack. Transient phrenic nerve palsy occurred in 1 patient of the Cryoballoon group (P=0.693). Two patients (1 in the Mediguide group and 1 in the CARTO group) had pericardial bleeding requiring percutaneous drainage (P=0.476). During a mean follow-up of 11±4 months, 23 (32%) patients had AF recurrence. Kaplan-Meier curve demonstrated that there was no significant difference in the recurrence of AF among the 4 groups (P=0.753 by log-rank test).

Discussion

Main Findings

The main findings of the present study are as follows: (1) patients undergoing a first PVI by an experienced operator with the use of Mediguide in combination with Ensite Velocity had a shorter radiation time and received less radiation effective dose compared to those undergoing PVI with a stand-alone nonfluoroscopic system (CARTO) or a single-shot device (either PVAC or Cryoballoon); (2) a lower body mass index, a shorter left atrial diameter and the use of Mediguide were independently associated with a lower radiation effective dose; (3) procedure time was significantly shorter when a single-shot device was used (Cryoballoon or PVAC); and (4) the prevalence of procedure-related complications and the incidence of AF-recurrence during follow-up did not differ among groups.

Importance of reducing radiation exposure during ablation procedures

To minimize radiation exposure is important for both patients and physicians. Statistically significant increases in brain cancer and leukemia have been reported with doses as low as 30 mSv in children[10]. Previous studies estimated that a radiation exposure of 53 to 60 minutes during radiofrequency catheter ablation would result in 0.7 to 1.4 excess fatal malignancies per 1000 women and 1.0 to 2.6

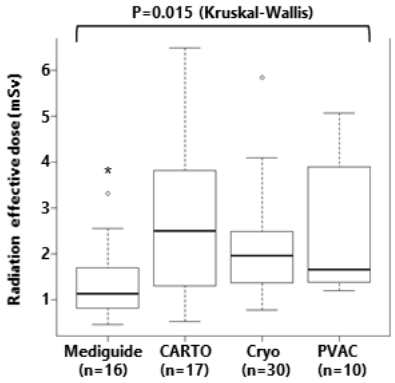

Figure 4: Radiation effective dose among 4 groups.* P<0.05 vs. Cryo

per 1000 men[11]. Roguin et al. reported the occupational radiation exposure-induced brain and neck tumors among 31 physicians performing interventional procedures. In this group, approximately 85% of the brain tumors were located in the left cerebral hemisphere, while brain tumors are normally evenly distributed between both hemispheres. The fact that the brain is relatively unprotected and that the left side of the head is known to be more exposed to radiation could explain these findings[12].

Impact of use of a Non-fluoroscopic Catheter Tracking System during AF ablation on radiation exposure

In the early 2000's, several studies reported mean radiation times of 57–130 minutes in patients undergoing fluoroscopy-guided PVI[11,13]. The advent of three-dimensional non-fluoroscopic EAMS (CARTO and Ensite) resulted in a significant reduction in radiation exposure during AF ablation[14,15]. Fluoroscopy-guided single shot devices (PVAC/Cryoballoon) were subsequently developed to reduce procedural duration[16-18] However, the beneficial effect of single shot devices on reducing radiation exposure remains controversial[16-18]. The usage of a novel non-fluoroscopic catheter tracking system (Mediguide technology) in combination with an EAMS (Navx Ensite Velocity) has enabled operators to further minimize radiation exposure compared to use of an EAMS only[3]. However, no data are available comparing radiation exposure during PVI performed with a single shot device or with the Mediguide technology.

In line with previously reported, in our study, procedural time was shorter when PVI was performed with a single shot device (cryoballoon or PVAC) than when point-by-point ablation was performed using an EAMS (Carto or Ensite). However, and, of importance, radiation time were shorter when the combination of Mediguide/Ensite was used for ablation than when either a single shot device or the Carto system alone were used

Although single shot devices create larger ablation lesions with a single application resulting in reduced procedure time, they rely on fluoroscopy to verify catheter positions resulting in a relatively high radiation dose in spite of short procedure time. On the other hand, point-by-point ablation using a conventional EAMS requires a large number of catheter manipulations, which may increase radiation dose as well, even when the procedure is performed by an experienced operator (as it was the case in our study). These factors may explain why radiation exposure did not differ among the

CARTO, Cryoballoon, and PVAC groups

Our findings demonstrate that a technology which enables the visualization of catheters on prerecorded Cine loops can successfully help to reduce radiation exposure during AF ablation. Currently, the CARTO system has also a module for integrating fluoroscopy with EAMS (UNIVU) that has proven to reduce radiation exposure[19].

In addition to the use of Mediguide technology, body mass index and LA diameter were independently associated with radiation dose during PVI. It is well known that obesity is associated with an increase in radiation dose[20]. However, the association between LA size and radiation dose has not been reported so far. We speculate that in patients with an enlarged LA, catheter manipulation and catheter contact might be more difficult. Furthermore, in the presence of the larger PV antra, more ablation lesions might be needed to achieve PVI, both factors resulting in prolonged radiation time and dose.

Although the risk of carcinogenesis with the reported radiation exposure levels during PVI might be low, it is prudent to follow the principles of keeping the radiation dose "as low as reasonably achievable" not only for patients but also for physicians[21]. Our findings indicate that the Mediguide technology can contribute to follow this policy without an increase in complication and AF recurrence. In addition, the Mediguide system might enable operators to perform PVI without wearing a lead apron as the necessity of fluoroscopy is rare after pulmonary venography. This may result in a decrease in operator fatigue and musculo-skeletal problems

Study Limitations

The present study has several limitations. First, our study had a retrospective design with a relatively small sample size and should be considered as a hypothesis-generating study, not a conclusive trial. However, in our center the selection of mapping systems for an individual procedure is rather arbitrary and depends more on availability of different cathlab rooms than on patient characteristics. In addition, our study population was relatively homogeneous, since we excluded patients with prior PVI, additional ablation besides PVI, and patients treated by an electrophysiological fellow. Nonetheless, further prospective and ideally multicenter randomized studies with larger sample sizes are necessary to confirm our results. Second, the cost of the system itself and the increased costs associated with Mediguide sensor-equipped tools may be a drawback for implementation of this system. Third, the reported findings come from an experienced operator at a high-volume referral center and may therefore not be applicable to smaller less experienced centers.

Conclusion

The use of Mediguide system in combination with Ensite Velocity during PVI reduces radiation exposure compared to other ablation systems without increasing AF recurrence or procedure-related complications. Therefore, physicians should consider the usage of new fluoroscopy integrating technology in an EAMS (Mediguide or CARTOUNIVU) to minimize radiation exposure.

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Rate Versus Rhythm Control in Patients with Normal to Mild Left Atrial Enlarge-ment: Insights from the AFFIRM Trial

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Abstract

Background: Atrial fibrillation is the most commonly encountered sustained arrhythmia and is asso-ciated with significant morbidity and mortality. Several trials have demonstrated that no mortality benefit exists when choosing a rhythm-control strategy over a rate-control strategy, with some trials suggesting an increase in mortality. Using the AFFIRM trial database we sought to determine the effect of rhythm control strategy in patients with normal or mild atrial enlargement.

Methods: AFFIRM Trial database was used to evaluate the effect of rhythm-control strategy com-pared to rate-control strategy in a subgroup of patients with normal to mild left atrial (LA) enlargement. The primary outcome measures of this study were all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, and hospitalization/ED visit.

Results: We identified a subgroup of subjects from the AFFIRM trial with normal or mild LA en-largement (n=2022 of 4060 total subjects). Subjects in the rhythm-control group(n= 1022) had an increased risk of all-cause mortality by 34% (RR 1.34, 95% CI 1.08-1.67; P=0.007) and hospitalization/ED visits by 10% (RR 1.10, 95% CI 1.05-2.16; P=<0.001) compared to rate control group(n= 1000).

Conclusion: This study demonstrated that rhythm-control strategy increases the risk of mortality and hospitalization in a subgroup of patients with normal to mild atrial enlargement com-pared to rate-control strategy. Amiodarone use in this subgroup of patients likely drove these findings.

Introduction

The concept that "atrial fibrillation begets atrial fibrillation" is well described and poses a challenge to physicians hoping to restore sinus rhythm [1,2].Atrial remodeling occurs on an electrical, contractile, and structural level while patients are in atrial fibrillation (AF) [3,13].These changes make patient's atria more susceptible to developing ep-isodes of AF and make the restoration of sinus rhythm more unlikely [14-24]. Left atrial (LA) enlargement is a typical structural change observed as a result of long-standing AF and predicts failure to maintain sinus rhythm [25-30].

Atrial fibrillation is the most commonly encountered sustained arrhythmia and is associated with significant morbidity and mortality [31,37]. Despite the increased mor-tality that comes with AF, multiple trials have demonstrated that no mortality benefit ex-ists when choosing a rhythm-control strategy over a rate-control strategy, with some tri-als suggesting an increase in mortality [38-44]. The Atrial Fibrillation Follow-up Investi-gation of Rhythm Management (AFFIRM) study compared rhythm-control and rate-control strategies for the treatment of atrial fibrillation [40]. The trial included patients at least 65 years of age or at increased risk for stroke. The rhythm-control group was pri-marily treated using anti-arrhythmic drugs (AADs) and electrical cardioversion with a small percentage undergoing ablation. The AFFIRM investigators found that more pa-tients in the rhythm-control group were hospitalized, had more adverse drug effects, and had a non-significant trend towards higher mortality compared to patients in the rate-control arm. The study's aim in AFFIRM trial was to compare strategies in a heterogeneous patients population with atrial fibrillation. As a result, the patients included in the trial had a wide range of atrial remodeling and structural changes.

Using the AFFIRM trial database we sought to determine the effect of a rhythm-control strategy in patients with normal or mild LA enlargement. The presence of LA en-largement was collected during the AFFIRM trial based on the LA dimension. We chose the size of LA as a surrogate marker for LA remodeling as it has been demonstrated to occur in patients with long-standing AF and predicts difficulties in maintaining sinus rhythm.

Key Words

Atrial Fibrillation, Rhythm Management, Rate Control, Atrial Size.

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Materials and Methods

Study population

Data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial were used in this study. The AFFIRM study was a multi-center rando-mized clinical trial comparing rhythm-control to rate-control for patients with atrial fibrillation. The patients included were those who were at least

65 years of age or who had other risk factors for stroke or death. Additionally, patients included were those in which long-term treatment was warranted, were candidates for either treatment strategy, did not have contraindications to anticoagulation, and had a high likelihood of recurrent atrial fibrillation. In our study, patients from the AFFIRM trial who had normal or mild LA enlargement based on echocardiography were included in our study.

Intervention

The patients in AFFIRM trial were randomized to rhythm-control or rate-control strategies. In the rhythm-control arm, patients were maintained in sinus rhythm by AADs (class Ia, Ic or III), as well as electrical cardioversion, if necessary. The AADs were amiodarone, flecainide, dofetilide, propafenone, disopyramide, procainamide, quinidine, sotalol, and moricizine. In the rate-control strategy, the ventricular rate was controlled using beta-blockers, digoxin, and/or calcium-channel blockers (verapamil and diltiazem). The target ventricular rate was =< 80 beats per minute at rest and =< 110 beats per minute during a six-minute walk test.

Outcome

Outcomes include all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, and the rate of hospitalization.

Statistical analysis

Comparisons between the two treatment arms, rhythm-control strategy and rate-control strategy, were conducted between baseline demographic and health characteristics using chi-square test and student's t-test. Baseline demographic characteristics included age, sex, and body mass index. Baseline health characteristics included past medical history, predominant cardiac diagnosis, blood pressure, and left ventricular ejection fraction.

Table 1: Baseline demographic and health characteristics. *

Characteristics	Rhythm-control (N=1022)	Rate-control (N= 1000)	P Val-ue
Age (year)	70±8	70±8	0.71
Female sex (% of patients)	42.47†	47.60	0.02
Body mass index	28±6	29±6	0.23
Medical history (% of patients)			
• Diabetes (DM)	17.91	19.80	0.28
• Hypertension (HTN)	70.06	69.90	0.94
• Angina pectoris	24.07	21.40	0.15
• Myocardial infarction	15.95	12.90	0.05
• Coronary artery disease	34.83	32.70	0.31
• Coronary artery bypass graft	10.08	8.20	0.14
• Stroke or TIA	13.50	14.50	0.52
• Valvular heart disease	10.76	10.70	0.96
• Congestive heart failure	18.49	19.10	0.73
• Congenital heart disease	0.39	0.20	0.43
• Peripheral vascular disease	6.46	6.30	0.88
• Hepatic or renal disease	4.99	6.40	0.17
• Pulmonary disease	14.48	12.30	0.15
• First episode of atrial fibrillation (AF)	36.32	37.89	0.47
• Duration of qualifying of AF ≥ 2 days	62.72	64.00	0.94
Predominant cardiac diagnosis (% of patients)			
• Dilated non-ischemic cardiomyopathy	54.11	55.60	0.50
Blood pressure before run-in phase (mm Hg)			
• Systolic	136±19	136±19	0.97
• Diastolic	77±10	77±10	0.99
Ejection fraction (%)	57±8	57±7	0.55
The follow-up period (year)	3.53±1.28	3.54±1.28	0.85
Change treatment strategy (% of patients)	0.26	0.11	

* Plus–minus values are means ±SD.

Table 2: The incidence of the outcomes in patients with normal and mild left atrial enlargement, rhythm control vs. rate control

	Rhythm-control (N=1022)	Rate-control (N= 1000)	Relative Risk (95% CI)	P-Value
	no. of patients (%)			
All-cause mortality	169 (16.54)	123 (12.30)	1.34 (1.08-1.67)	0.007
Cardiovascular mortality	74 (7.24)	75 (7.50)	0.97 (0.71-1.32)	0.823
Non-cardiovascular mortality	88 (8.61)	45 (4.50)	1.91 (1.35-2.71)	<0.001
Hospitalization/ED visit.	796 (77.89)	707 (70.70)	1.10 (1.05-1.16)	<0.001

An intention-to-treat analysis was used to compare outcomes of the two groups in patients with normal or mild LA enlargement. A chi-square test was used to test for differences between the treatment group's outcomes. A logistic regression model was also used to adjust for the difference in sex distribution between the two groups. The statistical analyses were performed using SAS version 9.4. All tests were conducted using an α=0.05 as the probability for a Type I error.

Results

Baseline Characteristics

The total number of subjects with normal or mild LA enlargement in the AFFIRM trial was 2,022 out of 4,060 subjects. Of the 2,022 subjects with normal or mild LA en-largement; 1,022 were assigned to the rhythm-control group, and 1,000 were assigned to the rate-control group. [Table 1] displays the descriptive baseline demographics and health characteristics of the two groups.

The mean (±SD) age, body mass index, and ejection fraction were 70±8 years, 28±6 kg/m2, and 57±7%, respectively. A total of 70 percent of the subjects had hypertension; 18.8 percent of the subjects had diabetes; 33.8 percent of subjects had coronary artery disease; 18.8 percent of the subjects had a history of congestive heart

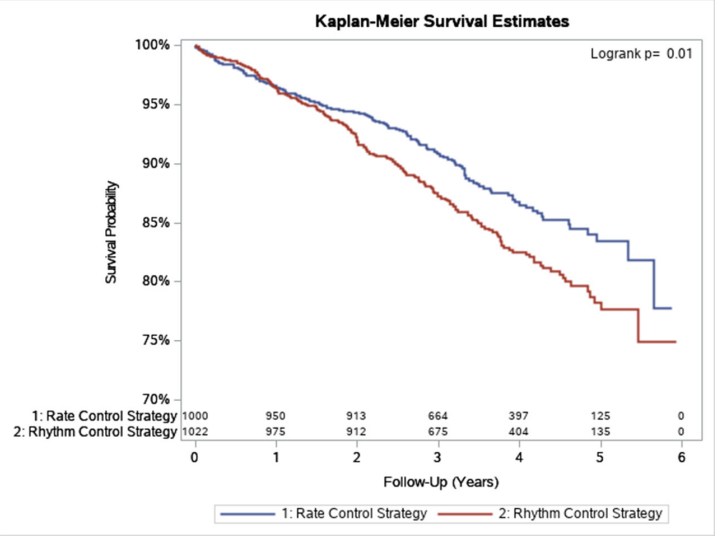

Figure 1: Kaplan-Meier Survival for All cause Mortality:Rhythm Control vs. Rate.

Table 3: The incidence of the outcomes in patients with normal and mild left atrial enlargement based on the initial antiarrhythmic therapy

	Amiodarone (N= 334)	Rate-control (N= 1000)	Relative Risk (95% CI)	P-value
All-cause mortality	57 (17.07)	123 (12.30)	1.39 (1.04-1.85)	0.027
Cardiovascular mortality	23 (6.89)	75 (7.50)	0.92 (0.59-1.44)	0.710
Non-cardiovascular mor-tality	32 (9.58)	45 (4.50)	2.13 (1.38-3.29)	0.001
	Sotalol (N= 322)	Rate-control (N= 1000)	Relative Risk (95% CI)	P-value
All-cause mortality	43 (13.35)	123 (12.30)	1.09 (0.79-1.50)	0.620
Cardiovascular mortality	16 (4.97)	75 (7.50)	0.66 (0.39-1.12)	0.119
Non-cardiovascular mor-tality	24 (7.43)	45 (4.50)	1.66 (1.03-2.67)	0.038

failure. The total proportion of subjects with their first episode of atrial fibrillation was 37.1 percent, and 63.4 percent of the qualifying episodes of atrial fibrillation lasted more than two days. There was no significant difference between the baseline characteristics of the two groups except for sex distribution; 42.5 percent in rhythm control group vs. 47.6 percent in the rate control group were women (p= 0.02).

Outcome

[Table 2]outlines the comparisons inthe risk of all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, and hospitalization/ED visit between the two treatment groups. The risk of all-cause mortality (RR 1.34, 95% CI 1.08-1.67; P=0.007) and non-cardiovascular death (RR 1.91, 95% CI 1.35-2.71; P<0.001) were higher among rhythm-control subjects compared to rate-control subjects. These risks did not change after adjusting for sex distribution between the two groups. The risk of hospitalization/ED visits was also higher among the rhythm-control group (RR 1.10, 95% CI 1.05-2.16; P=<0.001). However, there was no significant difference in cardiovascular mortalityamong the two treatment groups (RR 0.97, 95% CI 0.71-1.32; P=0.823).

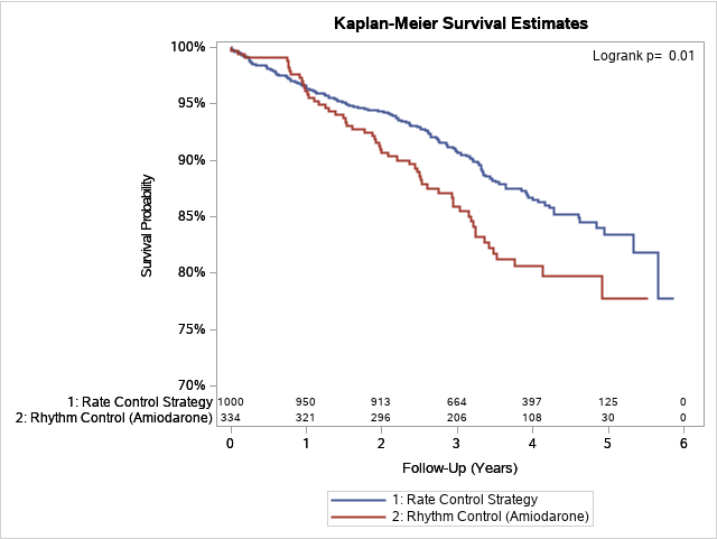

Figure 2: Kaplan-Meier Survival for All cause Mortality:Amiodarone Use vs. Rate Control.

[Table 3] compares the outcomes based on the type of the initial antiarrhythmic medications that was started after randomization. All-cause mortality was significantly higher among patients who received amiodarone as initial therapy (RR 1.39, 95% CI 1.04-1.85; P=0.027) compared to patients who received rate-control therapy. In contrast, patients who received sotalol as an initial therapy (RR 1.09, 95% CI 0.79-1.50; P=0.620) did not have an increase in all-cause mortality compared to patients who re-ceived rate-control therapy received rate-control therapy. [Figure 1] shows Kaplan Meier Survival for the differences in all-cause mortality-between subjects in rhythm control strategy and subjects with rate control strategy for approximately six years of follow-up. Subjects who received rhythm control strategy had significantly shorter survival than subjects who received rate control strategy (p-value = 0.01). [Figure 2] and Figure 3 show Kaplan Meier Survival for the differences in all-cause mortality between amiodarone and sotalol compared to rate control strategy. Subjects who received amiodarone as initial rhythm control strategy had significantly shorter survival than subjects who received rate control strategy (p-value = 0.01). However, there was no significant difference between in the survival between subjects who received sotalol as initial rhythm control strategy and subjects who received rate control strategy.

Discussion

In this subgroup analysis, rate-control and rhythm-control strategies were compared in patients with atrial fibrillation who had a normal or mildly enlarged left atrium. Despite this subgroup had a more favorable atrial substrate for to maintain sinus rhythm, attempts to pursue a rhythm-control strategy resulted in a higher risk of mortality and hospitalization/ED visits. The increased mortality in the rhythm-control group was primarily related to non-cardiovascular events. However, there was no significant difference in the risk of cardiovascular mortality in the two groups. These findings suggest that the mortality associated with a rhythm-control strategy is related to adverse effects of AADs.

The increase in adverse events is likely a result of the high rate of amiodarone use. In the rhythm-control group, 21.27% of patients had been started on amiodarone as the initial therapy after randomization. When we evaluated outcomes based on the type of antiarrhythmic medications used, we found that those who received amiodarone had higher rates of all-cause mortality (RR 1.39, 95% CI 1.04-1.85; P=0.027) compared to the rate-control group. This finding was driven by non-cardiovascular death (RR 2.13, 95% CI 1.38-3.29; P=0.001). However, the second most common AAD used, sotalol, did not lead to an increased risk of all-cause mortality compared to rate-control group (RR 1.09, 95% CI 0.79-1.50; P=0.620).

Amiodarone's toxicities are well described, and its negative impacts have been demonstrated in previous clinical trials. The Rhythm of Rate Control in Atrial Fibrilla-tion—Pharmacological Intervention in Atrial Fibrillation (PIAF) study exclusively used amiodarone as its AAD. The trial found that patients in the rhythm-control group had a significantly higher rate of hospital admission and adverse events that led to a change in therapy [38]. The Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study used a stepwise algorithm

of escalating AADs and cardioversion in the rhythm-control group. Ultimately 56 percent of patients in the rhythm-control group received amioda-rone. Like the PIAF trial, the HOT CAFE trial found an increase in the rate of hospitali-zations with amiodarone use [42]. The Japanese-RHYTHM Study randomized patients with paroxysmal atrial fibrillation, with most patients having normal to mildly enlarged left atria. The J-RHYTHM study found no increase in mortality or rate of hospitalization. In fact, rhythm control strategy was associated with fewer cardiovascular events than rate control strategy. The findings of this study are contrary to what had been observed in other trials likely due to the low rate of amiodarone use (< 1%) in this trial. This trial suggests that AADs other than amiodarone are better tolerated in patients when a rhythm-control strategy is pursued[43].

Supplementary materials

Table 4: Proportionate mortality in all patients with atrial fibrillation regardless the size of atrium, rhythm control vs. rate control.

	Rhythm control (N= 356)	Rate control (N= 310)	Relative Risk (95% CI)	P Value
	no. of patients (%)			
Cardiovascular mortality	171 (48.44)	182 (51.56)	0.82 (0.71-0.94)	0.006
Non-cardiovascular mortality	175 (59.73)	118 (40.27)	1.29 (1.08-1.54)	0.004

Table 5: Incidence of the outcomes based on the size of atrium.*

	Normal to mild atrial enlargement (N=2022)	All patients regardless the size of atrium (N= 4060)
	no. of patients (%)	
All-cause mortality	292 (14.44)	666 (16.40)
Cardiovascular mortality	149 (7.37)	353 (8.69)
Non-cardiovascular mortality	133 (6.58)	293 (7.22)
Hospitalization or Emergency visit.	1184 (59.68)	3058 (75.32)

Table 6: The model evaluates the effect of rhythm control after adjusting for sex distribution

	Adjusted OR	95% Wald Confidence Limits	Adjusted P-value
All-cause mortality	1.40	1.09-1.80	0.009
Cardiovascular mortality	0.96	0.69-1.34	0.822
Non-cardiovascular mortality	1.96	1.35-2.84	<0.001

The AFFIRM study included patients with atrial fibrillation with different atrial size, ranging from normal to severe atrial enlargement [40]. In this group of patients with dif-ferent atrial size, patients who were on rhythm control had a higher proportionate mor-tality ratio of non-cardiovascular disease and lower proportionate mortality ratio of car-diovascular disease compared to patients who were in the rate-control group. The car-diovascular benefit of rhythm-control in this group neutralized the effect of non-cardiovascular side effect of anti-arrhythmic medications. Therefore, the overall death rate was not significantly different between the rhythm-control and rate-control groups. In contrast, patients with normal or mild atrial enlargement did not have a significant cardiovascular benefit to neutralize the effect of non-cardiovascular mortality. Those patients did not have a significant cardiovascular benefit, in part, due to the lower rate of cardiovascular mortality (7.37% vs. 8.69%) compared to the pool of patients that include moderate to severe atrial enlargement.

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Some limitations are worth mentioning. Although we include only patients with normal to mild LA enlargement, this was based on the LA dimension, which was the method that was used at that time.

Therefore, future studies should use LA volume divided by body surface area, which is reliable and the standard 2D echocardiographic method that is recommended by the American Society of Echocardiography to confirm the results of our study [50].

Conclusion

This study demonstrated that rhythm-control strategy is associated with an increased risk of mortality and hospitalization in patients with normal to mild atrial enlargement. These findings were likely driven by amiodarone use in this subgroup.

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Safety of Twice Daily Sotalol in Patients with Renal Impairment: A Single Center, Retrospective Review

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Abstract

Background: The class III antiarrhythmic sotalol is renally eliminated with a dose-related propensity to cause adverse drug reactions (ADR) potentially leading to life-threatening arrhythmias. Although product labeling recommends once daily dosing in patients with renal impairment, twice daily dosing is commonly utilized. This study evaluates the safety of this practice.

Methods: This retrospective, observational study examined renally impaired patients with atrial fibrillation or atrial flutter admitted for sotalol initiation from July 1, 2012 - December 31, 2014, then for up to 20 months after initiation. Primary endpoints included rates of ADR and therapy changes due to ADR. Secondary endpoints included therapy changes due to arrhythmia recurrence, admissions due to arrhythmia recurrence, and therapy changes for any cause.

Results: Analysis included 134 patients with an average creatinine clearance of 51 ml/min, followed over a median of 170 days. Length of stay averaged 3 days withADR occurring in 53.7% of patients, most commonly QT prolongation or bradycardia. Therapy change due to ADR occurred in 45.5% of patients (n=61). Therapy change due to arrhythmia recurrence occurred in 23.1% (n=31), admission due to arrhythmia recurrence occurred in 24.6% (n=33), and therapy change for any cause occurred in 74.6%(n=100).

Conclusion: Initiating sotalol twice daily in renally impaired patients results in ADR and therapy change rates consistent with rates seen in clinical practice for non-renally impaired patients, with minimal length of stay.This practice may be reasonable when initiated in the acute care setting with subsequent outpatient monitoring, however further study is needed.

Introduction

Proarrhythmia and sudden cardiac death are significant concerns linked to the use of antiarrhythmic drugs. Sotalol, a Class III antiarrhythmic agent with non-selective beta-blocking properties, is known to effectively treat atrial arrhythmias. However, its dual mechanism of action may cause adverse drug reactions (ADRs) including bradycardia and QT prolongation, which can lead to life threatening arrhythmias . Sotalol does not undergo first pass metabolism, and 80-90% of its elimination occurs by renal excretion of unchanged drug . The half-life varies from 7 -18 hours based on renal function. Sotalol has been shown to have dose-dependent proarrhythmic effects,thus it is essential to consider the renal elimination of sotalol when selecting a dosing strategy.

Atrial fibrillation (AF) and atrial flutter (AFL) are two of the most common arrhythmic disorders, leading to significant morbidity and mortality worldwide. Yet, for patients with renal impairment, there is limited data regarding use of antiarrhythmic drugs (AAD). For sotalol specifically, many studies evaluating its safety exclude patients with renal impairment, or do not disclose creatinine clearance (CrCl) of subjects. Studiesincluding renally impaired patients with a CrCl 40-60 ml/min utilized a once daily dosing schedule, with doses ranging from 80-160mg. Therefore, the product labelling for sotalolrecommends once daily dosing (specifically 80mg once daily, titrated up to 160mg once daily as tolerated) when sotalol is used to treat AF or AFL for patients with a CrCl of 40-60 mL/min. The product label also recommends monitoring patients within an inpatient setting for the first five doses when starting sotalol .However, the ACC/AHA/HRS AF guidelines have differed on their recommendations for sotalol initiation. In 2011, the guidelines recommended outpatient initiation of sotalol in patients with little or no heart disease, QT interval <450 ms, and minimal risk factors for proarrhythmia. The 2014 ACC/AHA/HRS AF Guidelines acknowledge that practice patterns vary widely. Authors note while inpatient initiation should be considered given the package insert warning, there is considerable experience with outpatient initiation as well and the initiation strategy should be individualized.

Admission for initiation of an AAD can be a costly endeavor for the patient and health system. A two to three day admission for sotalol initiation may cost over $3,000[9]. Patients with renal impairment receiving once daily dosing of sotalol would need to be hospitalized for five days, resulting in a greater cost burden. Due to these

Key Words

Sotalol, Renal Impairment, Renal Dysfunction, Atrial Fibrillation, Dosing.

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concerns as well as clinical experience, patients with a CrCl 40-60 ml/min are often initiated on sotalol twice daily in an acute care setting. This allows patients to remain monitored during their first five doses, while decreasing length of stay. This practice commonly occurs at The Ohio State University Wexner Medical Center (OSUWMC). Patients are often discharged on twice daily sotalol with follow-up in the OSUWMC AAD clinic. Patients with renal impairment presenting to clinic on twice daily dosing are considered for conversion to once daily dosing based on package insert recommendations and/or presence of ADRs.

Although twice daily initiation dosingof sotalol is common in renally impaired patients, a formal evaluation of safety has not yet been conducted. Little is known concerning outcomes of this dosing strategy, or the effect of dose changes in the outpatient setting.The purpose of this study is to describe the safety of sotalol, initiated in the acute care setting at a twice daily dose in patients with renal impairment, during their inpatient stay and outpatient course.

Methods

This retrospective, observational study evaluated patients with AF/AFL admitted for initiation of sotalol from July 1, 2012 through December 31, 2014 at the Richard M. Ross Heart Hospital, a 172-bed cardiovascular hospital at OSUWMC (Columbus, OH). Data werecollected on patients seen up to 20 months after sotalol initiation to characterize presence of and response to ADRs, as well as arrhythmia control. Upon discharge, information in the ambulatory setting was obtained from notes written by electrophysiology, cardiology, or AAD clinic visits. The AAD clinic is a pharmacist-run, physician-supervised service and aims to monitor and assess antiarrhythmic therapy[10]. The study was granted exemption from review through the OSUWMC Institutional Review Board. Our patient did not demonstrate a high risk accessory pathway ERP on or off isoproterenol. However, AV conduction over the accessory pathway improved on isoproterenol from 230ms to 200ms, suggesting a very high risk accessory pathway.

Participants were identified by a computer generated list of patients with an order for sotalol while admitted to the Ross Heart Hospital with concomitant diagnosis of AF or AFL. Patients were then further evaluated by manual chart review to ensure the sotalol prescription identified was the patient's first. During admission, sotalol dose was determined based on provider discretion and patient's QT response after the first dose. All patients continuing sotalol upon discharge were in sinus rhythm at the time of discharge. Patients were eligible for inclusion if all of the following criteria were met: age 18-89 years of age, indication for sotalol of AF or AFL, renal impairment (defined as CrCl 40-60 ml/min) upon admission for sotalol initiation, and sotalol initiated at twice daily. Pregnant women and prisoners were excluded, as well as patients receiving sotalol for other atrial or ventricular arrhythmias. To provide continuity throughout the study, all CrCl calculations were based on clinic protocol. For patients over age 65, if serum creatinine was <1.0, it was rounded to 1.0.Adjusted body weight was utilized in the Cockroft-Gault equation for those with an actual body weight greater than 20% over their ideal body weight.

The primary endpoints of this study included[1] describing the overall proportion of patients who experience ADRs, and[2] the proportion of therapy changes (dose adjustments, drug discontinuations, and additional interventions such as device implantation) related to ADRs. Specific ADRs included: bradycardia (heart rate <50), QT interval prolongation (QT interval >500 ms or >550 ms if ventricular pacing), incidence of torsade de pointes, or other ADR resulting in significant symptoms. Secondary endpoints included proportion of patients with therapy changes due to arrhythmia recurrence, admissions due to arrhythmia recurrence, and therapy changes for any cause (e.g. CrCl).Arrhythmia recurrence was defined as documentation of recurrent AF/AFL after initial discharge requiring intervention such as dose adjustment, or admission for intervention (direct current cardioversion, ablation, or therapy change). Those who failed sotalol at the time of initiation due to ineffectiveness were not included in this definition.

Patients were evaluated for the above pre-specified endpoints during 1) hospitalization for sotalol initiation, 2) "1-month clinic visit" occurring 0-3 months after initiation, 3) "6 month clinic visit" occurring 4-8 months after initiation, 4) "12 month clinic visit" occurring 9-14 months after initiation, and 5) "18 month clinic visit" occurring 15-20 months after initiation. For patients who did not have clinic follow-up at every time point but continued on sotalol therapy, dosing data from the prior visit was carried forward. For these patients, it was presumed no significant adverse events or arrhythmia events occurred prompting evaluation.

Statistical analysis

Baseline demographic and disease-related characteristics were compared across two dose groups (80 mg twice daily and 120 mg twice daily) using t-test, Fisher's exact, and chi-square tests as appropriate. The prevalence of adverse effects leading to changes in therapy, including dosage adjustment, drug discontinuation, and additional intervention, was calculated separately at discharge and post-discharge for the two dose groups. Chi-square tests were performed for comparison. Specific ADRs were described. A two-sided significance level of α=0.05 was used for all tests. Analyses were performed in SAS version 9.3 (SAS institute, Cary, NC).

Results

There were 1,202 patients identified with an active prescription for sotalol during admission from July 1, 2012 through December 31, 2014. After review, 1,068 patients were excluded . The most common reasons for exclusion were CrCl > 60 ml/min (n=664) and sotalolinitiation occurring prior to study period (n=327).Therefore 134 patients were included as initiated on sotalol twice daily during the study period, with 63.5% (n=85) started on sotalol 80 mg twice daily , 35% (n=47) on 120 mg twice daily, and 1.5% (n=2) on 40 mg twice daily. Patients taking 40 mg twice daily were excluded from statistical comparison between these groups, but included in the overall evaluation. The majority of patients were white females, with an average

age of 71.9 years and an average CrCl of 51 ml/min [Table 1]. Characteristics were well matched between the two dosing groups, with the exception of age and CrCl.Patients were followed for a median of 170 [IQR: 7-560.75] dayswith 15 patients lost to follow-up after discharge. Length of stay was similar between the two groups, approximately 3 days.

Table 1: Baseline characteristics

	Total N=132	80mg BID n=85	120mg BID n=47	P-value
Age (years), mean ± SD	71.9 ± 7.1	73.5 ± 7.1	69.0 ± 6.1	0.0004
Male, n (%)	47 (35.6%)	35 (41.2%)	12 (25.5%)	0.072
BMI(kg/m2), mean ± SD	29.4 ± 6.9	28.8 ± 6.9	30.4 ± 6.8	0.21
White, n (%)	122 (93.1%)	77 (91.7%)	45 (95.7%)	0.90
SCr (mg/dl), mean ± SD	1.14 ± 0.21	1.1 ± 0.2	1.1 ± 0.2	0.51
Number of patients with SCr rounded to 1, n (%)	58 (44%)	38 (45.2%)	20 (43.5%)	0.94
Calculated CrCl (ml/min), mean ± SD	50.9 ± 6.5	49.5 ±6.6	53.3 ± 5.6	0.0013
LVEF >40, n (%)	110 (83.3%)	72 (84.7%)	38 (80.9%)	0.82
Bundle branch block, n (%)	20 (15.2%)	10 (11.8%)	10 (21.3%)	0.14
Device, n (%)	56 (42.4%)	34 (40%)	22 (46.8%)	0.45
Permanent pacemaker	44 (33.3%)	27 (31.7%)	17 (36.1%)	0.84
ICD	9 (6.8%)	5 (5.9%)	4 (8.5%)	...*
Bi-ventricular ICD	3 (2.2%)	2 (2.3%)	1 (2.1%)	...*
No Device	76 (57.6%)	51 (60%)	25 (53.19%)	0.32
AARx clinic follow-up, n (%)	38 (28.8%)	24 (28.2%)	14 (30.0%)	0.85
Length of Stay (days), mean ± SD	3.09 ±0.03	3.08±0.02	3.04±0.04	0.45
Total Follow up (days), mean ± SD+	309.5 ±353.5	318.9 ± 362	292.5 ± 340.8	0.69
Baseline HR (bpm), mean ± SD	86.5 ± 27.6	86.7 ± 27.6	86.1 ± 27.9	0.92
Baseline QRS (msec), mean ± SD	99.2 ± 29.6	98.3 ± 31.6	101 ± 25.9	0.61
Baseline QT (msec), mean ± SD	390.5 ± 58.5	390.8 ± 63.7	389.9 ± 48.3	0.93
Baseline QTc (msec), mean ± SD	455.8 ± 39.7	454.2 ± 38.4	458.6 ± 42.1	0.55
AF/AFL upon admission, n (%)	66 (50%)	41 (48.2%)	25 (53.2%)	0.586

*Unable to calculate
+Range: 1-600days
AARx= Antiarrhythmic medications; BBB= bundle branch block; CrCl= Creatinine clearance; HR= heart rate; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; SCr= Serum creatinine

Overall, 53.7% (n=72) patients experienced at least one ADR throughout the study. The most common were QT prolongation (27.6%) and bradycardia (20.2%). There were no reports of torsades de pointes or death due to ventricular arrhythmias. ADRs were further separated into occurrence during admission and post-discharge [Table 2]. While admitted, 37.3% (n=50) of patients experienced at least one ADR with no difference between patients initiated on120 mg twice daily versus 80 mg twice daily (42.6% vs 34.1%, p = 0.34). At time of discharge, 74.6% (n=100) of patients continued on sotalol, and of those, 22% (n=22) experienced ADRs after dischargewith no difference between ADR rate in patients discharged on 120mg versus 80 mg twice daily (19% vs 25%, p = 0.57).

Therapy change due to ADR occurred in 45.5% (n=61) of patients throughout the study period with no difference inADR rate betweenpatients on 120mg versus 80 mg twice daily (51.1% vs 41.2%, p = 0.27)and occurring more often inpatient than outpatient [Figure 1]. Therapy change due to ADR during admission for sotalol initiation occurred in 34.3% (n=46) of patients,more often in patients initiated on 120 mg twice daily versus 80 mg twice daily (42.6% vs 29.4%, p=0.10). Of the 100 patients discharged on sotalol, following initiation, therapy change due to ADR for occurred in 15% (n=15) of patients, with no difference between patients on 120mg versus 80mg twice daily (15.8% vs 11%). Outpatient ADRs prompting therapy change included: QT prolongation in 6% (n=6), fatigue in 3% (n=3), bradycardia in 3% (n=3), and other in 3% (n=3).

Table 2: Adverse drug reactions on sotalol therapy in renally impaired patients

ADR, % (n)	Total (N=134)	Inpatient course (N=134)	Outpatient course (n=100)
Total ADRs	53.7% (72)	37.3% (50)	22% (22)
1 ADR	40.1% (54)	27.5% (37)	17% (17)
2 or more	13.6% (18)	9.8% (13)	5% (5)
QT prolongation	27.6% (37)	23.1% (31)	6% (6)
Bradycardia	20.2% (26)	15.9% (21)	5% (5)
Fatigue	4.3% (5)	0	5% (5)
Dizziness	2.6% (3)	0	3% (3)
SOB	4.3% (5)	3% (4)	1% (1)
HF exacerbation	1.5% (2)	1.5% (2)	0
Other	7% (9)	3% (4)	5% (5)

ADR= Adverse Drug Reaction

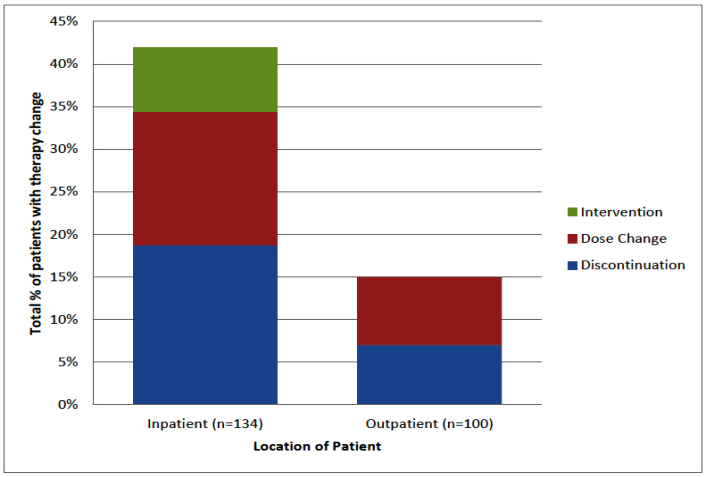

Figure 1: Types of Therapy changes due to ADR on solatol twice daily

Therapy change due to any cause occurred in 74.6% (n=100) of patients, some with more than one change, including drug discontinuationin 59.7% (n=80), dosage adjustment in 19.4% (n=26), and additional intervention in 9.7% (n=13).Therapy change during admission for sotalol initiation occurred in 47.7% (n=64) of patients with a higher rate noted in patients initiated on 120 mg versus 80 mg

twice daily (63.8% vs 40%, p=0.0087).

Therapy changes due to arrhythmia recurrence occurred in 23.1% (n=31) of patients with recurrence less common in patients on 120mg versus 80mg twice daily (4.5% vs. 11.2%).Admission related to arrhythmia recurrence occurred in 24.6% (n=33) of patients for a total of 36 admissions. During admission additional rhythm control strategies were utilized such as direct current cardioversion or radiofrequency ablation.

Of the 100 patients discharged on sotalol, 38% (n=38) subsequently established in theAAD clinic. Of those that did not, reasons included: 18% (n=18) discontinued drug before scheduled visit, 17% (n=17) had no appointment, 12% (n=12) cancelled appointment and 15% (n=15) were lost to follow-up. Dose frequency change occurred for 21% (n=8) of these outpatients in the AAD clinic, in these casessotalol was adjusted to once daily. One subsequently discontinued sotalol due to arrhythmia recurrence.

Continuation of sotalol therapy was low overall, with 31.3% of the initial 134 patients (n=45) remaining on drug at the end of the20 month study period. Most common reasons for sotalol discontinuation included: ADR in 23.8% (n=32), therapy ineffectiveness in 17.2% (n=23), stopped after ablation 5.2% (n=7), and worsening renal function in 5.2% (n=7) of patients.

Discussion

This study establishes a point of reference for the safety and effectiveness of twice daily sotalol in patients with renal impairment in clinical practice.Over half of renally impaired patients started on sotalol twice daily experienced at least one ADR, most commonly bradycardia and QT prolongation. Length of inpatient stay remained minimal with more ADRs and therapy changes occurring in the first days of therapy.Patients on higher sotalol doses experienced more therapy changes during admission anddose changes due to ADR.

Despite dose adjustments and ADRs reported, starting sotalol at twice daily dosing in renally impaired patients did not result in increased length of stay for patients started on either high or lower doses. In order to receive appropriate monitoring utilizing once daily dosing and five doses, length of stay would have been five days at minimum, compared to average of three days seen in this study. Therefore, twice daily dosing did minimize length of stay.

During sotalol initiation, several studies report the rate of discontinuation due to ADRs. One randomized controlled trial of patients with paroxysmal AF/AFL, evaluated sotalol vs placebotolerability over the course of 12 months. Sotalol was given once daily in patients with CrCl 40-60 mL/min (20% of patients) at doses of 80 mg, 120 mg and 160 mg and twice dailyto non-renally impaired patients. Investigators found discontinuation due to adverse events was dose dependent, occurring in 12%, 18%, and 29% of patients in the 80, 120, and 160mg dose groups (6). Another study of patients admitted for antiarrhythmic drug initiation noted 18% of patients on sotalol experienced a cardiac ADR significant enough to result in discontinuation or intervention (5). Sotalol dose was at the discretion of the treating physician, but most patients received 80mg twice daily. These findings are consistent with the 25.4% discontinuation rate and 18.7% discontinuation rate due to ADR specifically during admission for drug initiationin our study of renally impaired patients on twice daily sotalol.

The incidence of ADRs on sotalol therapy during initiation in non-renally impaired patients has been studied. Agusala et al. evaluatedpatients (average GFR of 78.2 ml/min) admitted for initiation of sotalol and dofetilide, looking at risk prediction for ADRs. Of 227 patients treated with sotalol, 43.5% experienced bradyarrhythmia and 56.9% QTc prolongation(defined as increase in 15% from baseline; or exceeding 500 ms) during admission for initiation.Agusala and colleagues were not able to identify any significant predictors of ADRs. The authors concluded ADRs are common during initiation and that these results establish need for close inpatient monitoring[11].The rates of bradycardia and QT prolongation during admission in our study of renally impaired patients (15.9% and 23.1%, respectively) are lower than that reported despite twice daily dosing strategy. Furthermore, sotalol product labeling describes bradycardia incidence of 13.1%[3]. The outpatient rate of bradycardia in our study was lower (5%).

There is currently a lack of literature evaluating out patient sotalol therapy changes due to ADRs. In theory, the extended half-life of sotalol in renal impairment may result in delay in achieving steady state concentrations by the time of discharge, even after 5 doses. Despite this concern, we found only 15% of patients discharged on sotalol required therapy change due to ADRs in the outpatient setting.

Sotalol therapy is known to have shortcomings in maintaining sinus rhythm. The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) assessed amiodarone versus sotalol for treatment of AF, following 655 patients for a minimum of 1 year.Amiodarone and sotalol were equally effective in converting AF to sinus rhythm; however, amiodarone was superior in maintenance of sinus rhythm. On average, 60% of patients in the sotalol group experienced recurrence of AF within 1 year. Weekly rhythm assessments were conducted telephonically[12]. Although our study was not designed to detect all AF recurrence, we found comparable results with 40% experiencing arrhythmia recurrence (based on our definition) and 23.5% had arrhythmia recurrence prompting therapy change over the 20 month study period.Sotalol was discontinued in this population at a high rate of 59.7% with twice daily dosing of sotalol.

During outpatient course, dose frequency change occurred in 21% of patients following in the AAD clinic, with only one patient experiencing arrhythmia recurrence subsequently. Although the low volume of patients makes the safety of this practice difficult to assess, considering the overall number of therapy changes that occurred in

our study population, this does not demonstrate a significant trend.

There are several limitations to our study. This study was a single-center, retrospective chart review. Our study was not initially designed to compare the 80mg and 120mg twice daily dosing groups, thus was underpowered to do so . Additionally, the number of patients in the two groups was uneven. Variation in CrCl calculation among practitioners and individual patient characteristics likely impacted dose selection. Confounding variables were not accounted for in assessment, including concomitant medications (such as additional QT-prolonging drugs, or negative inotropes such as non-dihydropyridine calcium channel blockers orbeta-blockers), RR and QT intervals, electrolytes, and device pacing which may have which may have contributed to ADRs .Serum sotalol levels were not measured directly, so the impact of dosing changes on therapeutic drug concentrations is unknown though assessment of changes in the QT interval serves as a surrogate estimate of serum sotalol levels. Another limitation is only 38% discharged on sotalol presented for follow up in the AAD clinic in this study, making it difficult to assess safety in the other 62% after discharge. Lastly, safety and efficacy were not compared directly to once daily dosing in this practice setting.

This study serves to establish a point of reference for the safety of twice daily sotalol in patients with renal impairment. A prospective assessment with a larger sample size, analysis of other contributing risk factors for ADRs, and standardized outpatient monitoring is warranted.

Conclusion

Initiating sotalol twice daily in renally impaired patients results in ADR and therapy change rates consistent with rates seen in clinical practice for non-renally impaired patients, with minimal length of stay. Inpatient monitoring of this practice may be reasonable, further analysis of this patient population in a randomized, controlled study is needed.

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Value of Interatrial Block for the Prediction of SilentIschemic Brain Lesions

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Abstract

Introduction: Previous studies demonstrated that interatrial block (IAB) is associated with atrial fibrillation (AF) in different clinical scenarios. The aim of our study was to determine whether IAB could predict silent ischemic brain lesions (sIBL), detected by magnetic resonance imaging (MRI).

Methods: Patients presented to a neurology clinic with transient ischemic attack (TIA) symptoms and underwent brain MRI were included to the study. sIBL were defined as lesions without corresponding clinical symptoms regarding lesion localization evaluated by two neurologists. A 12-lead surface ECG was obtained from each patient. IAB was defined as P-wave duration > 120 ms with (advanced IAB) or without (partial IAB) biphasic morphology in the inferior leads.

Results: sIBL was detected in 61 (49.6%) patients. Patients with sIBL were older (P<0.001), had more left ventricular hypertrophy (LVH) (P=0.02) and higher CHA2DS2-VASc score compared to those without (P<0.001). P-wave duration was significantly longer in patients with sIBL (124 [110.5 – 129] msvs 107 [102 – 116.3] ms) (P<0.001). IAB was diagnosed in 36 patients (59%) with sIBL (+) and in 11 patients (18%) with sIBL (-); p<0.001. Multivariate logistic regression analysis identified age [Odds ratio (OR), 1.061; 95% confidence interval (CI), 1.012 - 1.113; p=0.014], CHA2DS2-VASc score (OR, 1.758; 95% CI, 1.045 - 2.956; p=0.034), LVH (OR, 3.062; 95% CI, 1.161 - 8.076; p=0.024) and IAB (including both partial and advanced) (OR, 5.959; 95% CI, 2.269 - 15.653; p<0.001) as independent predictors of sIBL.

Conclusion:IAB is a strong predictor of sIBL and can be easily diagnosed by performing surface 12-lead ECG.

Introduction

Interatrial block (IAB) refers to a conduction delay or block between the right and left atrium and is manifested as P-wave duration greater than 120 ms[1] . Multiple studies have demonstrated the association of IAB with atrial fibrillation (AF) and ischemic stroke in many different clinical scenarios[2-10]. Fibrosis of the atrial conduction system, mainly in the Bachmann region, contributes to the alteration in structural and electrical properties of atrial myocytes and development of IAB. Magnetic resonance imaging (MRI) allowsfor detection of both symptomatic and silent ischemic brain lesion (sIBL) with high accuracy. SIBL is encountered with high prevalence following short pulmonary vein isolation[11], transcutaneous aortic valve replacement[12] and carotid stent implantation procedures[13]. Although its clinical significance is still being debated, several studies have demonstrated sIBLis a predictor of future ischemic stroke, decline in cognitive function and depression[14]. In this study, we evaluated the predictive value of IAB for sIBL detected by MRI.

Key Words

Interatrial Block, Atrial Fibrillation, Silentischemic Stroke

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Methods

The study population consisted of patients who presented to a neurology clinic with transient ischemic attack (TIA)symptoms and had a brain MRI.SIBL was defined as lesions present on radiological assessment that did not correspondto clinical symptoms according to lesion localization. If symptoms did correspond with radiographic lesion localization, the patient was determined to have a symptomatic infarct and was excluded from the study. Patients underwent ECG, TTE and carotid Doppler examination as a routine evaluation for possible source of their clinical symptoms.Exclusion criteria were; 1) presence of non-sinus rhythm on ECG, 2) presence of any lesion on brain MRI corresponding to their clinical symptoms,3) history

of ischemic or hemorrhagic stroke or TIA, 4) history of atrial tachyarrhythmia, 5) valvular heart disease, valvuloplasty or valve replacement procedure and 6) detection of carotid artery disease during carotid artery doppler examination.All patients participating in the study provided informed written consent. The study was approved by the institutional ethics committee.

Baseline patients' characteristics and medical history were recorded. A standard 12-lead electrocardiogram (ECG) (Schiller, CardioVit, AT-10 plus) (Filter 150 Hz, 25 mm/s, 10 mm/mV) was obtained for all study patients. ECG's were scanned at 300 DPI and images were amplified 10x. The P-wave onset was defined as the point of initial upward or downward deflection from the baseline and the offset as the return of the waveform to the initial baseline[Figure 1].

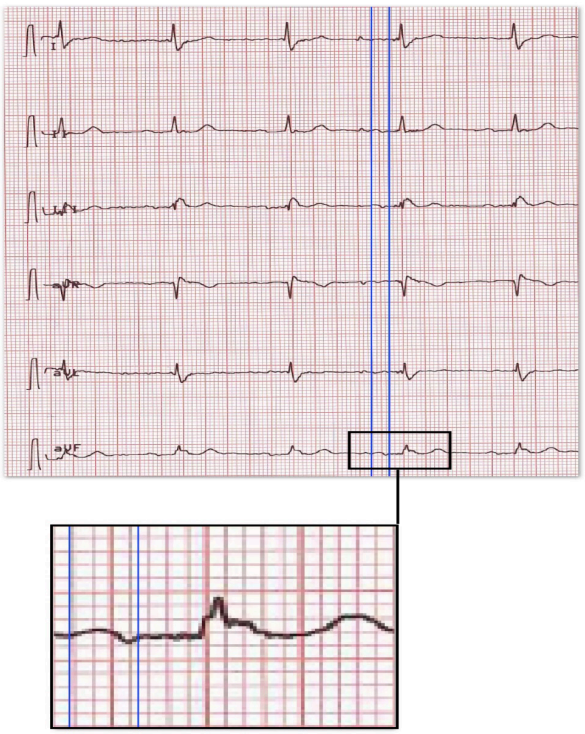

Figure 1: An example of advanced interatrial block (a-IAB) (P-wave duration ≥120 ms with biphasic (±) morphology).

Partial and advanced IAB were classified as recommended in the international consensus report(1):1) Partial IAB: P-wave duration ≥120 ms without negative final component in the inferior leads; 2) Advanced IAB: P-wave duration ≥120 ms with biphasic (±) morphology in the inferior leads.

All patients underwent 2-dimensional transthoracic echocardiography (TTE) (Vivid 7, GE healthcare; Horten, Norway) evaluation by an expert on cardiovascular imaging.M-Mode and 2D measurements were performed in accordance withthe current guidelines on chamber quantification from the American Society ofEchocardiography[15].

Brain MRI scans were performed using 1.5 Tesla MRI scanners (MagnetomAvento, Siemens Healthcare, Erlangen, Germany). The imaging protocol included diffusion-weighted imaging (DWI) sequence and T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence.For each DWI sequence, the apparent diffusion coefficient (ADC) map was obtained by using appropriate software. sIBL were defined as hyperintensity on DWI sequence with corresponding hypointensity and hyperintensity on ADC map and FLAIR sequence respectively. Each individual sIBL was recorded independently of size. All MRI images were analyzed by a radiologist blinded to all other clinical data.

Statistical analysis

All data were evaluated using IBM SPSS 22 (IBM, SPSS, USA). Mean and standard deviations were used for quantitative variables. Student T test was used for normally distributed variables in both groups and Mann-Whitney U test was used for variables which were not normally distributed. Qualitative variables were evaluated by Pearson chi-square and continuity (Yates) correction. Logistic regression analysis was used for multivariate analysis to identify risk factors for the presence of sIBL. A P value of <0.05 was accepted as statistically significant.

Results

During the period from November 2016 through June 2017, 318 patients underwent brain MRI in neurology clinic due to TIA symptoms. 108 patients were excluded from the study due to presence of MRI findings corresponding to their clinical symptoms. 29patients were in AF, 32 patients had prior history of ischemic or hemorrhagic stroke, 9 patients had valvular heart disease, prior valve replacement or valvuloplasty procedure,10 patients had carotid artery disease detected during Doppler examination. These patients were excluded from the study. In addition, 7 patients were excluded from the study due to a conflict on their radiological and clinical data. A total of 123 patients constituted the final study population[Figure 2].

Patients were divided into two groups with respect to the presence of sIBL in brain MRI. sIBL was detected in 61 (49.6%) patients. Baseline demographic and clinical characteristics of each study group are depicted in [Table 1]. Presence of IAB, including both partial and advanced IAB, was significantly higher in patients with sIBL [36 patients (59%) vs 11 patients (18%), p<0.001]. The prevalence of advanced IAB was comparable between the two groups [5 patients (8%) vs 2 patients (3%), P=NS]. Patients with sIBL were more likely to have LVH compared to those without sIBL [29 patients (48%) vs 17 patients (27%), p=0.02].

Multiple logistic regression analysis demonstrated that age [Odds ratio (OR), 1.061; 95% confidence interval (CI), 1.012 - 1.113; p=0.014], CHA2DS2-VASc score (OR, 1.758; 95% CI, 1.045 - 2.956; p=0.034), LVH (OR, 3.062; 95% CI, 1.161 - 8.076; p=0.024) and the presence of IAB (including both partial and advanced) (OR, 5.959; 95% CI, 2.269 - 15.653; p<0.001) were independent predictors of sIBL in the overall population[Table 2].

Discussion

The major finding of this case-control study is that IAB is significantly associated with the incidence of sIBL detected during MRI examination in patients presented with TIA symptoms. IAB

Table 1: Baseline and clinical characteristics for study patients with sIBL (+) and sIBL (-).

Baseline characteristics	Group sIBL (+) (n = 61)	Group sIBL (-) (n = 62)	P value
Age (years)	68 [58.5 – 74.5]	55 [45 – 62.3]	> 0.001
Gender (male)(%)	19 (31)	25 (40)	0.289
BMI (kg/m2)	27.8 [25.4 – 29.4]	27.9 [24.2 – 30.2]	0.929
Hypertension (n) (%)	32 (53)	30 (48)	0.652
Diabetes Mellitus (n) (%)	25 (41)	23 (37)	0.659
Hyperlipidemia (n) (%)	11 (18)	13 (21)	0.681
Heart Failure (n) (%)	7 (12)	6 (10)	0.746
CKD (n) (%)	7 (12)	6 (10)	0.746
CAD (n) (%)	3 (5)	3 (5)	0.984
OSAS (n) (%)	6 (10)	7 (11)	0.793
Smoking (n) (%)	13 (21)	10 (16)	0.461
Hyperthyroidism (n) (%)	2 (3)	2 (3)	0.661
Hypothyroidism (n) (%)	1 (2)	3 (5)	0.317
CHA2DS-VASC	2 [2 – 4]	1 [1 – 2]	> 0.001
Beta-Blocker (n) (%)	8 (13)	6 (10)	0.548
ASA (n) (%)	21 (34)	13 (21)	0.095
P2Y12 inhibitor (n) (%)	3 (5)	3 (5)	0.984
Statin (n) (%)	6 (10)	1 (2)	0.049
ACEI/ARB (n) (%)	25 (41)	19 (31)	0,232
EF (%)	60 [55 – 60]	60 [55 – 60]	0.816
LVH (n) (%)	29 (48)	17 (27)	0.020
LA-AP diameter (mm)	37 [35 – 41]	39 [35 – 41]	0.400
P wave duration (ms)	124 [110.5 – 129]	107 [102 – 116.3]	> 0.001
Partial IAB (n) (%)	31 (51)	9 (14)	> 0.001
Advanced IAB (n) (%)	5 (8)	2 (3)	0.234
Total IAB (n) (%)	36 (59)	11 (18)	> 0.001

ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ASA: Acetylsalicylic acid, BMI: Body mass index, CAD: Coronary artery disease, CKD: Chronic kidney disease, EF: Ejection fraction, IAB: Interatrial block, LA-AP: left atrial antero-posterior, LVH: Left ventricular hypertrophy, OSAS: Obstructive sleep apnea syndrome, sIBL: Silent ischemic brain lesion.

was present in almost 60% of patients with sIBL. The other findings include that patients with sIBL were older, more likely to use statins, had greater incidence of LVH and higher CHA2DS2-VASc score as compared to patients without sIBL.

Other studies have looked at the prevalence of IAB in patients with neurological conditions. O'Neal et al. identified IAB as a risk factor for ischemic stroke[10]. Their findings were derived from the Atherosclerosis Risk in Communities Study of 14,716 adults with digital ECGs measured at baseline and then followed for more than 20 years for incident ischemic stroke events. Incidence of ischemic stroke was more than two-fold in patients with advanced IAB as compared to those without. After adjustment for traditional risk factors, advanced IAB continued to remain a significant risk factor for ischemic stroke. An interesting finding from that study was that advanced IAB is a risk factor for ischemic stroke independent from symptomatic AF. Similarly, Ariyarajah et al. investigated the frequency of IAB in patients with sinus rhythm hospitalized for stroke[16]. The prevalence of IAB in this cohort was 61% and LA thrombi were present in 15% of patients with IAB as compared to none in those without. In the present study we found that IAB was present in 59% of patients with sIBL. Our result was consistent with the previous studies showing that IAB was highly prevalent in ischemic stroke.

sIBL are frequently encountered in patients with AF[20].Gaita et al. evaluated 180 patients with AF and compared the prevalence of sIBL with 90 patients in sinus rhythm[21].On multivariate analysis the presence of AF was strongly associated with the presence of sIBL (OR: 7.2; 95% CI: 2.3 to 22.3; p = 0.001). In addition, patients with AF had worse performance on cognitive function assessed by neuropsychological test as compared to those in sinus rhythm. Recent studies identified sIBL as a significant risk factor for future symptomatic ischemic stroke, memory impairment and cognitive decline. Vermeer et al. studied an elderly population from The

Table 2: Prediction of sIBL by using multiple logistic regression analysis.

	OR	CI 95 %	P value
Age	1.061	1.012 - 1.113	0.014
Gender	1.025	0.352 - 2.987	0.964
CHA2DS2-VASc	1.758	1.045 - 2.956	0.034
LVH	3.062	1.161 - 8.076	0.024
t-IAB	5.959	2.269 - 15.653	> 0.001

LVH: Left ventricular hypertrophy, sIBL: Silent ischemic brain lesion, t-IAB: Total interatrial block

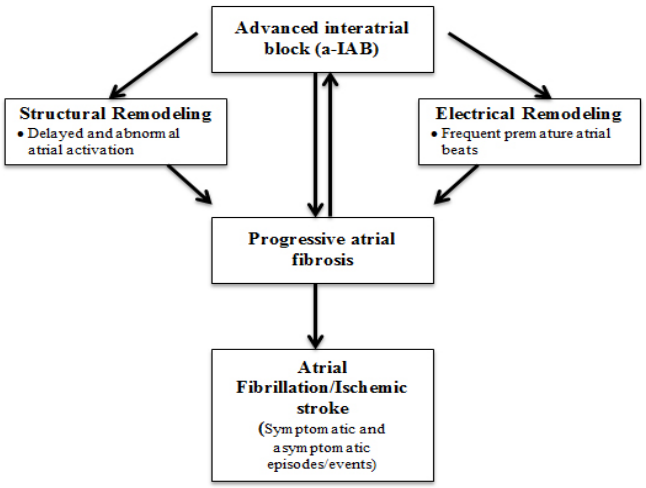

Figure 2: Pathophysiologic relationship between advanced interatrial block (a-IAB) with atrial fibrillation(AF) and ischemic stroke.

Rotterdam Scan Study and concluded that elderly patients with sIBL had three-fold increased risk of ischemic stroke compared to those without sIBL[22]. Patients with sIBL had comparable risk of ischemic stroke within 4 years with those who were diagnosed with a TIA. According to these data, we would argue that sIBL could be the harbinger of future ischemic stroke and cognitive decline in AF patients.

Age and hypertension are the most widely accepted risk factors for sIBL[25]. Similarly, our data indicates that older patient were more likely

to have sIBL. Although prevalence of hypertension was comparable between the two groups, LVH which is an echocardiographic predictor of uncontrolled hypertension was significantly more common in patients with sIBL. A possible explanation for this is the high percentage of patients with undiagnosed hypertension. In our data, patients with higher CHA2DS2-VASc were associated to the presence of sIBL. This finding is consistent with results of previous studies that identified CHA2DS2-VASc score as an independent risk factor for ischemic stroke and TIA in patients with IAB without AF [26]. CHA2DS2-VASc score includes various independent risk factors for sIBL. Although, presence of hypertension, diabetes mellitus, and congestive heart failure were comparable solitarily between the two groups, as a whole parameter, CHA2DS2-VASc score was associated with sIBL in our population.

Limitations

Some limitations of this study should be acknowledged. This is a single center study. Baseline characteristics and symptoms were self-reported by some patients. Other potential conditions that may predispose to arterial embolism were not evaluated.Patients with asymptomatic AF episodes could not be evaluated with clinical assessment only thus evaluation of patients with holter monitoring and other rhythm monitoring devices would effect results.

Conclusions

Interatrial block detected by the surface ECG can help in identifying patients at high risk of sIBL.

Disclosure

None.

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Risky Business: Judging the Use of Non-Vitamin K Antagonist Oral Anticoagulants for Non-Valvular Atrial Fibrillation in Patients with Renal Dysfunction

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Abstract

Warfarin, for many years, was the only oral anticoagulant available on the market for the prevention of stroke in patients with atrial fibrillation. Despite being safe and effective, warfarin's medication and food interactions, along with its requirement for frequent monitoring, make it less ideal in some patient populations. More recently, non-vitamin K oral antagonists (NOACs) have emerged as an appealing option as they have fewer medication interactions, do not have food interactions and do not require frequent monitoring. However, patients with a creatinine clearance (CrCl) of less than 30 mL/min were excluded in original drug trials for these agents. Leaving providers without certainty that these agents can be used safely and effectively in patients with renal dysfunction. This review article will summarize the current available data on the use of NOACs for the prevention of stroke in atrial fibrillation patients with renal dysfunction.

Introduction

Atrial fibrillation is a supraventricular tachyarrhythmia that affects millions of Americans.[1-2] Common causes of atrial fibrillation include uncontrolled hypertension, coronary heart disease, heart failure and congenital heart defects.[2] Patients that are female, are above 65 years of age, are of European descent or have heart disease are at greater risk for atrial fibrillation, which can result in heart failure and/or stroke.[2-3] The risk of stroke is increased 3 to 5-fold in patients with atrial fibrillation and anticoagulation may be required to prevent stroke and/or thromboembolism.[4]

Indication for anticoagulation in patients with atrial fibrillation is dependent upon the patient's specific risk factors for these complications. Although all patients with atrial fibrillation are at an increased risk of stroke, patients have different levels of risk. Validated scoring tools, such as the CHA_2DS_2VASc score, are available to assist in stratifying the risk of stroke in patients with atrial fibrillation. The 2014 ACC/AHA/HRS Guideline for the Management of Patients with Atrial Fibrillation: Recommendations for Non-Valvular Atrial Fibrillation, referred to from here on out as the current guidelines, recommends using the CHA_2DS_2VASc score to quantify a patient's risk of stroke, with a higher score signifying a higher level of stroke risk (Table 1). Recommendations, as shown in Figure 1, are based on a patient's risk for stroke. Of note, according to these guidelines, oral anticoagulation is recommended in patients with a CHA_2DS_2VASc score of ≥ 2, while oral anticoagulation may be considered in patients with a CHA_2DS_2VASc score of 1, as their risk for stroke is lower.[5] Oral anticoagulation options include warfarin, dabigatran, rivaroxaban and apixaban, although only warfarin is recommended for patients with end-stage chronic kidney disease (CKD) or on hemodialysis (HD). Warfarin is a vitamin K antagonist that for many years was the only oral anticoagulant available on the market for the prevention of stroke in patients with atrial fibrillation. Despite being safe and effective, warfarin's medication and food interactions, along with its requirement for frequent monitoring, make it less ideal in some patient populations. Dabigatran, rivaroxaban, and apixaban are agents that belong to a class called non-vitamin K antagonist oral anticoagulants (NOACs). These agents are an appealing option as they have fewer medication interactions and do not require frequent monitoring. An additional NOAC agent, edoxaban, was introduced to the market in 2015, however this agent is not in the current guidelines, as they have not been updated since 2014. In addition, the 2014 apixaban label change stating that apixaban 5 mg twice daily can be used in patients with creatinine clearance (CrCl) < 15 mL/min and in patients with hemodialysis is not reflected in the current guidelines.[5]

In addition to assessing a patient's risk of stroke when initiating anticoagulation, it is also important to assess the patient's risk of bleeding as bleeding is the major side effect of anticoagulation. Similarly to stroke risk, bleeding risk also varies between patients as it

Key Words

NOACs, Atrial Fibrillation, Renal Impairment, Renal Dysfunction

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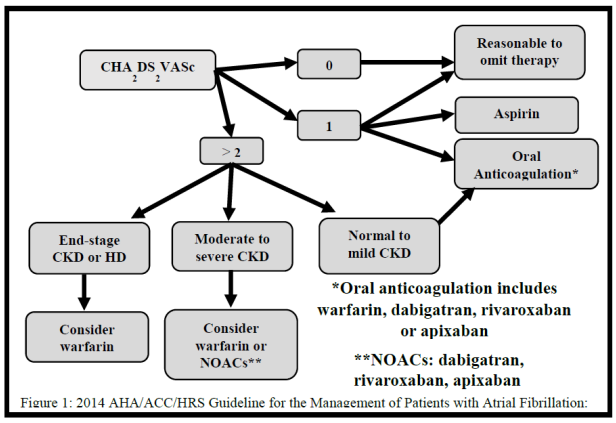

Figure 1: 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation.

Table 1: CHA2DS2VASc Score

RISK FACTOR	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease (prior MI, PAD or aortic plaque)	1
Age 65-74 years	1
Sex category (i.e. female sex)	1
Maximum score	10

is based on specific risk factors and should be taken into consideration when determining use of anticoagulation for the prevention of stroke or thrombosis in patients with atrial fibrillation. The HAS-BLED score is a validated scoring tool that can be used to determine a patient's risk for bleeding (Table 2)[5,6] .A score of ≥ 3 indicates the patient is at a high risk of bleeding[5,6] .The current guidelines do not make specific recommendations on the use of the HAS-BLED score, however, this scoring tool along with the CHA_2DS_2VASc score may be used to help guide clinical decisions by quantifying the risk of stroke versus the risk of bleeding[5].

Table 2: HAS-BLED Score

Risk Factor	Score
Age > 65	1
Hypertension Uncontrolled, > 160 mmHg systolic	1
Stroke History	1
Renal disease Dialysis, transplant, Cr > 2.26 mg/dL or > 200 µmol/L	1
Liver disease Cirrhosis or bilirubin > 2x normal with AST/ALT/AP > 3x normal	1
Alcohol use≥ 8 drinks/week	1
Prior major bleeding or predisposition to bleeding	1
Labile INR Unstable/high INRs, time in therapeutic range <60%	1
Medication usage predisposing to bleeding Antiplatelet agents, NSAIDs	1
Interpretation	High risk ≥ 3

Anticoagulation in Renal Impairment

The incidence of atrial fibrillation is 10 to 20-fold higher in patients with end-stage renal disease (ESRD)[1-2] .ESRD, independent of atrial fibrillation, is a risk factor for cardiovascular events, which may increase thromboembolic complications, such as arrhythmias, ischemic heart disease and peripheral vascular disease. Therefore, determining the need for anticoagulation in patients with ESRD and atrial fibrillation is especially necessary for the prevention of stroke and other thromboembolic complications.[7-9]Conversely, a complication of end-stage renal disease called uremia increases the risk for bleeding. Uremia develops from the accumulation of nitrogenous compounds and other toxic substances that are normally excreted by the kidney, resulting in defects in platelet aggregation, platelet secretion and platelet–vessel well interaction and adhesion, all of which predisposes patients to bleeding[10-12] .As a result, the use of anticoagulation in this patient population may predispose patients to an even higher risk of bleeding. This risk of bleeding is especially of concern in patients with renal dysfunction as all available oral anticoagulants depend on the kidney to some extent for elimination and, consequently, accumulation of these agents can increase the risk of bleeding. Anticoagulants that rely more heavily on the kidneys for elimination, and are more likely to accumulate in renal dysfunction, include warfarin (92 %), dabigatran (80 %) and edoxaban (50 %)[13-18]. Rivaroxaban (35%), apixaban (27%) and betrixaban (11%), however, rely less on the kidney for excretion, and are less likely to accumulate in renal dysfunction and they may be safer options compared to those agents that rely more heavily on the kidneys for elimination[19-24]. Despite their hesitation to use NOAC agents in the ESRD population due to limited data of their use in this patient population, health care providers are seeking anticoagulation alternatives to warfarin because of its interactions, frequent monitoring and high reliance on the kidney for elimination.

Current guidelines for non-valvular atrial fibrillation recommend against the use of dabigatran or rivaroxaban in patients with end-stage CKD or those receiving HD, but state that a dose reduction of dabigatran or rivaroxaban may be considered if a patient has moderate to severe CKD. The guidelines, however, do not make a recommendation regarding apixaban use in ESRD, because at the time of guideline publication the manufacturer did not comment on use of apixaban in this patient population. For patients with a CHA_2DS_2VASc score of ≥ 2 and a CrCl < 15 mL/min or on hemodialysis, the guidelines state it is reasonable to prescribe warfarin.[5]

The trials for which each NOAC was approved excluded patients with severe renal impairment. In the dabigatran, rivaroxaban and edoxaban trials, patients were excluded if their CrCl was < 30 mL/min and in the apixaban trial, patients were excluded if their CrCl was < 25 mL/min or SCr was ≥ 2.5 mg/dL.25-28 Despite excluding patients with severe renal impairment from trials, NOAC manufacturers have made recommendations for their use in this patient population based on pharmacokinetic studies (Table 3 & 4). Overall, these pharmacokinetic studies have shown that there is an increase in drug concentration in patients with renal impairment. It

Table 3: Pharmacokinetic Studies of NOACS in Renal Impairment.

Study	Drug	Study Design	Population	Results
Stangier 2010[29]	Dabigatran	• Open-label single dose study • 150 mg dose given to healthy patients and patients with mild to severe renal impairments • 50 mg dose given to patients with ESRD	• CrCl > 50mL/min to ≤ 80mL/min (mild): 6 patients • CrCl > 30 mL/min to ≤ 50 mL/min (moderate): 6 patients • CrCl ≤ 30 mL/min (severe): 11 patients • ESRD: 6 patients	• When compared to healthy patients' dabigatran increased by: o 1.5-fold in patients with mild impairment o 3.2-fold in patients with moderate impairment o 6.3-fold in patients with severe impairment o 2-fold in patients on hemodialysis • With increasing renal impairment increase the exposure to dabigatran • Dabigatran is partly removed by HD
Hariharan 2012[30]	Dabigatran	• Phase 1 Pharmacokinetic/ Pharmacodynamics study. • Evaluated 150 mg daily dose, 75 mg daily dose and 75 mg BID	• CrCl > 80 mL/min: 6 patients • CrCl > 50mL/min to ≤ 80 mL/min (mild): 6 patients • CrCl > 30 mL/min to ≤ 50 mL/min (moderate): 6 patients • CrCl ≤ 30 mL/min (severe): 11 patients	When compared to healthy patients, patients with severe renal impairment (CrCl 15-30 mL/min) had matched exposure to dabigatran when taking 75 mg BID
Kubitza[31]	Rivaroxaban	• Pharmacokinetic/ • Pharmacodynamics and safety of single 10 mg dose	• CrCl ≥ 80 mL/min (healthy): 8 patients • CrCl 50 to 79 mL/min (mild): 8 patients • CrCl 30 to 49 mL/min (moderate): 8 patients • CrCl < 30 mL/min (severe): 8 patients	Compared to healthy patients rivaroxaban exposure increased by: o 44 % in patients with mild impairment o 52 % in patients with moderate impairment o 64 % in patients with severe impairment
Dias 2015[32]	Rivaroxaban	• Open-label single dose study • 15 mg dose	• Healthy: 8 patients • ESRD: 8 patients	• 35% decrease in clearance when dosed after dialysis • 30% decrease in clearance when dosed before dialysis
De Vriese 2015[33]	Rivaroxaban	• Cohort dose finding study • 10 mg single dose	• 18 patients on HD • 12 patients received single dose administration • 6 patients multiple dose administration	• Dialysis has little effect on elimination • AUC of 10 mg dose in ESRD patients similar to 20 mg dose in healthy patients • Multiple 10 mg doses C-trough is similar to ROCKET-AF patients with residual kidney function
Chang 2015[34]	Apixaban	• Open-label single dose study • 10 mg dose	• CrCl > 80 mL/min: 8 patients • CrCl > 50mL/min to ≤ 80 mL/min: 10 patients • CrCl ≥ 30 mL/min to ≤ 50 mL/min: 7 patients • CrCl < 30mL/min: 7 patients	• CrCl > 50 mL/min to ≤ 80 mL/min →16% apixaban AUC increase • CrCl ≥ 30 mL/min to ≤ 50 mL/min → 29% increase in apixaban AUC • CrCl < 30mL/min → 38% increase in apixaban AUC
Wang 2016[35]	Apixaban	• Open-label parallel single dose study • 10 mg dose	• Healthy: 8 patients • ESRD: 8 patients	• Apixaban AUC was 36% higher when administered after HD

Table 4: Manufacturer Dosing Recommendations

Drug	CrCl > 50 mL/min	CrCl > 30 mL/min to < 50 mL/min	CrCl 15 to 30 mL/min	CrCl < 15 mL/min	Dialysis
Dabigatran	150 mg BID	150 mg BID	75 mg BID	Not approved	Not approved
Rivaroxaban	20 mg daily	15 mg daily	15 mg daily	Not approved	Not approved
Apixaban	2.5 or 5 mg BID	2.5 or 5 mg BID	2.5 or 5 mg BID	2.5 or 5 mg BID	2.5 or 5 mg BID
Edoxaban	60 mg daily	60 mg daily	30 mg daily	Not approved	Not approved

is important to note that the majority of these studies were based on a single dose and therefore do not give insight into the extent of accumulation of the drug over time and its effect on patients with renal impairment[29-35].

Dabigatran was the first NOAC approved by the FDA in 2010. The Randomized Evaluation of Long-Term Anticoagulant Therapy, Warfarin compared to Dabigatran (RE-LY) trial, was the trial for which dabigatran received approval. Dabigatran 150 mg twice daily was shown to be superior to warfarin in preventing stroke and systemic embolism. Dabigatran was also shown to have significantly less major and minor bleeding when compared to warfarin, which had more intracranial bleeding, but less gastrointestinal bleeding. Patients with mild to moderate renal impairment were included in this study[25] . A RE-LY trial analysis compared the safety and efficacy of dabigatran to warfarin in regards to renal function, with patients divided into groups of CrCl ≥ 80 mL/min, 50 to < 80 mL/min and 30 to < 50 mL/min. There was no statistically significant difference in efficacy or safety of dabigatran 150 mg twice daily with changing renal function. Based on this analysis, patients with mild to moderate renal dysfunction are able to take the full recommended dose of 150 mg twice daily. There are no studies that evaluate the clinical efficacy and safety of dabigatran in patients with a CrCl < 30 mL/min, however there is a pharmacokinetics study that was conducted in patients with renal impairment including those with a CrCl < 30 mL/min. The study showed that a dose of 75 mg twice daily in patients with a CrCl

of 15 to 30 mL/min rendered a matched exposure to dabigatran when compared to 150 mg twice daily in healthy patients.36 Based on these findings, the manufacturer recommends a dose reduction to 75 mg twice daily in patients with a CrCl of 15 to 30 mL/min.[16]

Edoxaban was approved by the FDA in 2017 for the prevention of stroke and systemic embolism in patients with atrial fibrillation. In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48), the study for which edoxaban was approved, edoxaban 60 mg daily was shown to be superior to warfarin in preventing stroke and systemic embolism and associated with fewer bleeding events. Patients with mild to moderate renal impairment were included in the study and the dose of edoxaban was divided in half if patients had a CrCl of 30 to 50 mL/min.[26] A sub-analysis of the ENGAGE AF-TIMI 48 trial evaluated the impact of renal function on outcomes in patients treated with edoxaban. There was no significant difference in safety or efficacy outcomes based on renal function, which was evaluated in three groups: CrCl > 95 mL/min, > 50 to 95 mL/min and 30 to 50 mL/min. However, although not statistically significant, there was a decrease in efficacy seen in patients with a CrCl > 95 mL/min[37]. As a result, the manufacturer recommends a dose reduction to 30 mg daily in patients whose CrCl is 15 to 50 mL/min and avoiding edoxaban in patients with a CrCl > 95 mL/min as patients with this renal function clear the drug too quickly and are not able to maintain therapeutic drug concentrations.[10,11]

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) was the trial for which rivaroxaban was approved by the FDA in 2011. Rivaroxaban, 20mg daily for patients with a CrCl over 49 mL/min and 15 mg daily for patients with a CrCl of 30 to 49 mL/min, was shown to be non-inferior to warfarin in preventing stroke and systemic embolism. Although there was no statistically significant difference in overall bleeding events, warfarin had significantly more critical bleeding, fatal bleeding and intracranial bleeding.[27] An analysis of treatment outcomes based on baseline renal function was conducted on the ROCKET-AF trial and patients were grouped based on renal function: CrCl of ≥ 80 mL/min, 50 to < 80 mL/min and 30 to < 50 mL/min. There was no significant difference between rivaroxaban and warfarin in safety or efficacy outcomes based on renal function.[38] There are no studies that evaluate the clinical efficacy and safety of rivaroxaban in patients with a CrCl of < 30 mL/min, but the manufacturer currently recommends a dose of 15 mg daily in patients with a CrCl of 15 to 50 mL/min and 20 mg daily for patients with a CrCl of > 50 mL/min[13].

In the Apixaban for the Reduction of Stroke and other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, the study for which apixaban was approved, apixaban was shown to be superior to warfarin in preventing stroke and systemic embolism and had significantly less major bleeding compared to warfarin. Patients with mild to moderate renal impairment were included in the study and in an analysis of ARISTOTLE, the efficacy of apixaban compared to warfarin was evaluated based on renal function.[28] In this analysis, patients were grouped based on renal function: CrCl > 80 mL/min, > 50 to 80 mL/min and ≤ 50 mL/min. There was no statistically significant difference in efficacy and safety between warfarin and apixaban regardless of renal impairment[39]. Originally, in 2012, when apixaban was approved by the FDA, the manufacturer did not have a recommendation on the use of apixaban in patients with a CrCl of < 15 mL/min or those on hemodialysis. However, in 2014, the manufacturer updated its package insert and stated that patients with a CrCl of < 15 mL/min and those on hemodialysis could receive the 5 mg twice daily dosing, which is the same dosing as those with normal renal function. This recommendation was based on pharmacokinetic studies.[40-41] However, the manufacturer does not recommend a dose reduction based on renal function alone. Per the manufacturer, apixaban should be dose-reduced to 2.5 mg twice daily if the patient meets two of the following criteria: age ≥ 80 years old, weight of < 60 kg and a SCr ≥ 2.5 mg/dL.[14,15]

The data for NOAC use in patients with severe renal dysfunction is limited; apixaban is currently the only NOAC with clinical data in patients with severe renal dysfunction. Until 2017, there were no published studies that evaluated the clinical efficacy and safety of apixaban in patients with severe renal impairment or those on hemodialysis. Steuber, Stanton, Sarratt and colleagues have set the stage for the use of apixaban in patients with atrial fibrillation and severe renal impairment through three studies. Steuber and colleagues, for example, conducted a multicenter cohort study to determine variables that were associated with bleeding events in hospitalized patients on chronic HD taking apixaban. This study found that bleeding occurred in 15 % of patients and the likelihood of bleeding increased as the total daily dose of apixaban increased, as well as with continuation of apixaban from the outpatient setting. Of the 17 patients who bled, 7 were on the 2.5 mg twice daily dose (median dose in the study), 3 were on 10 mg twice daily and the remaining were on 5 mg twice daily. Although the study demonstrated that apixaban was safe in 85 % of hospitalized patients on chronic hemodialysis, there are several limitations of this study, including a retrospective study design, a small sample size, short duration of follow-up and lack of efficacy outcomes. Furthermore, while apixaban was shown to be safe in patients with renal impairment, this study did not demonstrate the efficacy of these reduced doses.[42]

Sarratt and colleagues had similar limitations to their study, including a retrospective study design, a small sample size, a lack of efficacy outcomes and failure to meet power. Sarratt compared bleeding rates in patients with atrial fibrillation and on chronic hemodialysis taking either apixaban or warfarin. More than half of the patients taking apixaban were on 2.5 mg twice daily. This study found that there was no statistically significant difference in bleeding between apixaban and warfarin. Although apixaban had less major bleeding, it had a higher rate of clinically relevant non-major bleeding events when compared to warfarin. While apixaban appears to be safe in this patient population, similarly to the other studies, this study did not evaluate efficacy. [43]

Stanton and colleagues were the first to evaluate both efficacy and safety of apixaban compared to warfarin in patients with severe renal impairment. There was no statistically significant difference in efficacy or safety between warfarin and apixaban; however, apixaban had fewer bleeding events. Similarly to the patients in the study by Sarratt and colleagues, the majority of the patients taking apixaban

were on 2.5 mg twice daily. This study suggests that apixaban 2.5 mg twice daily may be just as safe as warfarin in patients with a CrCl < 25 mL/min, SCr > 2.5 mg/dL or on dialysis. However, there were several limitations to this study, such as the retrospective study design and small sample size. If the study had a higher power, a difference between the two study arms may have been detected. Despite the limitations of this study, there was a 5-month follow-up period, which makes this study unique compared to the studies by Steuber, Sarratt and colleagues, as the follow-up periods in those studies did not extend past hospitalization. Apixaban 2.5 mg twice daily appears to be safe; however, efficacy was not a primary outcome and therefore we are unable to definitively conclude if apixaban 2.5 mg twice daily is effective in this patient population.[44]

These studies assessed patients with renal impairment including patients with ESRD. There are several scenarios in which a patient's renal function can be acutely impaired, such as in settings of an adverse medication reaction, infections, and heart failure. Unfortunately, these studies did not specifically address acute kidney injury, however, anticoagulants should be dosed adjusted for the patient's renal function during the acute injury phase, as it is possible that the drug could accumulate and increase the patient's risk of bleeding. With the lack of evidence in patients with acute or transient renal impairment, comes a lack of direction on how to dose and how often renal function should be monitored in these patients. In addition, these studies, in addition to the original drug approval trials, used CrCl as a measure of kidney function. The different methods, including eGFR, that are used to measure a patient's kidney function are all estimates of kidney function; however, the estimates are not interchangeable. Therefore, CrCl should be used as a measure of kidney function in patients on anticoagulants as this was the method of measuring kidney function used in clinical trials.[25-44].

Antidote Availability

Patients who are on anticoagulation with renal impairment are at an increased risk of experiencing a bleeding event. The ability to reverse anticoagulation or the ability to prevent further bleeding should be evaluated and taken into consideration when choosing an anticoagulation agent. Warfarin does not have a reversal agent currently on the market, however, in the event of a bleed, vitamin K can be given to prevent further bleeding.[6] Management of bleeding in patients on a NOAC, however, remains widely unknown and recommendations are based largely on expert opinion. In 2017, the American Heart Association (AHA) released a statement on the management of patients on NOACs in both acute care and periprocedural settings. For patients who experience a major bleed on dabigatran, the AHA recommends compression when possible, supportive care, and idarucizumab.[45] Idarucizumab, a monoclonal antibody fragment that binds specifically to and neutralizes dabigatran and its metabolites, was approved by the FDA in October of 2015 for the reversal of dabigatran in cases of emergency surgery and urgent procedures for uncontrollable or life-threatening bleeding.[46] In the Reverse-AD (Idarucizumab for Dabigatran Reversal) trial, idarucizumab was shown to completely reverse the anticoagulant effects of dabigatran, with a median time of 11.4 hours to cessation of bleeding.[47]

The AHA was unable to make a recommendation for patients with a bleed taking apixaban or rivaroxaban in their 2017 statement because the Andexxa-4 (Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors) trial was still in process at the time the AHA statement was released.45 However, andexanet alfa (Andexxa), which binds and sequesters rivaroxaban and apixaban, has recently been FDA approved for anticoagulation reversal in patients on rivaroxaban or apixaban who have life-threatening or uncontrollable bleeding. In addition, andexanet alfa inhibits the tissue factor pathway inhibitor, which can increase tissue factor-initiated thrombin generation.48 Although it was shown to reduce anti-factor-Xa activity and return patients to hemostasis in 79% of cases, andexanet alfa was only studied in patients on rivaroxaban and apixaban and thus should not be used for reversal of any other anticoagulant.[49] Edoxaban and betrixaban, the two newest NOACs on the market, do not have antidotes currently available on the market, and therefore supportive care is the only treatment option for patients who experience bleeding on these agents.

Conclusion

Patients with CKD and atrial fibrillation are at both an increased risk of bleeding and increased risk of stroke and thromboembolism.[1-2, 4, 7-9,10,12] Anticoagulants, such as warfarin and NOACs may be considered in these patients to prevent these complications.[5] NOACs provide healthcare providers and patients with an alternative option to warfarin, the use of which may result in a complicated regimen with its medication and food interactions, requirement for frequent monitoring, and high reliance on the kidney for elimination. However, for our patients with CKD choosing an anticoagulant can be difficult. All anticoagulants rely on the kidney to some extent, increasing the risk of bleeding in renal impairment due to accumulation. Apixaban is of particular promise because it has the least reliance on the kidney for elimination compared to other NOACs approved for the prevention of stroke and systemic embolism in patients with atrial fibrillation. In addition to apixaban, betrixaban, the newest NOAC approved in 2018, also has great potential in this patient population. Betrixaban is less reliant on the kidney for elimination as compared to apixaban, but currently it has only been studied and approved for extended duration thromboembolism prophylaxis in hospitalized patients who are acutely medically ill.[15-24] With additional studies, this medication may become a viable option for this patient population.

There is a delicate balance between the risk of cardiovascular events and the risk of bleeding in this patient population. NOACs have been shown to be just as efficacious if not superior to warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation. Although there are several retrospective studies that show promise with the use of apixaban in this patient population, the data is not robust enough to support its routine use in patients with severe renal impairment and ESRD over warfarin, with its long history of use and the availability of vitamin K to prevent further bleeding if needed. Choosing an anticoagulant in this patient population should be based on individual patient parameters, such as renal function, stroke risk, bleeding risk, adherence and affordability. The risks and benefits to the individual patient must be taken into consideration. For patients with atrial fibrillation and renal impairment that require anticoagulation but are unable to take warfarin, apixaban would be the

best alternative agent based on currently available data. In the future, large, long-term randomized control trials evaluating the efficacy and safety of NOACs in patients with severe renal impairment and ESRD are needed to determine appropriate doses and support their routine use in this patient population..

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Life's Simple 7 Approach to Atrial Fibrillation Prevention

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Abstract

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice. It constitutes a major public health problem, with total related annual expenses estimated at $6.65 billion. The American Heart Association developed Life's Simple 7 (LS7) to define and monitor ideal cardiovascular health (CVH). In this review, we examine the role of individual components of LS7 to provide further insight regarding potential influence of achieving AHA's strategic goal on AF prevention. While significant advances have been made in the secondary prevention of AF, little progress has been made to prevent the first occurrence of this arrhythmia in at-risk patients. Improvement of overall cardiovascular health as defined by LS7 may substantially reduce AF risk.

Introduction

Atrial fibrillation (AF) affects 33.5 million people globally. In the United States (US) alone an estimated 3 to 6 million individuals have AF with prevalence projected to double by 2050.[1-3] The lifetime risk of developing AF is 1 in 3 among whites and 1 in 5 among African Americans, [4,5] and is associated with increased morbidity and mortality with a 5-fold increased risk of stroke and substantially increased risk of systemic thromboembolism.[6] It is also associated with increased risk of dementia,[7] physical disability,[8] heart failure,[9] myocardial infarction[10] and sudden cardiac death.[11] AF thus constitutes a sizeable and growing public health problem, with total health-related annual expenses estimated at $6.65 billion and projected to rise. [12],[13]

The American Heart Association's (AHA) impact goal is to improve the cardiovascular health (CVH) of all Americans by 20% by 2020, while reducing deaths from CVD and stroke by 20%. To help achieve this goal of primary prevention of CVD and ideal cardiovascular health, the AHA identified seven modifiable factors, also called Life's Simple 7 (LS7). It consists of 3 health factors (cholesterol level, blood pressure, and blood glucose) and 4 behavioral factors (cigarette smoking, physical activity, diet, and body mass index (BMI)). An overall LS7 score ranges 0 to 14 and is calculated as the sum of the LS7 component scores (2 points for ideal, 1 point for intermediate, and 0 for poor).[14] This CV health metric has been previously shown to predict CVD and heart failure. Recent data suggests reduced risk of AF with favorable LS7 score. [15,16] We review the current literature on the potential role of individual LS7 components in AF prevention.

Key Words

Interatrial Block, Atrial Fibrillation, Heart Failure

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Hypertension

Hypertension is a strong independent predictor of AF. [17-19] High BP promotes left ventricular diastolic dysfunction, left atrial (LA) dilation, cardiac fibrosis and dilation of pulmonary veins, which in turn shortens refractoriness and increases risk of AF. [20] Higher pulse pressure is a better predictor of AF than systolic or diastolic BP alone. Higher systolic blood pressures are associated with higher AF risk, whereas diastolic BP was inversely related with AF incidence.[21] [17][22] This suggests increased pulse pressure associated with vascular aging may be a factor related to increased AF incidence in the elderly.

As part of the ARREST AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of

Ablation) study, strict blood pressure control among other aggressive risk factor modification (RFM) strategies significantly reduced AF recurrence.[23] In high-risk patients, primary prevention of AF via renin-angiotensin-aldosterone system (RAAS) inhibition has shown promise. A meta-analysis by Healey et. al suggested that the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) in patients with left ventricular (LV) hypertrophy or LV dysfunction can prevent 20%–30% of new-onset AF.[24] Angiotensin II increases sympathetic nervous system activity, oxidant production, atrial inflammation and fibrosis, all of which could increase risk of AF. This is further supported by the effectiveness of ACEI/ARBs in preventing AF over beta blockers and diuretics in patients without structural heart disease. [25] Assessment of the effectiveness of RAAS inhibition for preventing recurrent AF has shown mixed results. This may be due to confounding factors such as the timing of treatment onset, and existing irreversible LA structural changes. [26] Thus, existing evidence suggest a beneficial effect of BP control, specifically lowering systolic BP, as maybe an important factor in AF prevention.

Diabetes Mellitus

Optimal, ideal blood glucose is a component of LS7. Diabetes Mellitus (DM) is a well-established risk factor for AF[27].It is estimated that DM explains 2.5 % of the AF burden[28] .Mechanisms linking DM to an increased risk of AF remain speculative. It is suggested that cardiac autonomic neuropathy leads to impaired parasympathetic tone and this dysfunctional cardiac autonomic activity then leads to propagation of AF[29] .

In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, 5250 patients of 15,245 hypertensive patients had DM at baseline. Over 4.2 year follow-up 551 patients developed new-onset AF and 1298 of the initially non-diabetic patients developed DM. Investigators demonstrated that patients with new-onset DM had a significantly higher rate of new-onset AF with a hazard ratio of 1.49 (1.14 to 1.94, p = 0.003) compared to patients without DM. [30] Dublin et al. showed that the risk of developing AF was higher with longer duration of treated diabetes and worse glycemic control, specifically for every 1% increase in HbA1c, a 14% increased risk for incident AF was observed[31] .

There is conflicting data based upon the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in which 10,082 patients with diabetes were randomized into intensive vs. standard glycemic control groups. Targeting a glycated hemoglobin level of <6.0% (intensive group) did not affect the rate of new-onset AF. However, given the study was focused on intensive and standard glycemic control strategies, conclusion regarding the incidence of AF in patients with poor glycemic control cannot be obtained. [32] In a meta-analysis by Huxley et al. involving 108,703 cases of AF in 1,686,097 subjects, it was found that patients with DM had an approximate 40% greater risk of AF compared to unaffected patients. After taking confounders into account, the subsequent risk of AF may be closer to 25% rather than 40% as indicated by the overall summary estimate. 28 Given the inconsistencies in these results, there is a need for more randomized controlled trials or observational studies to look at management strategy for diabetes that would be favorable for AF prevention.

Hypercholesterolemia

Optimal or ideal cholesterol levels are a component of LS7. The literature on the role of blood lipid levels, especially total cholesterol, and AF risk is inconsistent, and the precise role of total cholesterol in the development of AF, if any, remains to be determined.

Potential pathophysiologic mechanisms by which high density lipoprotein cholesterol (HDL-C) can prevent AF could be its direct anti-inflammatory and antioxidant properties [33]. In addition it may be though indirect effects by preventing coronary heart disease and heart failure[34] .Elevated triglycerides are associated with metabolic syndrome which has been associated with increased AF incidence[35].

In an analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Heart Study (FSH) cohorts in a fully adjusted model, including BMI, HDL-C was associated with reduced risk of AF (HR 0.89, CI 0.80 to 0.99) and high triglycerides were associated with higher risk of AF (HR 1.16, CI 1.06 to 1.27), whereas level of low density lipoprotein cholesterol (LDL-C) and total cholesterol did not have effect on AF risk (HR 1.04, CI 0.94 to 1.15 and HR 1.05, CI 0.96 to 1.15 respectively)[36]. In contrast, the Atherosclerosis Risk in Communities study (ARIC) study reported that high LDL-C and total cholesterol are associated with a lower risk of AF, whereas HDL-C and triglycerides were not related to AF risk. [37] Similarly, the Cardiovascular Health Study also found lower risk of AF among subjects with higher total cholesterol[38]. Inconsistent results are likely due to impact of comorbid conditions and lack of adjustment of those factors in addition to difference in demographics. The role of lipid lowering with statins in AF prevention is unclear, with observational studies suggesting reduced AF risk and clinical trials failing to do so[39] .For now, there is insufficient evidence to support targeting specific lipid-related measures for AF prevention.

Obesity

Obesity is a major public health problem with increasing prevalence in the US and is an important, potentially modifiable risk factor for AF[40][41]. Several studies have shown adiposity measures other than body mass index (BMI) to be associated with increased AF such as waist circumference,[42] bioelectrical impedance derived measures of body composition and body fat distribution43]. In a longitudinal cohort study, BMI also independently predicted the progression to permanent AF.[44] The pathophysiology linking obesity to AF is multifactorial. Animal models have shown that sustained obesity leads to the development of a global electrophysiological and structural substrate for AF[45]. Pericardial fat is highly associated with paroxysmal and persistent AF independent of traditional risk factors including left atrial enlargement[46] .It is also associated with worse outcomes after AF ablation. The pericardial adipose tissue is highly metabolically active and has been linked to the increased local release of various pro-inflammatory mediators, such as interleukin-6 and tumor necrosis factor-α, which may promote the activation of ectopic foci in the pulmonary vein ostium contributing to AF[47].A recent study has shown favorable structural remodeling and a reduction in a pericardial adipose tissue after weight loss.[48] Increased left atrial (LA) size is also associated with obesity. [49] An analysis of

the Framingham cohort showed a stepwise increase in risk for AF with ascending quartiles of LA size. It has been suggested that LA dilatation is associated with structural and functional atrial tissue alterations that facilitate the disturbed impulse propagation of AF.[50]

Several trials have evaluated the impact of weight loss on AF and explored the sustainability of weight loss effects, in addition to a potential dose-response relationship. In the LEGACY (Long-Term Effect of Goal-Directed Weight Management on Atrial Fibrillation Cohort) prospective cohort, subjects with >10% weight loss had a 66-fold greater probability of arrhythmia-free survival compared to those who had <10% weight loss. In addition to AF free state, subjects with >3% weight loss had evidence of reverse atrial remodeling, specifically left atrial volume indexed for body surface area decreased significantly.[51] In a recently published study of 4021 obese subjects, bariatric surgery was associated with significantly reduced risk of AF (hazard ratio: 0.69; 95% confidence interval: 0.58 to 0.82; p < 0.001). Of note, this effect was found with significant obesity at baseline: men with BMI ≥34 kg/m2 and women with BMI ≥38 kg/m2. [52] However, an analysis of The Action for Health in Diabetes (Look AHEAD) trial did not find an effect of weight loss on AF incidence. Notably, the weight loss achieved in Look AHEAD was less than that reported in the bariatric surgery study, thus it may be that only more extreme weight loss reduces the risk of AF. [53]

Although obstructive sleep apnea (OSA) is not component of LS7, obesity is strongly associated with this disorder [54], OSA is an independent risk factor for AF. [55] In the large cross-sectional Sleep Heart Health study looking at the prevalence of cardiac arrhythmias in patients with OSA, AF rate was 4.8% compared to 0.9% in subjects without OSA [56].

There is a clear epidemiological association between obesity and AF. There is also substantial evidence that weight control may reduce the increasing incidence of AF, making it an important component for the primary prevention of AF.

Fitness or Physical Activity

The association between physical activity or fitness and AF is complex. It is important to account for pathophysiologic differences between cardiorespiratory fitness in the general population in comparison to high-intensity physical activity among elite athletes. [57] Studies that found increased risk of AF with vigorous physical activity mainly included subjects with moderate to high exercise level such as professional cyclists[58] and endurance athletes[59] among others. In contrast, the population-based Cardiovascular Health Study of 5446 subjects showed that light to moderate physical activity was associated with significantly lower AF incidence in older adults and high-intensity exercise did not have an effect. [60] However, another population-based (n=38,000) study of light to moderate exercise showed no effect on AF. [61] Studies looking specifically at fitness level and AF have consistently shown protective effects of fitness. Faselis et al. found high levels of fitness was associated with reduced risk of AF (odds ratio, 0.37 p<0.001). [62] Similarly, two other studies found reduced risk of AF with increasing level of fitness.[63] Pathak et al showed that among 308 obese (BMI >27) subjects in the CARDIO-FIT (Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation) study, patients who had high cardiorespiratory fitness had less AF. Patients who improved their fitness level by >2 metabolic equivalents (METs) had a 2-fold higher probability of AF-free survival, as well as lower AF. However, Khan and colleagues found a nonlinear relationship between the higher level of cardiopulmonary fitness and AF. Given inconsistency in the available literature, a recent meta-analysis by Zhu et al. looked at the association of physical fitness and AF among 205,094 subjects pooled from 6 studies. Per incremental increase in physical fitness, a 9% reduction in the risk of AF was seen. When physical fitness was assessed, the risk of AF was highest in individuals with the lowest level of physical fitness. [64]

Overall, physical activity may have a U-shaped relationship with the risk of AF in athletes and non-athletes, and a non-linear relationship is observed between physical fitness and the risk of AF. However, studies have consistently shown benefit or no harm of light-moderate exercise or fitness at the general population level for AF prevention.

Dietary Patterns

There is paucity of data on the effect of dietary patterns and development of AF. Most studies are small and include non-homogenous populations. PREDIMED (Prevención con Dieta Mediterránea) trial is the only interventional study evaluating the impact of dietary patterns on AF risk. It enrolled 6705 subjects in Spain, who were randomized into three groups (Mediterranean diet enriched with extra virgin olive oil(EVOO), or mixed nuts or control group). The former intervention reduced AF risk compared with control group; (Hazard Ratio 0.62, 95% confidence interval 0.45–0.85) however, there was no effect in the group with mixed nuts. [65] There are no specifics on the quantity of EVOO being consumed, which makes it difficult to reach a feasible conclusion. As well, it is unclear to what degree EVOO was consumed in the control and mixed nuts groups. Data from the Framingham Heart Study found no association between caffeine, fiber, and fish-derived polyunsaturated fatty acids with AF risk. [66] Alcohol intake, both “binge” drinking and moderate consumption 67is a risk factor for AF.[68] The Women’s Health Study showed that consumption of even 2 drinks/day was associated with risk of AF.[69] The mechanism is thought to be direct toxic effect on the cardiomyocytes, altered atrial conduction, short refractory period and altered autonomic balance with sympathetic predominance. [70,71] In ARREST AF trial, reduction in alcohol use contributed to improved AF ablation outcomes.[23]

In a case-control study of 800 patients, those with AF were found to have lower adherence to a Mediterranean diet and lower antioxidant intake compared to a control population (odds ratio (OR) 1.9, 95% confidence interval (CI) 1.58–2.81). In addition, patients in the highest quartile of the Mediterranean Score had higher probability of spontaneous conversion of atrial fibrillation to sinus rhythm (OR1.9; 95%CI 1.58-2.81).[72] Thus, current data suggests potential protective effect of EVOO for AF prevention, however future research on the clinical significance of these associations is needed. Effect sizes of dietary exposures are modest leading to potential residual confounding. Lacking direct evidence, Mediterranean dietary pattern with possible EVOO supplementation coupled with an emphasis on

physical activity, maintenance of a healthy lifestyle and weight seem reasonable guidance for AF patients, and for those with significant risk of AF.

Smoking

Smoking has been reported to predict AF among racially different populations.[73,74] Data from the atherosclerosis risk in communities (ARIC) study suggests a dose–response relationship, with the highest risk of AF observed in individuals with the greatest cigarette pack-years of smoking.[73] Current smoking was more strongly and consistently associated with AF compared with former smoking status. [75] The results of smoking cessation interventions in AF have not been well studied. Smoking cessation was one of the risk modification measures of ARREST AF trial which showed the reduction of AF incidence. [23] However, despite the absence of studies looking at the effect of smoking cessation alone and AF risk, available evidence supports smoking cessation to be encouraged for prevention of AF and overall cardiovascular health. As other recreational substance use is not included in LS7, we briefly mention their role in AF. In addition to the well-known association of "binge" drinking and AF,[67]even moderate intake of alcohol is a risk factor for atrial fibrillation. [68] Caffeine consumption on a regular basis was not associated with increased incidence of AF. A meta-analysis of six cohorts and one case-control study with 115,993 subjects showed 13% odds reduction in AF among subjects with regular caffeine intake (OR 0.87; 95% CI 0.80 to 0.94; I2=39%). [76] Thus, based on existing evidence, recommendations against caffeine intake should not be practiced for the purpose of AF prevention.

While, Desai et al. have shown increased risk of arrhythmias, including AF in hospitalized marijuana users, no prospective trials have been conducted to assess this relationship. [77]

Overall Life's Simple 7 and Atrial Fibrillation

Two recent studies showed role of favorable LS7 in AF prevention. Analysis of Reasons for Geographic and Racial Differences in Stroke (REGARDS) study showed 5% reduction of AF risk with 1 point improvement in LS7score. Out of individual components only blood pressure and body weight were associated with risk of incident AF. This study had significant limitation in that AF cases were ascertained by self-recall at a single follow up visit, about 10 years after baseline one.16 More robust results were seen in ARIC study, where 1 point improvement in LS7 score was associated with 17% lower risk of AF. Additionally, improvement of individual components of LS7 by 1 level was associated with 12% lower AF risk. Here, in component analysis tobacco use and fasting blood glucose level were associated with lower AF risk in addition to blood pressure and body weight in REGARDS

Conclusions

There is evidence that most of the components of LS7 are risk factors for development of AF and are both preventable and modifiable. Presence of shared risk factors for CAD and AF rises question whether AF is actually a vascular disease. Interestingly, Weijs, et al. found subclinical CAD in high proportion of patients with original diagnosis of lone AF. [78] Treatment of HTN, smoking cessation, weight loss, regular physical activity, preventing and controlling diabetes have been shown to have a potential role in AF prevention, while data on lipids and dietary modification is limited. Although some individual components of LS7 may not have strong AF risk, it is possible that these components are related and improvement in one could result in reduction of AF by preventing development of the other component or modifying its effect. Thus, by achieving optimal cardiovascular health profile, as defined by LS7, it is possible to substantially reduce AF risk. Nonetheless, further prospective studies are needed to better understand implications of favorable LS7 profile on AF incidence.

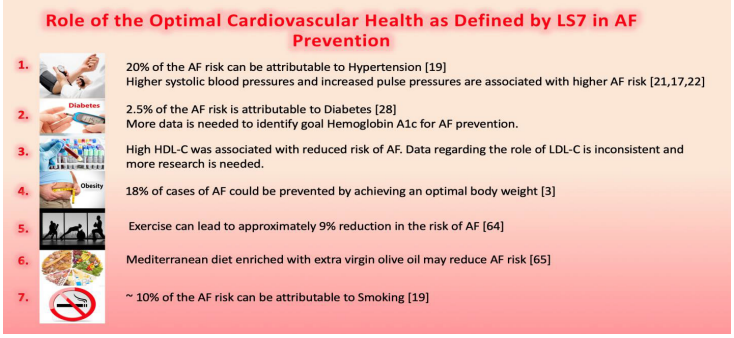

Figure 1: **Figure shows individual components of Life's Simple 7 (LS7) and their role in atrial fibrillation (AF) prevention.**

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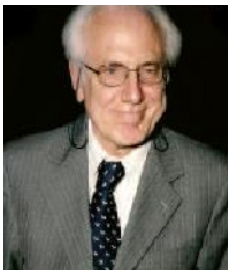

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