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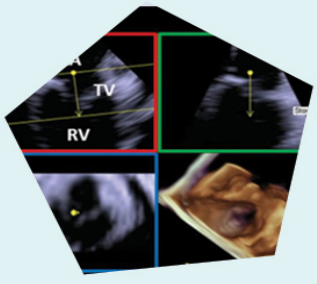

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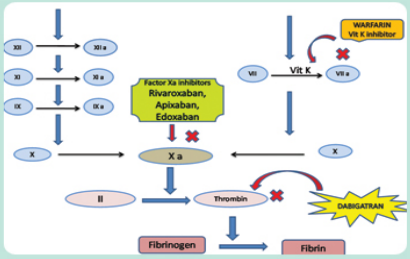

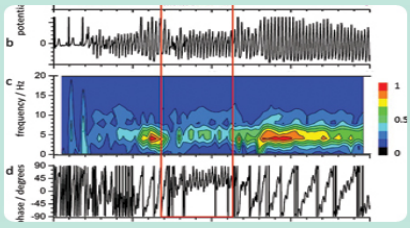

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Editorial

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From the Editor's Desk

Journal of Atrial Fibrillation (JAFIB)

Feb - Mar 2020

Issue 5

Volume 12

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

Dear Colleagues

Hope this issue of JAFIB finds you all safe and well. I want to first acknowledge and thank you all for your unfettered dedication to taking care of patients during a global pandemic. COVID-19 posed a tremendous threat to humanity and brought in many unprecedented challenges to our personal and professional lives. Some of us were more affected than the others but in the end our collective resolve and solidarity to fight this global threat will succeed.

With the world shutting down for over 6 weeks we have figured out how to live in a lockdown, prioritize our priorities and yet provide the necessary care to our patients in a measured fashion with the limited frame work in which we had to operate. As we restart our efforts to slowly resume normalcy to life it is important to understand the responsibilities and create a pathway to safely get patients back into the clinics and hospitals. Elective procedures could be resumed soon with aggressive testing of the patients, healthcare teams and creating workspace that are relatively COVID safe at institutions that have the capacity. In cities where the entire infrastructure is overwhelmed by COVID resumption of elective cases might take longer for the mere limitation of resources and capacity and the burden of the disease in the community.

Stay safe and protect yourself and your families as you take care of the rest of the humanity.

DJ Lakkireddy

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Incidence of Atrial Fibrillation in African Americans post Atrial Flutter Ablation

Robert L. Percell[1], *Robert Helm*[2], *Kevin Monahan*[2]

[1]Electrophysiology Department, Bryan Heart Institute, 1600 S 48th Street, Lincoln, NE 68506, Lincoln, NE 68506.
[2]Boston Medical Arrhythmia Center, 830 Harrison Avenue, Moakley Building, 3rd floor, Suite 3500, Boston, MA 02118.

Abstract

Background: African Americans have a lower incidence of atrial arrhythmias, both atrial fibrillation (AF) and atrial flutter (AFL), despite a greater number of traditional risk factors. The incidence of AF after cavotricuspid isthmus (CTI) ablation in patients with typical AFL is markedly increased, approaching 40% in some studies. It is unknown if African Americans specifically have a similar rate of increased AF after CTI ablation for typical AFL.

We sought to identify differences in development of AF after CTI ablation for typical AFL with regards to race, between African American and non- African Americans. The hypothesis is that African Americans will have a lower incidence of AF after CTI ablation for typical AFL.

Methods: The electronic medical records of first time, successful CTI ablations performed for typical AFL were retrospectively reviewed over a 48 month period. Clinical variables were retrieved from the EMR. AFL was documented on ECG, Holter/ event monitor or device interrogation at clinical follow up visits. Follow up was obtained over a 1 year period. Patients were self-identified as African American, White, Hispanic or Other.

Results: The records of a total of 201 patients - 51 African Americans (25.4%) and 150 non-African Americans (74.6%) - who underwent CTI ablation for typical AFL were examined. Average age was similar (67.8 vs 66.3, p=NS) with a preponderance of men (77.6% vs 23.5%). There was a significantly lower rate of development of AF post CTI ablation for typical AFL in African Americans vs non-African Americans (22.2% vs 46.6%, p=0.002). Additionally, women were more likely to develop AF (53.1% vs 36.2%, p=0.026). African American men were the least likely to develop AF post AFL ablation (p=0.0062).

Conclusions: We observed a significantly lower incidence of AF among African American patients after CTI ablation for typical AFL.

Introduction

Atrial fibrillation (AF) is recognized as the most common clinically relevant arrhythmia and it is ubiquitous in general practice. In 2010, between 2.7 and 6.1 million Americans suffered from AF. Similarly, this figure is expected to rise to 12 million by 2050[1]. The pathophysiology has been scrutinized extensively including multiple genetic and environmalestal factors; however, the totality of all contributing risk factors has not yet been elucidated. AF and atrial flutter (AFL) are two arrhythmias that may be commonly associated. This association generally reflects a similar arrhythmogenic substrate.

Key Words

Atrial fibrillation, Ablation, Same day discharge, Complications.

Corresponding Author
Robert Lee Percell, Jr. MD,
Bryan Heart Institute, Electrophysiology Section, 1600 S 48th Street, Lincoln, NE 68506

It has been observed that the development of isthmus-dependent AFL is often followed by AF[13].

More recently, it has been demonstrated that despite similar or greater numbers of established risk factors, African Americans have a lower rate of AF as compared to white patients [2-7]. Additionally, the development of AF after AFL ablation is markedly increased in some studies approaching 40% [8-10] and continues to rise thereafter [15]. Patients with a prior history of AF, female sex, and those treated with class I antiarrhythmic drugs or amiodarone prior to AFL ablation, as well as post CABG, the risk of development of AF is even higher [11-12, 14].

It is less well known if African American patients have similar increased rates of development of AF after AFL ablation. The goal of this study was to investigate in patients with typical (clockwise, isthmus dependent) AFL who underwent successful cavo-tricuspid isthmus (CTI) ablation whether the prevalence of AF was lower in

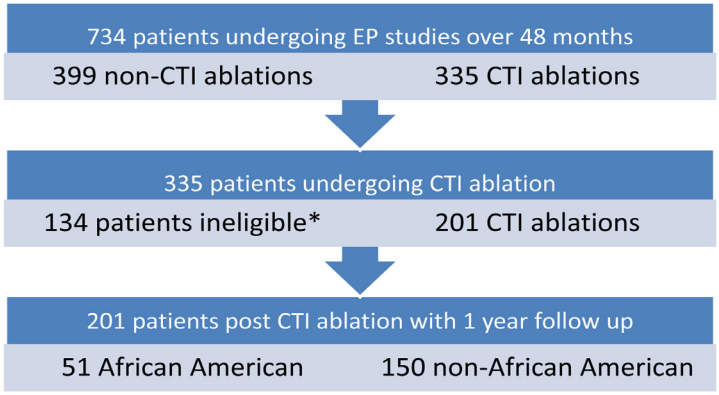

Figure 1: Patient Selection Flow.

African American patients compared with non-African American patients.

Materials and Methods

The electronic medical records (EMR) of first time, successful CTI ablations performed for typical AFL were retrospectively reviewed for 48 months. Ablations were performed at a single, urban, tertiary-care, academic hospital. Success was defined as development of bi-directional block across the CTI. Clinical variables were retrieved from the EMR. AF was documalested on ECG, via Holter/ Event monitor, via device interrogation at clinical follow up visits during a 1 year period after AFL ablation. Patients records were included if 1 month, 6 month, and 1 year data was obtainable. Patients were self-identified as African American, white, Hispanic or Other. Patients were excluded if they had a prior history of AF, or if complete follow up could not be obtained.

Study Population

Over a 48 month period, we identified 734 patients who underwent electrophysiology studies. 335 patients were identified who had typical AFL and underwent CTI ablation at a single academic, urban, tertiary care center. Patients were excluded for prior history of AF, incomplete follow up information (9%), unsuccessful ablation (3%) or those who required repeat ablation procedures (4%), and absence of ethnicity. The final number of patients was 201 (table 1).

Outcome Measures

The principal objective of the study was to assess AF prevalence and patient characteristics among African American and non-African American patients with AF who underwent CTI ablation. Other data collected for secondary analyses included the following clinical variables: age, sex, hypertension, ejection fraction, diabetes, device (pacemaker vs ICD), antiarrhythmic drug, beta blocker, digoxin, and anticoagulation status (fig 2).

Statistical Analysis

Sociodemographic factors and clinical variables were compared between African American and non-African American patients. The null hypothesis was that there was no difference between the development of AF based on race or ethnicity. All statistical analysis was performed using SPSS version 21.0 (SPSS Inc, Chicago, IL). For comparison of numerical values, Student's t- tests were used. Categorical variables were compared using chi square analysis. A p value of <0.05 was considered statistically significant (two-sided).

Table 1: Clinical Variables

Variable	African patients	American	Non-African patients	American	P value
LV EF	0.49		0.51		ns
Male Sex	0.73		0.76		ns
Age (yrs)	67.8		66.3		ns
ICD	0.14		0.046		<0.02*
Pacemaker	0.06		0.03		ns
Anti-arrhythmic	0.18		0.265		ns
Beta Blockers	0.62		0.83		<0.01*
Digoxin	0.04		0.02		ns
Diabetes	0.43		0.26		<0.05*
HTN	0.63		0.62		ns
Anticoagulation	0.9		0.86		ns
CAD	0.2		0.3		ns
Irrigated catheter	0.18		0.11		ns

*Denotes statistical significance p <0.05. All values are absolute.

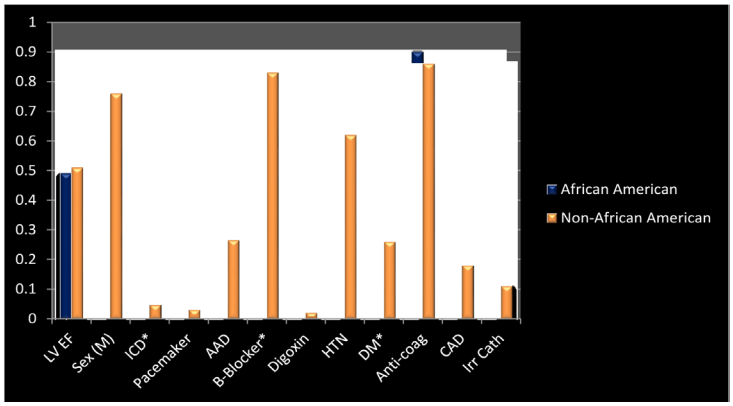

Figure 2: Patient Selection Flow.

Clinical Variables

The records of a total of 201 patients - 51 African American patients (25.4%) and 150 non-African American (74.6%) - who underwent successful CTI ablation for typical atrial flutter were examined. African Americans were more likely to have a pacemaker or defibrillators placed (p<0.02) and more likely to be diabetic (p<0.05) than non-African Americans. Additionally, African Americans were less likely to be prescribed beta blockers (p<0.01). Other selected variables were not statistically significant. Average age was similar (67.8 vs 66.3, NS). There was a preponderance of males (77.6% vs 23.5%) (Table1).

Results

There was a significantly lower rate of development of AF post CTI ablation for typical AFL in African Americans vs non-African

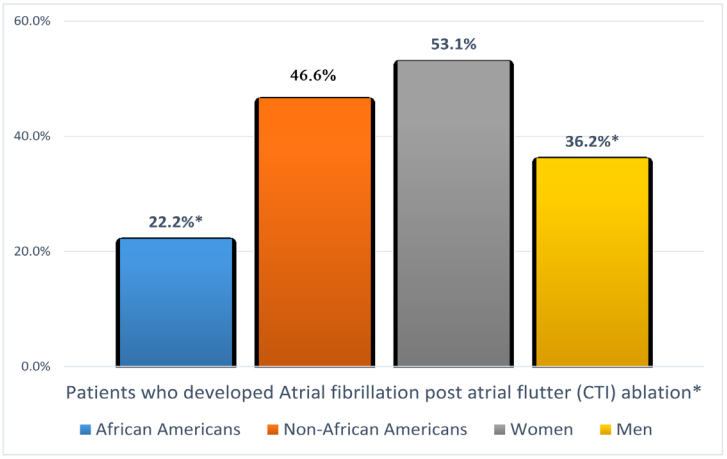

Figure 3: **Patients who developed Atrial Fibrillation Post Atrial flutter(CTI) Ablation***

Americans. The probability of developing AF post CTI ablation was 22.2% for African Americans vs 46.6% for non-African Americans (chi square statistic of 9.969, p=0.002). Additionally, women were more likely to develop AF at 53.1% compared to their male counterparts at 36.2% (chi square statistic 4.958, p=0.026) (figure 3). The odds ratio was much less than 1. This finding was highly statistically significant with p value of 0.01. Furthermore, African American Males were much less likely to develop AF post AFL ablation compared to non-African American Males (p=0.0062). There was no statistically significant difference in the development of AF between African American women versus non-African American women (p=0.975) (figure 4).

Discussion

Our results that suggest that African Americans may have a lower rate of development of AF after AFL ablation despite the lower use of beta blockers and the greater amount of diabetes. More precisely, these results are greatly driven by the lack of development of AF by African American Males after AFL ablation. This reflects the "paradox" that African Americans have a lesser rate of AF despite a greater number of risk factors [7]. Similar to previous results, female sex, hypertension, and diabetes were also more likely to develop AF after AFL ablation. From a greater perspective, the overall number of patients who developed AF after AFL ablation is higher than previously published [9]. This may represent a plethora of issues including: access to care, socioeconomic and insurance status, late presentation, and inability of recognition of symptoms.

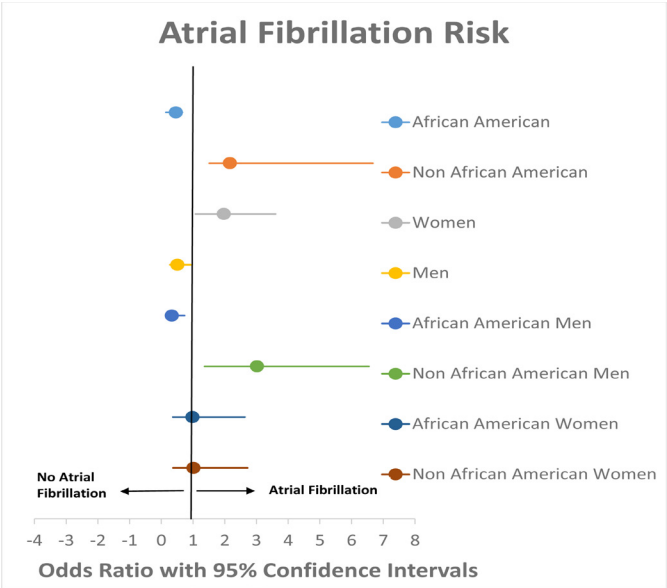

Figure 4: **Atrial Fibrillation Risk with 95% Confidence Intervals**

If indeed there is a reduced occurrence of AF in African American patients, even those post successful AFL ablation, how does this phenomena affect treatment? More specifically, could there potentially be a protective factor especially in African American males that reduces AF origination? It is possible in the future that rate controlling agents, anti-arrhythmic drugs, anticoagulation and further ablations may become tailored to patients based on racial (and possibly gender) identity. Although AF rates have been shown to be significantly less in African Americans, rates of stroke are still markedly increased to the point that some have suggested adding ethnicity to the standard CHA_2DS_2-VASc score due to the elevated morbidity and mortality from cerebral vascular events[15].

If there is a protective gene(s) that could be identified, isolated, and reverse engineered, this could conceivably lead to protection and possible correction / cure of AF in multiple populations. Race is largely a social construct and patients frequently self-identify; currently, there is no identifiable race-based biological mechanism increasing the propensity of stroke[16]. Obviously, this is an area that needs to be meticulously scrutinized with larger randomized trials; However, historically, it has been a tremendous challenge to enrol minority populations (i.e. African American males) in great numbers in clinical studies. This has been demonstrated over and over again due to many of the following factors: distrust of the medical establishment (ie. Tuskegee experiment), diminished access to care due to decreased healthcare providers and absence of healthcare coverage, as well as overall reduced adherence to guideline directed therapy.

Limitations

There are multiple limitations with this study. First, this is a single center, urban, retrospective, observational, non-randomized study. The size of the data sample as well as the preponderance of males may have skewed the interpretation. Second, the 1 year follow up period may not have been adequate to determine a significant difference as well as patients may have developed AF in the interim and not been detected. However, a single 20 patient study demonstrated that most patients developed AF in the first 4 months after AFL ablation using an implantable loop monitor[15]. Additionally, spurious factors that may confound the results could have been introduced which would have been impossible to control for. Finally, patients self-identified race. As a greater number of Americans are of mixed race, this was not specifically examined. Ideally, a prospective, randomized study with equal racial and gender proportions would definitively answer the question.

Conclusions

The development of AF after successful AFL ablation is a frequent occurrence. This study appears to demonstrate that there

are differences in the rates of development due to racial ethnicity. African Americans, specifically males, appear to be at less risk of developing AF after AFL ablation than non-African Americans.

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Comparative Study of Cryoballoon versus Radiofrequency for Pulmonary Vein Isolation when Combined with Vein of Marshall Ethanol Infusion for Paroxysmal Atrial Fibrillation

Kaoru Okishige[1], Naohiko Kawaguchi[1], Shinsuke Iwai[1], Yasuteru Yamauchi[1], Takehiko Keida[2], Tetsuo Sasano[3], Kenzo Hirao[3] Miguel Valderrabano[4]

[1]From the Heart Center, Japan Red Cross Yokohama City Bay Hospital, Yokohama, Japan
[2]Division of Cardiology, Edogawa Hospital.
[3]Arrhythmia Center, Tokyo Medical and Dental University.
[4]Division of Cardiac Electrophysiology, Methodist DeBakey Heart and Vascular Center and Houston Methodist Research Institute, Houston, TX.

Abstract

Introduction: Ethanol infusion (EI) in the Vein of Marshall (VOM) has multifactorial effects that could be synergistic to pulmonary vein isolation (PVI) in ablation of atrial fibrillation (AF). The efficacy of radiofrequency (RF) versus cryoablation when combined with a VOM-EI has never been investigated. The aim of this study is to evaluate outcome differences of AF ablation using RF versus cryoablation when combined with VOM-EI.

Materials and Methods: Consecutive patients (n=132) underwent catheter ablation of paroxysmal AF with either RF or cryoballoon (CB) for PVI combined with VOM-EI. Bi-directional conduction block at the mitral isthmus was attempted. The end-point was the freedom from any atrial arrhythmias documented after a blanking period of 90 days after the procedure.

Results: Kaplan-Meier estimates of the arrhythmia-free survival after 1 year were 63.8 (RF + VOM), and 82.7 % (CB + VOM), respectively. Comparison between CB + VOM versus RF + VOM reached statistical significance (p=0.0292). The periprocedural complication rate was comparable in both groups (5.0 % RF, 5.8 % CB; p=0.14) with a significant difference in the incidence of phrenic nerve palsy (0 % RF, 2.0 % CB; p<0.05).

Conclusions: PVI with CB had an increased freedom from AF recurrence compared to RF combined with VOM-EI. The present results suggest a potential additive effect of VOM-EI to CB application.

Introduction

Catheter ablation is a well-established technique for treating atrial fibrillation (AF) via pulmonary veinisolation (PVI), with a variety of energy sources used, most commonly radiofrequency (RF) or cryoablation energy [1,2]. RF ablation has been widely performed and shown to be a highly effective treatment for AF, However, it can be associated with serious complications [3, 4, 5]. The recently introduced therapeutic technology of using a cryoballoon catheter (CB) for PVI has produced satisfactory results in a number of trials providing comparable efficacy [6,7]. Recently, infusion of ethanol into the vein of Marshall (VOM-EI) has been proposed as a potentially synergistic adjunctive therapeutic strategy for AF [8,9]. The aim of this study is to investigate whether a VOM-EI translates into an improved rhythm control in paroxysmal AF, and whether the technique chosen for the PVI (RF or CB) has any influence when combined with a VOM-EI.

Key Words

Atrial Fibrillation; Chemical Ablation; Catheter Ablation; Cryoballoon; Radiofrequency Current

Corresponding Author
Kaoru Okishige, M.D.
Heart Center, Japan Red Cross Yokohama City Bay Hospital
1-12-3 Shinyamashita, Naka-ward, Yokohama city, Japan

Methods

Patients Population

Patients 44 to 82 years of age who had experienced multiple episodes of AF within the previous 6 months were consecutively enrolled in the study. Patients were excluded if their left atrium (LA) was >55 mm in diameter, or if there was evidence of any LA thrombus. Further exclusion criteria included unstable angina, myocardial infarctions within the previous 6 months, percutaneous transluminal coronary angioplasty within the previous 6 months, an ejection fraction of

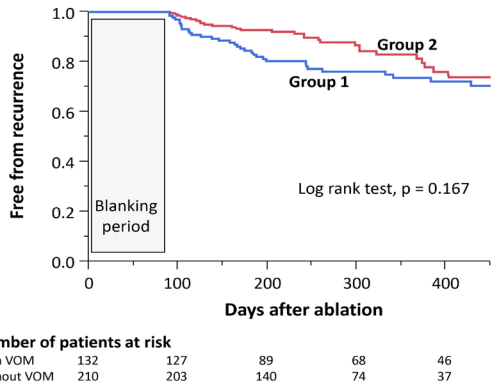

Figure 1A: Kaplan-Meier curve comparing the freedom from AF/AT recurrence between Group 1 and 2.

<40 %, heart failure grade III or IV (New York Heart Association criteria), and strokes or transient ischemic attacks within the previous 6 months. The patients provided informed consent and the protocol was approved by the local ethical committee of all institutions.

Patient groups

RF only; n=90, CB only; n=120, RF combined with VOM-EI; n=80, CB combined with VOM-EI; n=52.

A total of 132 patients underwent VOM-EI, 80 of which underwent PVI using RF, and 52 using CB (Group 1). For comparison, a total of 210 patients underwent PVI without VOM-EI (Group 2), ninety of which with RF, and 120 with CB. Patients in Group 1 underwent ablation of the mitral isthmus, the aim of which was to achieve bidirectional block. Patients in Group 2 did not undergo any mitral isthmus ablation.

Ablation strategy in each patient was selected by the discretion of the attending physician at each institution in a random fashion. When the VOM was absent as assessed by the venography of the coronary sinus, such patients were assigned into Group 2. All centers involved in this study enrolled the patients into these four groups. Data were collected prospectively.

Pre-procedural management

Cardiac computed tomography (CT) and transesophageal echocardiography (TEE) were performed the day before the ablation to analyze the LA and PV anatomy and to rule out any intracardiac thrombus. For patients receiving novel anticoagulant agents, our practice was to stop the anticoagulation as follows: (i) the last dose of rivaroxaban and edoxaban were given in the morning 1 day prior to the procedure, and (ii) the last dose of dabigatran and apixaban were given in the evening 1 day prior to procedure. Warfarin was not interrupted.

Ethanol ablation procedure

Under general anesthesia, a quadripolar catheter was positioned at the His bundle recording site, and a decapolar catheter was inserted into the coronary sinus (CS) via the right jugular vein. A balloon occlusion venogram of the CS was performed to delineate the CS anatomy. The presence of the VOM was established when a posteriorly directed vein branch was visible in the right anterior oblique projection.

The VOM was cannulated as previously described, using outer (GCS aim SL 59cm, St Jude Medical Inc., Minneapolis, MN) and inner sheaths (GCS direct SL II 50cm, St. Jude Medical Inc., Minneapolis, MN) designed for a left ventricular pacing lead delivery that was inserted in the CS via the right jugular vein [8, 9, 10, 11]. The inner sheath was manipulated so that its tip faced posteriorly and superiorly toward the orifice of the VOM. Angiographic contrast was slowly injected and the VOM was identified as an atrial branch of the CS that arose from the level of the valve of Vieussens. A single transseptal puncture was undertaken after venous and arterial access had been achieved. A duodecapolar catheter was inserted in the left atrium through the long guiding sheath and used to pace from the left atrial appendage (LAA). Heparin was administered to maintain the Activated Clotting Time (ACT) between 300 and 350 seconds throughout the procedure. Three-dimensional mapping of the left atrial geometry and bipolar voltage amplitude was performed using the NavX system (St. Jude Medical Inc., Minneapolis, MN).

An angioplasty wire (Runthrough, TERUMO, Tokyo) was advanced into the VOM. An angioplasty balloon (8mm length, 1.5 mm diameter, Ryujin, TERUMO, Tokyo or 10 mm length, 2.0 mm diameter, Ottimo, Japan Lifer Line, Tokyo) was then advanced over the wire as distally as possible. Depending on the length of the VOM, up to three balloon occlusive injections of 98 % ethanol (1.5 cc over 90 seconds) were delivered. Starting in the most distal VOM, the balloon was slightly retracted sequentially after each EI, so that the last EI was undertaken from the most proximal portion of the VOM. After completion of the VOM-EI, a repeat voltage map was performed to delineate the ethanol-induced low voltage area. A low voltage area was defined as a bipolar voltage amplitude of <0.05mV. The VOM-EI was performed as the first step during the ablation procedure. Ablation effects of this procedure on the mitral isthmus area were also investigated.

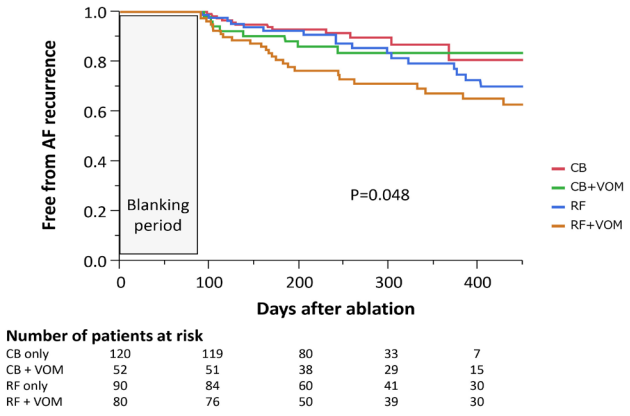

Figure 1B: Kaplan-Meier curve comparing the freedom from AF/AT recurrence across the four study sub-groups

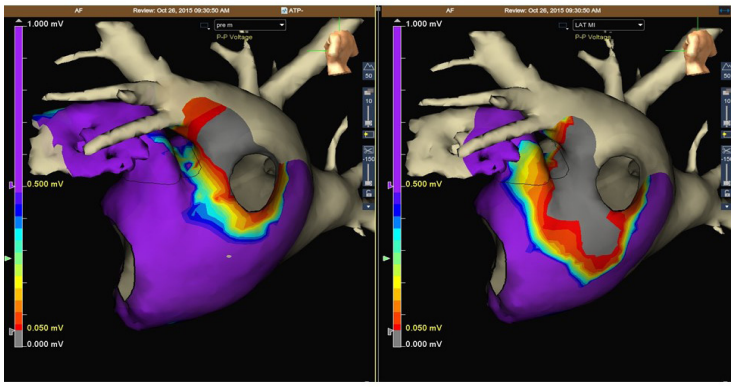

Figure 2: Low voltage scar creation in the mitral isthmus area.

RF Ablation Procedure

A Thermocool Smart Touch (Biosense Webster, Johnson & Johnson) was introduced into the LA through a transseptal long guiding sheath, and a circumferential PV ablation was performed by systematic RF applications around the PV ostia, consisting of an encirclement of the ipsilateral pairs of the PV antra. The power was limited to 30W at the anterior, superior, and inferior sites (flow rate, 17-20 mL/min) and 25W at all posterior sites (flow rate, 17mL/min) with the temperature limited to 48^{0}Cfor each lesion. The power was not adjusted according to the contact force (CF). The CF data were available to the operator throughout the procedure. The aim was to achieve a CF of at least 10 grams (mean) with a vector perpendicular to the tissue. The upper limit was defined as a 50 grams force. These values were chosen based on animal studies showing that to be effective for lesion formation while avoiding perforations [12, 13]. The PVI was first performed anatomically under guidance using CARTO navigation (Biosense Webster, Diamond Bar), and RF applications were not performed at the left-sided PV area where a low voltage zone was already created by the VOM-EI. A circular mapping catheter (Lasso, Biosense Webster, Diamond Bar) was used only after the completion of the anatomic PVI to confirm a full PV disconnection. This was performed by testing for both entrance and exit block with a waiting time of 30 min after the last RF application. In cases of an incomplete PVI, touch-up RF applications were performed until all points of residual PV connections were eliminated.

	RF	CRYO	RF + VOM	CRYO + VOM	P value
Patients, n	90	120	80	52	-
Age (years)	62.2±9.6	63.1±11.7	63.5±10.0	62.8±14.2	0.73
Male (%)	61 (69)	89 (74)	57 (71)	39(75)	0.64
AF duration, months	28.8±29.6	27.4±27.9	25.9±32.8	28.3±31.9	0.69
heart failure (%)	2 (2.2)	5 (4.2)	4 (5)	5 (10)	0.32
Hypertension (%)	19 (21.1)	28 (23.3)	25 (31.2)	16 (30.8)	0.87
Diabetes mellitus (%)	11 (12.2)	17 (14.1)	6 (8)	5 (10)	0.75
Stroke/TIA (%)	5 (5.5)	7 (5.8)	5 (6)	2 (4)	0.70
CHADS2 score	0.87±0.66	0.91±0.78	0.76±0.83	0.88±0.83	0.41
BMI, kg/m2	22.7±2.9	22.9±3.2	23.8±3.5	24.5±3.6	0.29
BNP, pg/mL	101±33.3	98.8±78.6	96.1±182.6	72.4±87.7	0.39
LA diameter, mm	41.1±4.3	40.8±2.9	38.7±7.3	39.9±6.2	0.33
Ejection fraction, %	58.6±4.8	63.4±5.8	66.6±8.2	65.0±9.4	0.31

Tabble 1: Patient Clinical Characteristics

Cryoablation Procedure

Cryoballoon ablation was performed as previously described [14]. Briefly, a 14 French deflectable sheath (FlexCath, Medtronic) was introduced into the LA after a single transseptal puncture. Only the 28-mm CB was used. The cryoballoon catheter (Arctic Front Advance, Medtronic) was introduced into the sheath, inflated, and advanced to the ostium of each PV and ablation of the PV antra was performed with a single application of 180 seconds per vein. PV angiography and measurement of the PV potentials were carried out both before and after the PVI with the use of a circular mapping catheter (Achieve, Medtronic). Occlusion of each PV was assessed with venous angiography. Continuous monitoring of the phrenic nerve (PN) function during the freezing of the PVs was performed as previously described [14]. In short, PN was electrically stimulated through the electrode catheter positioned at the right and left subclavian veins at a rate of 40 bpm with an output of 10~20 % above the pacing threshold, and the compound motor action potential (CMAP) of the diaphragm was continuously monitored during cryoablation. If the PV remained connected, additional applications were performed using different angulations. The PVI was finally checked at least 30min after the last CB ablation. In cases of an incomplete PVI, touch-up RF applications were performed using irrigated-tip RF ablation catheters with a contact force system in addition to the CB when a gap conduction between the PV and LA was identified until all points of residual PV connections were eliminated. Patients with a left common PV were excluded from the study.

Linear lesion formation at the mitral isthmus

Mitral isthmus (MI) conduction was assessed during pacing from the base of the LA appendage using the ring catheter (Lasso, Biosense Webster). Distal-to-proximal activation of the CS indicated persistent isthmus conduction, and proximal-to-distal activation of the CS indicated conduction block at the MI. In groups A and B, no MI ablation was performed, because we have already reported the easiness of accomplishing MI ablation in patients after undergoing the VOM-EI as previously reported [15]. In Group RF + VOM-EI and the CB + VOM-EI, if the initial ablation lesion created by the VOM-EI failed to yield conduction block at the MI, ablation was performed using the irrigated-tip RF catheter at the conduction gap between the mitral annulus and ostium of the left-sided PVs. If there was a persistent conduction across the MI after the endocardial ablation, RF energy was then delivered in the distal CS. The ablation catheter was advanced into the distal CS to the level of the endocardial lesion, as visualized on the three-dimensional map. If conduction block was not achieved after the initial attempt in the CS, the process was repeated for a maximum of ten attempts for the prevention of damage to the CS as previously reported [16]. Linear block was confirmed by differential pacing [17]. RF energy was delivered at a maximum power of 25 W near the PVs and along the posterior wall, with 35W at the endocardial MI, and 20 W within the CS. The maximum temperature was set at 40^{0}C. All patients were observed at the catheter laboratory for approximately 1 hour after undergoing transthoracic echocardiography, and then transferred to the ward for further observation.

	RF	CRYO	RF + VOM	CRYO + VOM	P value
Isolated PVs , n (%)	360 (100)	480(100)	320 (100)	208 (100)	1.0
Procedure time					
PV isolation, min	59±18*	36±12	54±19**	35±12	
EI into VOM, min			18±8	17±6	0.09
Mitral isthmus ablation, min			11±9	15±12	0.09
Complications					
Phrenic nerve paralysis, n (%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0.39
Cardiac tamponade, n (%)	3(6.7%)	0 (0%)	1 (1%)	0 (0%)	1.0
Pericardial effusion, n (%)	0 (0%)	1 (0.8%)	1 (1%)	2 (4%)	0.56
Stroke./TIA, n (%)	2 (2.2%)	21 (21%)	0 (0%)	19(19%)	1.0
Coronary sinus dissection during EI into VOM, n (%)			2 (3%)	0 (0%)	0.51
Success rate of MIB (%)			68/80 (83 %)	47/52 (90 %)	0.23

* p<0.05 vs CRYO, ** p<0.05 vs CRYP + VOM

Tabble 2: **Procedural data**

Follow-up

After the index procedure, all patients underwent a cerebral magnetic resonance imaging examination three days after ablation procedure, and were followed for a total of 396 ± 67 days. Endoscopic examination was performed in patients who had a luminal esophageal temperature higher than 39^{0}C during RF application and lower than 15^{0}C during CB ablation. Patients were evaluated at 1, 2, 3, 6, 9, 12, and 15 months after the procedure. Information collected during follow-up included a 12-lead electrocardiogram (ECG) and 24-h Holter monitoring at each visit regardless of the symptoms. All patients had been instructed to maintain personal records with a description of every episode of symptomatic palpitations. The first 3 months post-procedure were considered as a blanking period [18]. Anticoagulant medication after the first 3 months was considered based on the CHA2DS2Vasc and HAS-BLED scores. If antiarrhythmic medications (AAD) were prescribed at discharge, they were discontinued at the 3-month office visit.

Outcomes

The procedure endpoint was a successful PVI confirmed by entry and exit block after a waiting time of 30 minutes. Regarding the long-term follow-up, the endpoint was defined as the absence of any symptomatic atrial arrhythmias lasting longer than 30 seconds after the blanking period of 3-months in combination with the absence of any persistent complications during the year after the ablation procedure. Persistent complications were defined as any new PV stenosis, PN palsy, cerebrovascular accidents, bleeding, or vascular complications that occurred during or within 48-hours after the ablation procedure. This was ascertained by Holter monitoring at each outpatient clinic visit or by 12-lead ECGs in the case of symptomatic palpitations during the clinical interview. Recurrence was defined as any symptomatic or asymptomatic AF/atrial tachycardias (AT) after the 3-month blanking period.

Statistical Analysis

Comparisons were performed between the treatment groups. A Student's t-test was used for the comparison of the continuous variables. The results with a p< 0.05 were regarded as significant. Variables that differed during the baseline between the two treatment groups and their impact on sinus rhythm maintenance were assessed using a Cox Regression. Kaplan-Meier curves were traced to compare the sinus rhythm maintenance among the two treatment strategies and the log-rank test was used for assessing existing differences. JMP Statistics version 10.0 software (SAS, Cary, NC) was used for the descriptive and inferential statistical analysis.

Results

Patient Characteristics

A total of 342 patients were enrolled between January 2014 and July 2018. The population characteristics are detailed in Table 1. The general patient characteristics were similar for all treatment arms. The mean age of the patients was 63.15 ± 11.2 years. The majority of the study patients were male (73 %). The mean follow-up was 396 ± 132 days. A repeat ablation procedure was undertaken in 26 (19.7 %) of the Group 1, and in 37 (17.6 %) of the Group 2. There were no significant differences in the symptomatic AF episodes before the inclusion in the registry among all four patients groups (RF, CB, RF + VOM-EI, and CB + VOM-EI).

Acute success

The VOM was absent in 15 out of 132 patients (11 %), which prohibited us from performing the EI into the VOM. We were able to successfully perform the EI-VOM in 117 out of 132 patients (88.6 %). PVI was acutely successful for 100 % PVs in Group 1 (80 with RF and 52 with CB). 5 CB patients (0.96 %) required RF touch-up ablation for successful PVI. PVI was acutely successful in 100 % of PVs in Group 2 (90 with RF and 120 with CB). 11 CB patients (0.92 %) also required RF touch-up ablation for accomplishment of PVI. The mean procedure duration for a successful PVI including all repeat PV assessments was 45 ± 15 minutes in Group 1, 48 ± 15 minutes Group 2, (p<0.01). Subgroup (CB vs RF) procedural metrics are shown in the Table. The mean procedure duration for the VOM-EI was 17.8 ± 5.6 minutes in Group 1. The VOM-EI was successfully performed in all study patients of groups RF + VOM-EI and CB + VOM-EI, even though the anatomical chraracteristics of the VOM varied. The mean total volume of the injected ethanol into the VOM was 4.4 ± 0.9 cc.

Dormant conduction assessment

The presence of dormant conduction (DC) was assessed by the injection of adenosine. DC was found in 34 % of Group RF, 4 % of

Log rank test

			p value
RF only	vs.	RF + VOM	0.2644
RF only	vs.	CB + VOM	0.2381
CB only	vs.	RF only	0.3091
CB only	vs.	RF +VOM	0.0033
CB only	vs.	CB+VOM	0.5205
RF + VOM	vs.	CB + VOM	0.0292
RF only and CB only	vs.	RF + VOM and CB + VOM	0.1896

Tabble 3: **Comparison of the freedom from any atrial arrhythmias between each treatment arm.**

	RF	CRYO	RF + VOM	CRYO + VOM	
Re-do ablation (%)	25/90 (28)	12/120 (10)	17/80 (21)	9/52 (17)	
Reconnected PVs					P value
LSPV (%)	5 (20)	2 (16.7)	2 (11.8)	2 (22.2)	0.877
LIPV (%)	9 (36)	4 (33.3)	16 (94.1)	4 (44.4)	0.0009
RSPV (%)	5 (20)	2 (16.7)	1 (5.9)	1 (11.1)	0.62
RIPV (%)	8 (32)	7 (58.3)	4 (23.5)	5 (55.6)	0.159
Reconnection of PV>1 PV (%)	21/25 (84)	3/12 (25)	1/17 (6)	4/9 (44)	
Single reconnection of PV (%)	4/25 (16)	9/12 (75)	16/17 (94)	5/9 (56)	
Endpoint (%)	24/90 (26.7%)	15/120 (12.5%)	23/80 (28.8%)	9/52 (17.3%)	

Tabble 4: **Data of the reconnections of the PVs among each treatment arm.**

Group CB, 38 % of Group RF + VOM-EI, and 4 % of Group CB + VOM-EI patients. All those all DCs were successfully eliminated by touch-up irrigated RF ablation procedures as previously reported [19].

Conduction block at the MI

In 10 out of 132 (7.7 %) Group 1 patients bidirectional MI block (MIB) was achieved solely by a VOM-EI. Conduction gaps at the MI were identified in the area where a low voltage zone (scar area) could not be created solely by the VOM-EI, and the viable portion of the MI area predominantly remained at its most annular portion. In 85 out of 132 (64.4 %) Group 1 patients, linear block was obtained after only an endocardial ablation. A CS ablation was performed in 30 out of 132 (22.7 %) Group 1 patients for a complete MIB. There were no significant differences between RF and CB in terms of the success rate of creating the MIB (68/80=83 % in Group RF + VOM-EI, and 47/52=90 % in Group CB + VOM-EI, p= 0.23) (Table 2). The mean procedure duration for the successful construction of the MIB was 13.5 ±11.2 minutes in Group 1. Ablation of the cavotricuspid isthmus in addition to the PVI was performed in all patients, and resulted in complete success in all patients using irrigated-tip RF catheters.

Long-term outcomes

The follow-up period was 402 ± 99 days in Group RF, and 388 ± 87 days in Group CB, 381 ± 152 days in the Group RF + VOM-EI, and 398 ± 139 days in Group CB + VOM-EI (p= n.s.).

There was a significant association among the types of treatment received and the rate of freedom from AF as shown in Figure 1A. Kaplan-Meier curve estimates of the freedom from AF after approximately 450 days were 0.73 for Group 1 and 0.77 for Group 2 (p=0.167). Per subgroups of RF vs cryo 58 out of 90 (64.5 %) in Group RF, 92 out of 120 (79.6 %) in Group CB, 51 out of 80 (63.8 %) in Group RF + VOM-EI, and 43 out of 52 (82.7 %) in Group CB + VOM-EI patients. Among the treatment arms, however, recurrent AF occurred in a significantly larger proportion of patients in Groups RF, CB and C RF + VOM-EI, than in Group CB + VOM-EI, and those differences reached statistical significance (Figure 1B)(p= 0.048). The comparison data between each treatment arm were as follows: Group RF vs. CB; p= 0.3091, Group RF vs. RF + VOM-EI; p= 0.2644, Group CB vs. RF + VOM-EI; p= 0.0033, Group CB vs. CB + VOM-EI; p= 0.5205, and Group RF + VOM-EI vs. CB + VOM-EI; p= 0.0292, Group RF + CB vs. Group RF + VOM-EI plus CB + VOM-EI; p= 0.1896. There were significant differences between Group CB and RF + VOM-EI, and between Groups RF + VOM-EI and CB + VOM-EI as shown in Table 3.

In the Group RF, CB, and CB + VOM-EI patients, recurrent AF was managed with a repeat catheter ablation using RF energy in 25 patients (Group RF), 12 patients (Group CB), and 9 patients (Group CB + VOM-EI), respectively, after 317 ± 48 days. Reconduction of >1 PV was observed in 21 patients (84 %) in Group RF, 3 patients (25 %) of Group CB, and 4 out of 9 (44.4 %) in Group CB + VOM-EI, and a single reconnection site was observed in 4 patients (16 %) in Group RF, 9 patients (75 %) in Group CB, and 5 out of 9 (55.6 %) in Group CB + VOM-EI, and a complete PVI could be accomplished in all patients as a result (Table 4).

In contrast, in the Group RF + VOM-EI patients, reconnection sites of PVs were observed in 23/65 (35.4 %) in the left inferior PVs (16/23=69.6 %) predominantly at the inferior aspect of the LIPV where low voltage areas had already been created by the VOM-EI and no further touch-up RF applications had not been required for a successful PVI in the first session in Group RF + VOM-EI. In 3 patients in Group RF + VOM-EI (3.8 %), such low voltage areas created by the VOM-EI were found at the posterior antral wall of the left superior PV (LSPV) as shown in Figure 2. Of note, no AT whose arrhythmogenic substrate involved the MI area was observed observed in Groups RF + VOM-EI and CB + VOM-EI during the follow-up period.

Predictors of recurrence

We assessed the prognostic role of the ablation approach. In a univariate Cox regression analysis, the use of the CB during the ablation procedure (HR 0.31; 95 % CI 0.13-0.73; p= 0.005) and Diabetes Mellitus (HR 2.94; 95 % CI 0.84-10.29; p= 0.09) were significant predictors of AF recurrence. In the multivariate Cox regression analysis, the only significant predictor of an AF-free survival was the use of the CB for the ablation (HR 0.29; 95 % CI 0.12-0.69; p= 0.005). The use of a VOM-EI was not a predictor of success.

Safety outcomes

Pericardial tamponade requiring percutaneous drainage occurred in 3/210 (1.4 %) Group 2, and 1/123 (0.8 %) Group 1 patients. Tamponade occurred approximately 60 minutes after acomplishment of the successful PVI procedure. No instances of arterial injury, symptomatic thromboembolism, or esophageal injury were observed. However, sustained phrenic nerve palsy was provoked in one Group 1 patient during right-sided PVI with the CB, and an asymptomatic cerebral infarction was provoked in approximately 20 % of the CB treated patients as reported previously [20,21]. Dissection of the CS was also provoked by the VOM-EI procedure in two Group 1 patients, and the EI could not be performed in those patients (Table 2).

Discussion

We report a large, prospective, multicenter series of paroxysmal AF patients undergoing 4 different treatment strategies including the largest experience using a VOM-EI over a 12-month follow-up

period.

Major findings

The main results of this study were: (1) Overall, the VOM-EI failed to significantly improve the clinical efficacy of the PVI for paroxysmal AF. (2) The success rate of RF combined with a VOM-EI was significantly lower than that of a CB alone (88 and 66 %, p= 0.0033). (3) The success rate of the MIB afforded by the VOM-EI was high and did not differ between Groups RF + VOM-EI and CB + VOM-EI. (4) Using the CB was the only predictor of an AF-free survival among all treatment arms.

We previously demonstrated that a VOM-EI was useful for treating perimitral atrial flutter by reliably achieving bidirectional MI block [15]. We were also able to show that there was regional parasympathetic denervation around the MI area [22]. These clinical aspects of the VOM-EI may be expected to facilitate the clinical efficacy of the ablation of AF.

The CB technology offers the possibility of the PVI with a single energy application as an alternative to a point-by-point RF current ablation [23, 24, 25], and the CB has been increasingly used for treating AF because of the relative technical simplicity and steeper learning curve [26]. However, the clinical results have been hampered by left-sided ATs in approximately 8~10 %, and those ATs were associated with the MI area [27, 28]. Macroreentrant tachycardia involving the mitral annulus-PMF causes 33 % to 60 % of post-PV isolation atrial flutters [29, 30]. Therefore, construction of MIB could be regarded as one of the necessary ablation procedures even in paroxysmal AF.

At 12-months of follow-up, approximately 65 % of the Group RF and 80 % of the Group CB patients were free of AF recurrences in the present study, and that was in line with the recent articles analysing the mid-term outcomes [4, 5, 27, 28]. However, no left-sided ATs have ever been documented in all four groups of patients during the follow-up period, and these results could be associated with the antiarrhythmic effects of preventiong AF recurrences by a VOM-EI procedure [8. 9]. Lyan et al reported that 26 out of 238 (10.9 %) AF patients underwent a redo ablation for AT. Nine out of 26 (34.6 %) patients had perimetral reentrant AT after the CB application. An additive EI-VOM might be beneficial in terms of preventing perimetral AT [31].

In Group RF + VOM-EI, reconnected PVs sites were observed in 20/52 (38.5 %) patients predominantly in the left inferior PVs where a VOM-EI had already created low voltage areas and no further touch-up RF applications were performed in the first session, because a successful PVI could be performed by applying RF energy at the antral area where the residual atrial electrograms remained. In general, the anatomical course of the VOM arises from the middle or proximal portion of the CS and runs toward the inferior aspect of the LIPV. Therefore, the antral atrial tissue at the inferior aspect of the LIPV is susceptible to be ablated by the VOM-EI. In those cases, our approach was to spare the RF energy applications in the area where no atrial electrograms were recorded from the tip of the ablation catheter for a successful PVI of the LIPV. In sporadic cases, such low voltage areas were detected at the posterior wall of the LSPV, and that kind of characteristic could be expected in cases that had a relatively long VOM coursing toward the LSPV area.

A high reconnection rate of the LIPV meant that the durability of the lesion around the PVs created by the VOM-EI was not sufficient. This might be the reason why the long-term clinical outcome of Group CB was significantly better than that of Group RF + VOM-EI. Considering that the VOM is an epicardial structure, the VOM-EI is expected to ablate the epicardium first and may not reach to the endocardial myocardium as effectively or as durably. CB ablation in the LIPV, when combined with a VOM-EI, did not have a high LIPV reconnection rate. It is possible that if RF energy applications had been performed at those "silent" areas, the rate of the freedom from AF in Group CB could have been comparable to that of Group RF. In addition, Guler et al demonstrated that CB provided additional substrate modification owing to the balloon and PV mismatch and could provide a lesion formation at the posterior wall of the left atrium, which is the most affected part of left atrium [32] This may have some influence on the results of the present study.

A previous report demonstrated the necessity of a combined epicardial (inside CS) and endocardial RF catheter ablation of the VOM area was required to eliminate the VOM potentials [33]. In the present study, the success rate of constructing an MIB was 68 out of 80 (83 %) in Group RF + VOM-EI and 47 out of 52 (90 %) in Group CB + VOM-EI, respectively (p= 0.23). This was overall a higher success rate than usually reported in the literature [34] with a lower rate of RF application inside the CS as compared to the other study [33], and may highlight a unique utility of this procedure.

In this study, we failed to demonstrate any significant further improvement in the clinical efficacy in terms of preventing AF recurrences by adding a VOM-EI to the PVI by ablation using the CB or RF energy in patients with paroxysmal AF. According to the recent report, the one-year clinical outcome using the CB for the PVI in patients with persistent AF was not satisfactory [35]. Even though the acute success rate of the PVI was 100 %, the 1-year clinical success rate was 69 % with the use of the second-generation CB. Of note, left-sided ATs were documented in 13 % of the study patients. Those ATs could have been prevented by adding a VOM-EI procedure to the PVI. A VOM-EI has multifactorial effects for facilitating the clinical efficacy of the catheter ablation of AF. As we previously reported, the VOM-EI was able to abolish the non-pulmonary vein ectopy, which degenerated into AF by the VOM-EI [36]. In addition, this procedure might be expected to provoke significant parasympathetic denervation effects in the left atrium, which could contribute to the improvement in the success rate of vagally mediated AF [9, 37]. A durable PVI in addition to a VOM-EI might be expected to improve the rate of freedom from AF recurrences, and further investigation will be required.

Limitations

This study constituted a nonrandomized analysis of consecutive patients, including our initial patients treated with the second-generation CB device. However, all operators were well trained in CB ablation beyond the learning curve, minimizing any time-dependent confounders. (2) The group sizes were small. However, a number of

the efficacy parameters differed significantly between the groups. (3) The assignment of the study patients into the four groups might not be appropriate, because grouping of patients depended on whether the VOM was present or not. (4) A comparison of PVI vs. PVI plus VOM-EI might be unfair due to the additive effects of creating a lesion in the mitral isthmus region. (5) The evaluation of the success and complication rates was complex. (6) A procedure trying to construct the MIB was not performed in Group RF+ VOM-EI, and this might have affected the rate of freedom from AF/ AT. However, all recurrent arrhythmias were AF instead of left-sided ATs rotating along the mitral annulus. Therefore, it was unlikely that the absence of the MIB could affect the clinical results in Group RF + VOM-EI. (7) By definition, successful maintenance of sinus rhythm strongly relies on the length of the follow-up, which varies from center to center. Because we reported on the 12-month follow-up data from outpatient clinic visits or telephone interviews, we could not exclude that AF recurrent episodes could have been missed in some patients. (8) The examinations to evaluate the efficacy of ablation procedure such as periodic 12-lead ECG and Holter monitoring recording might not be sufficient to strictly investigate the clinical efficacy of each ablation modality. (9) There was no comparison between a control group in the present study.

Conclusions

Overall, the VOM-EI failed to demonstrate any significant improvement in the ablation long-term results of paroxysmal AF. However, CB ablation combined with a VOM-EI had a significantly improved outcome compared to a PVI with RF ablation combined with a VOM-EI.

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Atrial Fibrillation is a Risk Factor for Worse Outcomes in Patients with End Stage Liver Disease

Muhammad Zia Khan[1], Muhammad U. Khan[1], Safi U. Khan[1], Anas Alharbi[1], Mohammed Osman[2], Pratik Agrawal[2], Mina M. Benjamin[2], Kinjan Patel[2], Sudarshan Balla[2], Muhammad Bilal Munir[2,3]

[1]Department of Medicine, West Virginia University, Morgantown, WV, USA.
[2]Division of Cardiovascular Medicine, West Virginia University Heart & Vascular Institute, Morgantown, WV, USA.
[3]Section of Electrophysiology, Division of Cardiovascular Medicine, University of California San Diego, La Jolla, CA, USA.

Abstract

Background: Liver disease is a risk factor for development of atrial fibrillation (AF). We aim to study inpatient mortality and resource utilization of end-stage liver disease (ESLD) patients with AF from a nationally representative United States population sample.

Methods: For the purpose of our study, we utilized data from National Inpatient Sample for calendar years 2005-2015. Patients with ESLD and AF were identified using relevant International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Key outcomes of inpatient mortality and resource utilization were assessed. We also constructed a multiple logistic regression model to determine predictors of mortality in ESLD patients. Propensity matching was also done to balance confounding variables.

Results: A total of 309,959 ESLD patients were included in final analysis. Out of these, about 32,858 (10.6%) patients have concomitant AF. ESLD patients with AF were older and had higher burden of key co-morbidities such as heart failure, diabetes and hypertension. Mortality was significantly higher in both unmatched (12.3% vs. 9.2%, $p < 0.01$) and matched cohorts (12.2% vs. 10.8%, $p < 0.01$). Additionally, ESLD patients with AF have longer length of stay, increased facility discharge and cost of hospitalization compared to ESLD patients without AF. In multivariate analysis, AF is an independent predictor of mortality in ESLD patients.

Conclusion: AF portends worse outcomes in patients with ESLD. Strong index of suspicion is warranted to timely identify AF in this patient population.

Introduction

End stage liver disease (ESLD) is a global health burden and one of the leading causes of mortality around the world [1,2]. Majority of ESLD patients frequently get admitted to hospital due to related complications of hepatic encephalopathy, spontaneous bacterial peritonitis (SBP) and gastrointestinal bleeding (3). ESLD is also associated with autonomic dysfunction and increase levels of circulating neuropeptides such as vasoactive intestinal peptide (VIP) and galactin-3 [4,5,6]. These physiological perturbations are proposed in pathogenesis of atrial fibrillation (AF) in ESLD patients [7]. Studies have shown that ESLD is a predictor for new onset AF with advanced ESLD as manifested by worsening Model for End-Stage Liver Disease (MELD) score associated with further increased risk [8]. Till to date, there is no data on how AF affects inpatient outcomes of ESLD patients who are at greatest risk for frequent hospitalizations. In this paper, we aim to study these parameters from a national United States population database.

Key Words

Atrial Fibrillation; End-Stage Liver Disease; Outcomes.

Corresponding Author
Muhammad Bilal Munir, MD
West Virginia University Heart & Vascular Institute and University of California San Diego Sulpizio Cardiovascular Center
1 Medical Center Drive, Morgantown, West Virginia 26505

Methods

Data was collected from National Inpatient Sample (NIS). NIS is part of Healthcare Cost and Utilization Project (HCUP) databases and is made possible by a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is derived from all States for national estimates of healthcare utilization, cost and outcomes [9]. Since NIS is compiled annually, the data can be used for analysis of disease trends over time. The study was deemed exempted from Institutional Review Board approval given the de-identified nature of the NIS database and public availability.

We analyzed NIS database from January 2005 to August 2015 using the International Classification of Diseases, 9th Revision,

Clinical Modification (ICD-9-CM) codes. Patients ≥ 18 years of age were included. Patients with ESLD were identified using Goldberg's third algorithm (10), a well-validated method for identifying ESLD from administrative datasets, generating a positive predictive value of 89.3%. Based on this algorithm, first ICD-9-CM codes were used to select chronic liver disease patients. (ICD-9-CM of 070.20-21, 070.23, 070.30-33, 070.40, 070.42, 070.49, 070.52, 070.59-60, 070.70-71, 070.90, 571.1, 571.40-41, 571.8, and 571.9), then a concurrent diagnosis code of cirrhosis was added (ICD-9-CM of 571.2, 571.5 or 571.6) and finally at least 1 concurrent diagnostic code for hepatic decompensation event (ICD-9-CM of 456.0-2, 789.5, 789.59, 572.2, 567.2, 567.21, 567.29, 567.8-9 or 572.4). Using this algorithm, we were able to extract a total of 309,959 ESLD patients that were included in final analysis. Please see figure 1 for detailed methodology of patient inclusion criteria.

Baseline characteristics and hospital outcomes were derived and compared among ESLD patients with and without AF. To account for potential confounding factors and selection bias, a propensity score-matching model was developed using logistic regression to derive two matched groups for comparative outcomes analysis. A nearest neighbor 1:1 variable ratio, parallel, balanced propensity-matching model was made using a caliper width of 0.2. Descriptive statistics were presented as frequencies with percentages for categorical variables and as means with standard deviations for continuous variables. Baseline characteristics were compared using a Pearson^{x}2 test and Fisher's exact test for categorical variables and independent samples t-test for continuous variables.

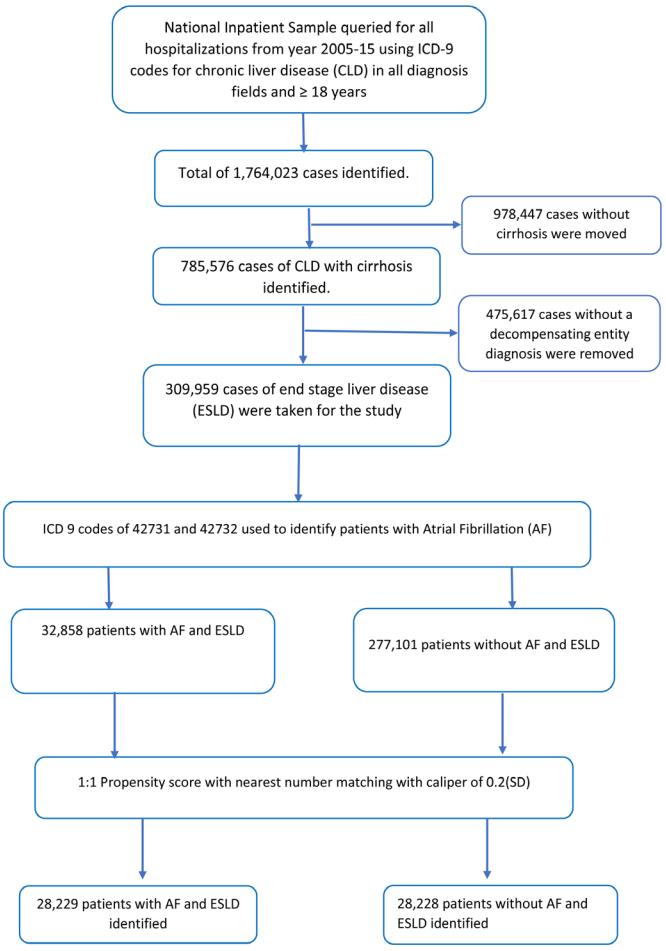

Figure 1: **Flow sheet of our paper**

Logistic regression was performed to estimate odds ratios (ORs) with 95% confidence intervals (CIs) to determine predictors of mortality in ESLD. Initially, binomial logistic regression model was used to identify variables from demographic data (Table 1) that were significantly associated with patient mortality (P value < 0.10). These variables were then subsequently utilized in a multiple logistic regression model to identify predictors of mortality. A type I error rate of <0.05 was considered statistically significant. All statistical analyses were performed using statistical package for social science (SPSS) version 26 (IBM Corp) and R 3.5 for propensity matching

Results

A total of 309,959 patients with ESLD were identified from the NIS dataset. Out of these 32,858 patients had AF (10.6%). Baseline characteristics of the study population are shown in table 1. ESLD patients with AF were older (68.46 vs. 58.14 years, p < 0.01) and had higher burden of key co-morbidities such as diabetes (29.9% vs. 25.3%, p < 0.01), hypertension (53.8% vs. 40.1%, p < 0.01) and congestive heart failure (31.2% vs. 9.3%, p < 0.01). Overall, about 29,487 (9.5%) ESLD patients died at discharge (see table 2). Mortality was 9.2% in ESLD without AF when compared to 12.3% in ESLD with AF (p < 0.01). In a propensity-matched cohort, this mortality difference continues to remain significant (12.2% vs. 10.8%, p < 0.01, supplemental table 2). A gradual downtrend trend in mortality was noted in ESLD patients with and with out AF over our study years (see figure 2). This downward trend is same across both genders although male patients had higher mortality when compared to female patients over our study period (see figure 3).

ESLD patients with AF have longer length of stay (9 vs. 7.36 days, p < 0.01) and increase costs of hospitalization (78,246 $ vs. 63,403 $, p < 0.01) when compared to ESLD patients without AF. Please see figure 4 for length of stay and costs of hospitalization trends over our study years. Predictors of mortality in ESLD are shown in figure 5. Advanced age, AF and African American race were independently associated with increased mortality. Urban and large hospitals were associated with lower mortality. Patients with metabolic acidosis, coagulopathy, pulmonary circulation disorders, congestive heart failure and cancers were also associated with increased mortality in our study cohort.

Discussion

The main findings of our current investigation are: (1) ESLD patients with concomitant AF have increased mortality when compared to ESLD patients without concomitant AF (12.30% vs. 9.20%, p < 0.01) and this difference persisted despite balancing covariates in a propensity matched model (12.2% vs. 10.8%, p < 0.01). (2) The presence of AF is an independent predictor of mortality in ESLD patients and about 10.6% patients in our cohort have AF. (3)

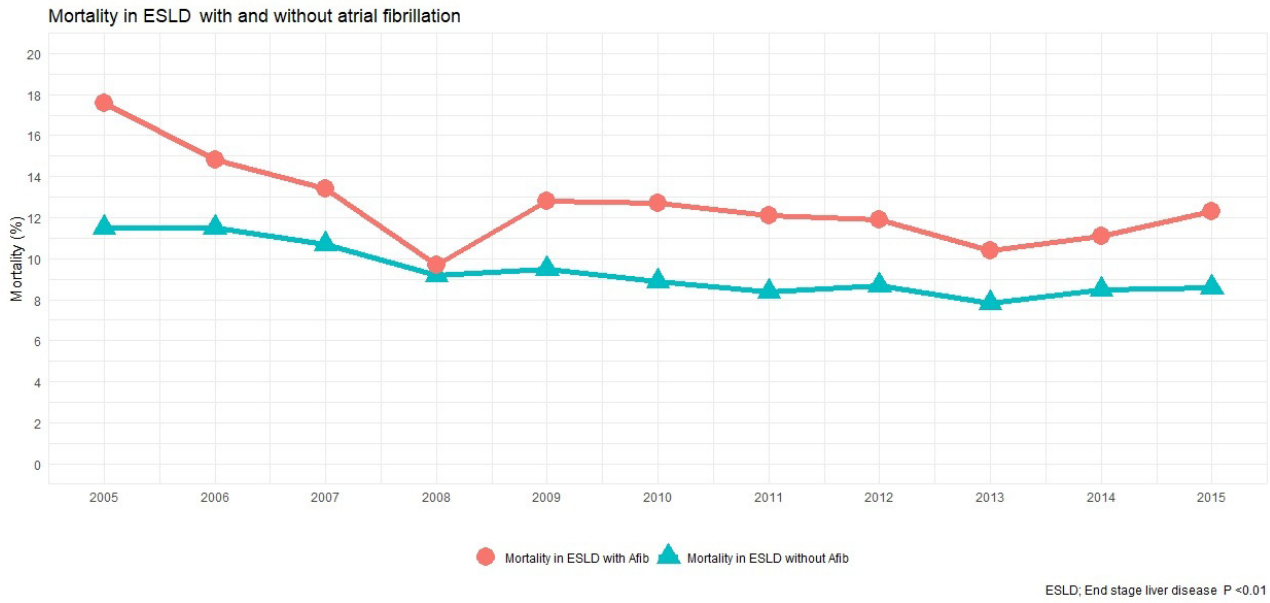

Figure 2: **Mortality in end stage liver disease with and with out atrial fibrillation over study years**

ESLD and AF patients have increased cost of hospitalization as well as length of stay when compared to ESLD patients without AF.

ESLD is a rising global health burden and represents a final sequel in natural history of liver cirrhosis [1,2]. Frequent hospitalizations are common in ESLD patients due to concomitant complications of hepatic encephalopathy, SBP and gastrointestinal bleeding [3]. ESLD patients are more prone to developing AF even in absence of structural heart disease. This increased propensity of developing AF is proposed to be due to autonomic dysfunction and increased levels of circulating neuropeptides such as VIP and galactin-3 that exercise their effect either through modulating autonomic system or inducing fibrosis within the heart muscle [4,5,6,7]. The prevalence of AF in our cohort is about 10.6%, which is consistent with earlier studies. The study by Huang et al. [8] on 1727 consecutive ESLD patients awaiting liver transplantation showed AF prevalence to be about 11.2%. They also found that liver disease is an independent predictor of new onset AF and increased MELD scores are subsequently associated with worsening risk of new AF development. Similarly, another study by Lee et al. [11] has found 46% relative risk of developing AF in patients with liver cirrhosis. In comparison to our study, they did not find AF to be significantly associated with all-cause mortality. It is pertinent to mention here that Lee et al. primarily enrolled patients with various stages of cirrhosis while our study exclusively focused on ESLD cohort which is comparatively more sicker and morbid and that may explain difference in mortality between both studies. In another study on ESLD patients undergoing liver transplantation [12], the occurrence of peri-procedural AF was associated with worsened mortality (HR 5.097, 95% CI 2.189-11.86). In our national cohort of ESLD patients, we have demonstrated that AF is associated with worse in-patient survival and that difference persists despite accounting for confounding variables. We also demonstrated that AF is an independent predictor of mortality in ESLD patients.

The strong association of worse outcomes of ESLD patients with AF poses unique management challenges. Stroke is a leading cause of mortality and disability in AF patients and anti-coagulation is often recommended to mitigate those risks [13,14]. The utilization of anti-coagulation can be especially challenging in ESLD patients due to increased bleeding risk associated with platelet dysfunction and esophageal varices [15]. Additionally, there are studies showing increased propensity of hemorrhagic stroke in ESLD patients and that risk in some cases exceeds those of ischemic stroke [16,17]. Our dataset, unfortunately, is not designed to ascertain causes of mortality but whether embolic or bleeding events contributed to poor outcomes needs further studies. Additionally, the association of worse mortality in ESLD patients with AF also calls into question measures to screen for AF in this patient population. Timely detection of AF and subsequent implementation of relevant therapeutic measures could result in improved outcomes in ESLD patients.

Limitations

NIS is an administrative claim-based database that uses ICD-9-CM codes for diagnosis that may be subjected to error. The hard clinical points such as liver cirrhosis and mortality are, however, less prone to error. There are no well-defined ICD-9-CM codes for ESLD and we have used Goldberg's third algorithm for stratifying these patients as mentioned in methods section. This method yields a positive predictive value of about 89.3% for ESLD but it is still plausible that some patients with ESLD may not have been captured using this methodology. NIS collects data on in-patient discharges and each admission is registered as an independent event. It is possible that same patient may have more than one subsequent admission over time. NIS samples are not designed to follow patients longitudinally so long-term outcomes could not be assessed from

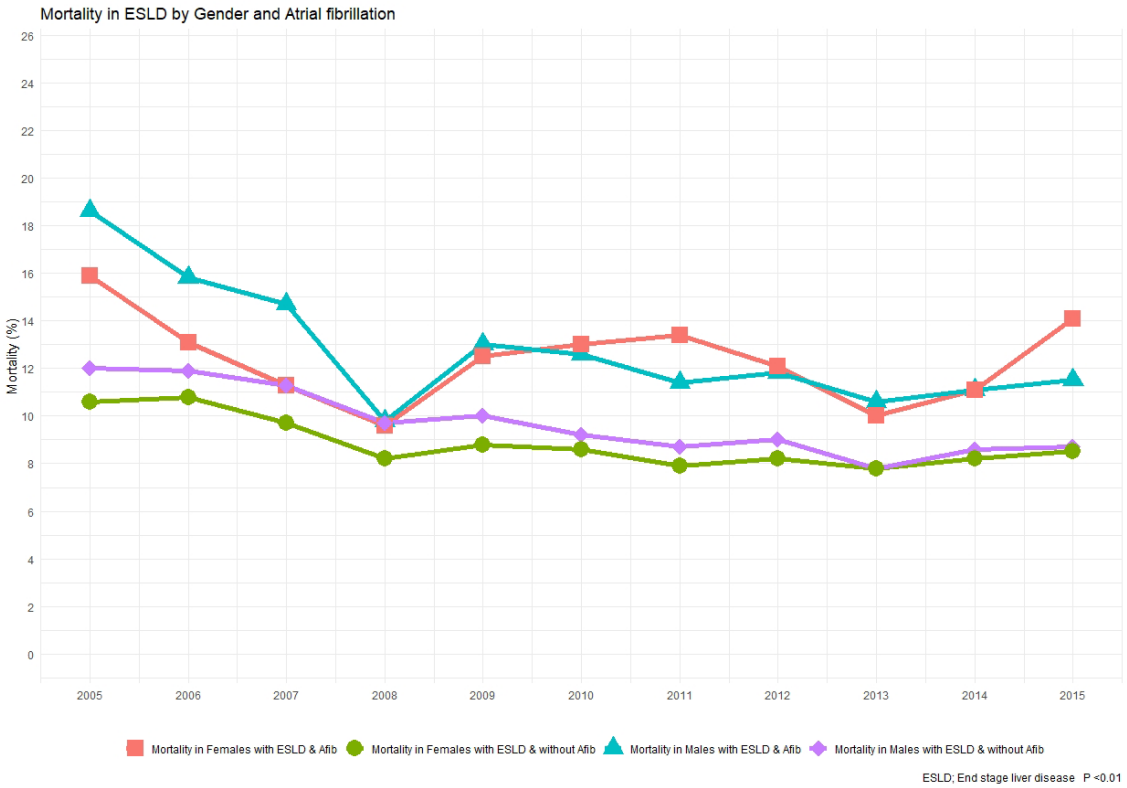

Figure 3: **Mortality in end stage liver disease by gender and atrial fibrillation over study years**

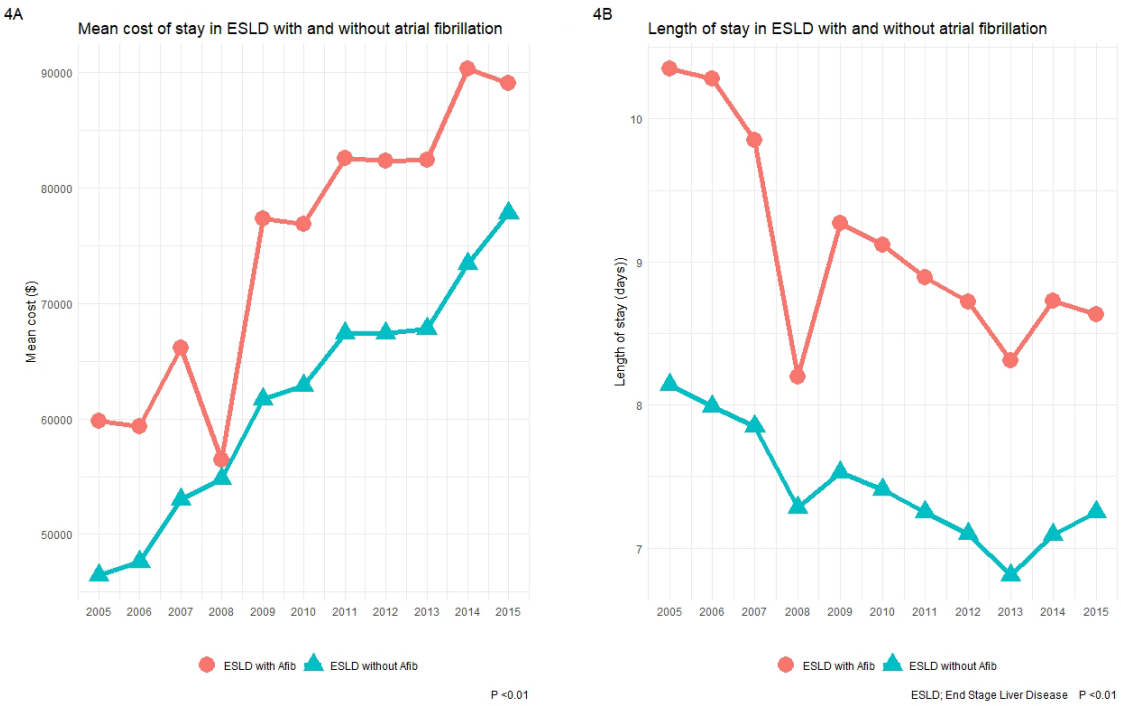

Figure 4: **Mean cost of hospitalization and length of stay over our study period**

Table 1: **Baseline characteristics of the study population**

Variable	Decompensated CLD† patients without atrial fibrillation (n=277,101)	Decompensated CLD† patients with atrial fibrillation (n=32,858)	All Decompensated CLD† patients (n=309959)	P value
Age (mean [SD]) years	58.14(12)	68.46(11.8)	59.23(12.4)	<0.01
Female	104775(37.8%)	11498(35%)	116273(37.5%)	<0.01
Race				
Caucasian	161236(65%)	21996(73.9%)	183232(66%)	<0.01
African American	25435(10.3%)	2895(9.7%)	28330(10.2%)	
Hispanics	44713(18%)	3215(10.8%)	47928(17.3%)	
Asian or Pacific Islander	5431(2.2%)	722(2.4%)	6153(2.2%)	
Native American	3532(1.4%	188(0.6%	3720(1.3%)	
Medical comorbidity				
Acquired immune deficiency syndrome	1920(0.7%)	80(0.2%)	2000(0.6%)	<0.01
Alcohol abuse	108711(39.2%)	8564(26.1%)	117275(37.8%)	<0.01
Anemia (chronic blood loss)	13485(4.9%)	1261(3.8%)	14746(4.8%)	<0.01
Anemia (Deficiency anemia)	83965(30.3%)	11119(33.8%)	95084(30.7%)	<0.01
Collagen vascular diseases	5393(1.9%)	644(2%)	6037(1.9%)	0.865
Congestive heart failure	25819(9.3%)	10260(31.2%)	36079(11.6%)	<0.01
Chronic pulmonary disease	48075(17.3%)	8940(27.2%)	57015(18.4%)	<0.01
Coagulopathy	107493(38.8%)	10294(31.3%)	117787(38%)	<0.01
Diabetes uncomplicated	70187(25.3%)	9821(29.9%)	80008(25.8%)	<0.01
Diabetes with chronic complications	16417(5.9%)	2839(8.6%)	19256(6.2%)	<0.01
Drug abuse	20523(7.4%)	993(3%)	21516(6.9%)	<0.01
Hypertension (combine uncomplicated and complicated)	111152(40.1%)	17685(53.8%)	128837(41.6%)	<0.01
Hypothyroidism	27026(9.8%)	5408(16.5%)	32434(10.5%)	<0.01
Lymphoma	2120(0.8%)	366(1.1%)	2486(0.8%)	0.11
Fluid and electrolyte disorders	125123(45.2%)	15859(48.3%)	140982(45.5%)	<0.01
Metastatic cancer	5567(2%)	594(1.8%)	6161(2%)	0.13
Neurological disorders	18870(6.8%)	2108(6.4%)	20978(6.8%)	<0.12
Obesity	22290(8)	3912(11.9%)	26202(8.5%)	<0.01
Peripheral vascular disorders	10755(3.9%)	2998(9.1%)	13753(4.4%)	<0.01
Pulmonary circulation disorders	8098(2.9%)	2969(9.0%)	11067(3.6%)	<0.01
Renal failure	47511(17.1%)	11568(35.2%)	59079(19.1%)	<0.01
Solid tumor without metastasis	13274(4.8%)	1380(4.2%)	14654(4.7%)	<0.01
Peptic ulcer disease	224(0.1%)	26(0.1%)	250(0.1%)	0.918
Valvular disease	9236(3.3%)	4007(12.2%)	13243(4.3%)	<0.01
Weight loss	35185(12.7%)	4209(12.8%)	39394(12.7%)	0.564
Associated diagnosis				
Acidosis	27135(9.8%)	3332(10.1%)	30467(9.8%)	0.11
Acute Myocardial Infraction	4174(1.5%)	982(3%)	5156(1.7%)	<0.01
Cardiogenic shock	920(0.3%)	452(1.4%)	1372(0.4%)	<0.01
Septic shock	14222(5.1%)	2331(7.1%)	16553(5.3%)	<0.01
Hepatorenal syndrome	15801(5.7%)	1729(5.3%)	17530(5.7%)	0.07
Hepatopulmonary syndrome	452(0.2%)	44(0.1%)	496(0.2%)	0.210
Hyponatremia	55730(20.1%)	6581(20%)	62311(20.1%)	0.722
Cardiac arrest	2656(1%)	561(1.7%)	3217(1%)	<0.01
				<0.01
Hospital Control and or funding				
Government or Private	25427(9.2%)	2539(7.7%)	27966(9%)	<0.01
Government, non-federal	115121(41.5%)	15483(47.1%)	130604(42.1%)	
Private, not-for-profit	32327(11.7%)	3797(11.6%)	36124(11.7%)	
Private, investor-owned	4281(1.5%)	508(1.5%)	4789(1.5%)	
Private, either not-for-profit or investor-owned	25427(9.2%)	2539(7.7%)	27966(9%)	

Hospital Location				
Rural	**23296(8.4%)**	**2823(8.6%)**	**26119(8.4%)**	**0.34**
Urban Non-teaching	**101223(36.5%**	**12801(39%)**	**114024(36.8%)**	
Urban Teaching	**152582(55.1%)**	**17234(52.4%)**	**169816(54.8%)**	
Bed size of the hospital				
small	**32833(11.8%)**	**4062(12.4%)**	**36895(11.9%)**	**0.39**
medium	**68367(24.7%)**	**8301(25.3%)**	**76668(24.7%)**	
large	**175901(63.5%)**	**20495(62.4%)**	**196396(63.4%)**	
Primary payer				
Medicare	**115370(41.7%)**	**22830(69.6%)**	**138200(44.7%)**	**<0.01**
Medicaid	**63817(23.1%)**	**3285(10%)**	**67102(21.7%)**	
Private insurance	**64509(23.3%)**	**5029(15.3%)**	**69538(22.5%)**	
Self-pay	**19293(7%)**	**825(2.5%)**	**20118(6.5%)**	
No charge	**2097(0.8%)**	**124(0.4%)**	**2221(0.7%)**	
other	**11418(4.1%)**	**725(2.2%)**	**12143(3.9%)**	
Region no. (%)				
Northeast	**79265(28.6%)**	**10017(30.5%)**	**89282(28.8%)**	**<0.01**
Midwest	**124166(44.8%)**	**13657(41.6%)**	**137823(44.5%)**	
South	**45619(16.5%)**	**5833(17.8%)**	**51452(16.6%)**	
West	**28051(10.1%)**	**3351(10.2%)**	**31402(10.1%)**	
Median household income no. (%)				
0–25th percentile	**87671(32.7%)**	**9096(28.3%)**	**96767(32.2%)**	**<0.01**
26–50th percentile	**70412(26.3%)**	**8211(25.6%)**	**78623(26.2%)**	
51–75th percentile	**62278(23.2%)**	**7859(24.5%)**	**70137(23.4%)**	
76–100th percentile	**47783(17.8%)**	**6931(21.6%)**	**54714(18.2%)**	
†chronic liver disease				

Table 2: **Outcomes and resource utilization of the study cohort**

Variables	ESLD† patients without atrial fibrillation (N=277,101)	ESLD† patients with atrial fibrillation (n=32, 858)	All ESLD† patients (n=309,959)	P value
Died at discharge	25441(9.2%)	4046(12.3%)	29487(9.5%)	<0.01
Discharge Disposition of surviving patients, No. (%)				
Routine/self-care	150811(60%)	12001(41.7%)	162812(58.1%)	<0.01
Short-term hospital	10822(4.3%)	1260(4.4%)	12082(4.3%)	
Another type of facility	46192(18.4%)	8907(30.9%)	55099(19.7%)	
Home Health Care	37756(15%)	6212(21.6%)	43968(15.7%)	
Resource utilization, Mean (SD), No. (%)				
Length of stay, mean (SD), days	7.36(8.9)	9(9.9)	7.54(9.1)	<0.01
Cost of hospitalization-mean (SD), $	63,403(111050)	78,246(124777)	64,972 (112673)	<0.01
Procedures during stay				
Left heart catheterization	2571(0.9%)	819(2.50%)	3390(1.1%)	<0.01
Undergoing Per Cutaneous Coronary intervention	659(0.2%)	150(0.5%)	809(0.3%)	<0.01
Vasopressin	3097(1.1%)	646(2%)	3743(1.2%)	<0.01
Hemodialysis	18667(6.7%)	4219(12.8%)	22886(7.4%)	<0.01
Ventilator	26963(9.7%)	3777(11.5%)	30740(9.9%)	<0.01
Gastrostomy	2039(0.7%)	406(1.2%)	2445(0.8%)	<0.01
Tracheostomy	2533(0.9%)	447(1.4%)	2980(1%)	<0.01
† End stage liver disease				

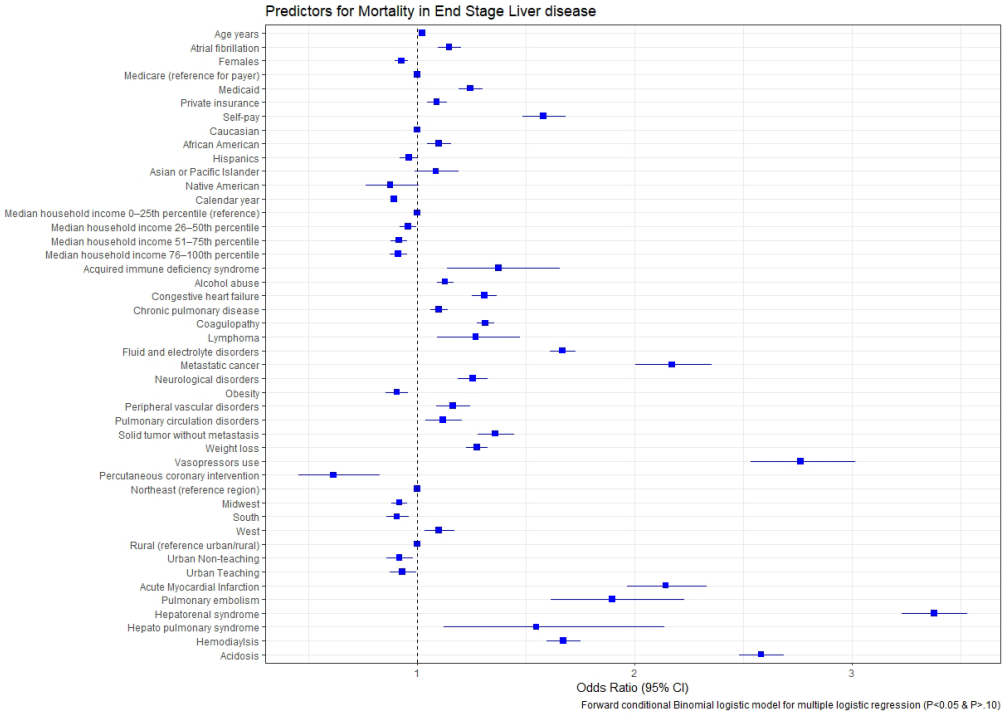

Figure 5: **Predictors of mortality in end stage liver disease patients**

the present dataset. Additionally, data on AF management is lacking from NIS which have important implications on conclusions drawn from the study.

Conclusion

Our study shows AF to be associated with worse outcomes in ESLD patients. It is therefore imperative that treating physicians should have a strong clinical suspicion for AF in this specific patient cohort as timely AF detection could result in improved outcomes.

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Supplemental Data

Table 1S: Baseline characteristics after propensity matching

Variable	DCLD† without Atrial Fibrillation (n=28,229)	DCLD† with Atrial Fibrillation (n=28,229)	P value
Age (mean [SD]) year	61.58(12.39)	68.46(11.81)	
Female	10006(35.4%)	9900(35.1%)	0.349
Race			
Caucasian	20912(74.1%)	20989(74.4%)	0.41
African American	2842(10.1%)	2748(9.7%)	
Hispanics	2944(10.4%)	2972(10.5%)	
Asian or Pacific Islander	671(2.4%)	660(2.3%)	
Native American	139(0.5%)	167(0.6%)	
AHRQ co morbidities			
Anemia (chronic blood loss)	1302(4.6%)	1060(3.8%)	<0.01
Anemia (Deficiency anemia)	9594(34%)	9594(34%)	0.05
Collagen vascular diseases	653(2.3%)	557(2%)	0.05
Congestive heart failure	8502(30.1%)	8502(30.1%)	0.03
Chronic pulmonary disease	7805(27.6%)	7805(27.6%)	0.5
Coagulopathy	9014(31.9%)	9014(31.9%)	0.52
Diabetes, uncomplicated	8762(31%)	8762(31%)	0.89
Diabetes with chronic complications	2372(8.4%)	2372(8.4%)	0.78
Hypertension (combine uncomplicated and complicated)	15832(56.1%)	15832(56.1%)	0.01
Hypothyroidism	4822(17.1%)	4822(17.1%)	0.8
Lymphoma	265(0.9%)	318(1.1%)	0.03
Fluid and electrolyte disorders	13957(49.4%)	13957(49.4%)	0.53
Metastatic cancer	608(2.2%)	608(2.2%)	<0.01
Obesity	3481(12.3%)	3430(12.2%)	0.51
Peripheral vascular disorders	2546(9%)	2532(9%)	0.86
Renal failure	10110(35.8%)	10110(35.8%)	0.6
Solid tumor without metastasis	1244(4.4%)	1225(4.3%)	0.7
Valvular disease	3135(11.1%)	3497(12.4%)	<0.01
Associated diagnosis			
Acute Myocardial Infraction	735(2.6%)	850(3%)	<0.01
Cardiogenic shock	364(1.3%)	399(1.4%)	0.2
Septic shock	2027(7.2%)	2050(7.3%)	0.70
Hepato renal syndrome	1775(6.3%)	1506(5.3%)	<0.01
Hepato Pulmonary syndrome	63(0.2%)	41(0.1%)	0.03
syndrome			
Acidosis	2980(10.6%)	2909(10.3%)	0.33
Hospital Location			
Rural	2201(7.8%)	2264(8%)	0.03
Urban Non-teaching	11053(39.2%)	11305(40%)	
Urban Teaching	14974(53%)	14660(51.9%)	
Bedside of the hospital			
Small	3428(12.1%)	3469(12.3%)	0.15
Medium	7012(24.8%)	7191(25.5%)	
Large	17788(63%)	17569(62.2%)	
Region			
Northeast	7999(28.3%)	8369(29.6%)	<0.01
Midwest	12177(43.1%)	11433(40.5%)	
South	5457(19.3%)	5566(19.7%)	
West	2595(9.2%)	2861(10.1%)	

Median household income no. (%)			
0–25th percentile	**8249(29.2%)**	**8109(28.7%)**	**0.2**
26–50th percentile	**7279(25.8%)**	**7165(25.4%)**	
51–75th percentile	**6724(23.8%)**	**6873(24.3%)**	
76–100th percentile	**5976(21.2%)**	**6082(21.5%)**	
† Decompensated Chronic Liver disease			

Table 2S: **Outcomes after propensity score matching**

Hospital Outcomes, No. (%)	ESLD without atrial fibrillation (28228)	ESLD with atrial fibrillation (28229)	P value
Died at discharge	3051(10.8%)	3457(12.2%)	P<0.01
Resource utilization, Mean (SD)			
Length of stay, mean (SD), days	8.11(9.6)	9.03(9.63)	<0.01
Mean cost	73408(128412)	80792(128241)	<0.01
PEG	248(0.9%)	357(1.3%)	<0.01
Tracheostomy	327(1.2%)	389(1.4%	0.02
†End Stage Liver Disease			

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Contact Force-Guided Ablation Reduced Poor Contact Segments and Improved Acute Reconnection in Patients with Atrial Fibrillation

So-Ryoung Lee[1,], Hyoung-Seob Park[2,*], Eue-Keun Choi[1], Soonil Kwon[1], Youngjin Cho[3], Il-Young Oh[3], Seil Oh[1], Seongwook Han[2]*

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea.
[2]Division of Cardiology, Department of Internal Medicine, Keimyung University, Dongsan Medical Center, Daegu, Republic of Korea.
[3]Department of Internal Medicine, Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Republic of Korea.
*The First Two Authors Equally Contributed.

Abstract

Background: There is a paucity of information regarding whether contact force (CF)-guided ablation improves the outcomes of pulmonary vein isolation (PVI) in patients with atrial fibrillation (AF) by achieving more optimal contact. We sought to assess whether real time CF-guided ablation has an impact on ablation parameters and acute pulmonary vein reconnection (PVR).

Methods: Left or right PVs were randomized to either CF-guided or blinded groups, and the order of CF blindness: CF-guided left PV/CF-blinded right PV, CF-blinded left PV/CF-guided right PV, CF-guided right PV/CF-blinded left PV, and CF-blinded right PV/CF-guided left PV groups. We compared CF parameters and acute PVR between segments ablated by CF-guided and CF-blinded strategies.

Results: Sixty patients with drug refractory symptomatic AF were included (paroxysmal AF 73%). CF-guided segments did not show significant differences in CF parameters compared to CF-blinded segments. However, CF-guided segments showed fewer segments with mean CF value <5 g than CF-blinded segments (4.3% vs. 12.4%, p<0.001). Forty-two patients showed acute PVR in 92 segments (8.5%). CF-guided PV segments showed lower acute PVR rate than CF-blinded segments (5.9% vs. 11.1%, p=0.011).

Conclusions: CF-guided ablation could reduce acute PVR after PVI by decreasing the number of segments with poor contact rather than increasing the mean CF during ablation. Better contact guided by CF information might help in improving the results of PVI. Further investigation will be needed to identify the association between the difference in acute reconnection and the long-term outcomes.

Introduction

Pulmonary vein isolation (PVI) is a fundamental procedure in atrial fibrillation (AF) ablation.[1] Permanent PVI is an important goal to improve outcomes after AF ablation and is related to the quality of energy delivery and transmural lesion formation. Contact between the tissue and ablation catheter is important when creating a transmural lesion, and ultimately creating a durable lesion.[2-4] Recent advancements in technology that can measure the contact between tissue and ablation catheter, represented as contact force (CF), could provide the operator with an accurate quantitative assessment of tissue contact in real time.[2,3]

Recent clinical studies using the CF reported that low contact force predicted PV reconnection (PVR).[5,6] These randomized clinical trials have been conducted to compare PVI using CF sensing catheters with PVI using non-CF sensing catheters.[7,8] These studies showed less AF recurrence or lower PVR rate and more optimal CF parameters in the CF-guided group. However, non-CF sensing catheters used in control group might have different catheter profiles compared to CF-sensing catheters, and there is no information of CF in the control group. Several studies used CF-sensing catheter to compare CF-blinded and CF-guided ablation.[9-11] CF-guided ablation showed a lower acute PVR rate, shorter procedure time, and additional touch-up ablation. Although the patients were randomized to either CF-guided or blinded group, there is still a possibility of patient bias. To avoid the patient bias, we randomized PVs, instead of patients, to CF-guided or CF-blinded ablation. We also randomized the order of

Key Words

Contact Force; Acute Pulmonary Vein Reconnection; Pulmonary Vein Isolation; Atrial Fibrillation

Corresponding Author
Eue-Keun Choi, MD, PhD
Department of Internal Medicine, Seoul National University Hospital
101 Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea.
Or Seongwook Han, MD, PhD
Department of Internal Medicine, Keimyung University, Dongsan Medical Center
56 Dalsungro Junggu, Daegu, 41931, Republic of Korea

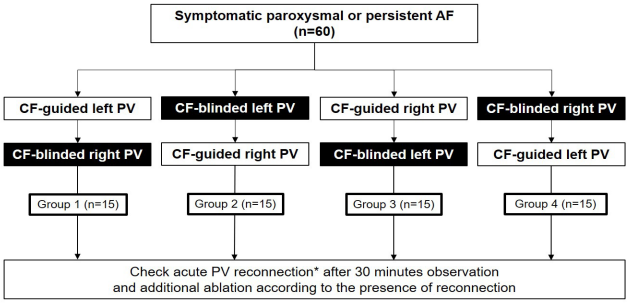

Figure 1: **Study flow.**

*acute pulmonary reconnection was defined as having spontaneous early reconnection (ER) of the left atrium to PV or dormant conduction (DC). If there was ER, additional ablation was performed. In the absence of ER, DC was assessed by intravenous adenosine bolus injection

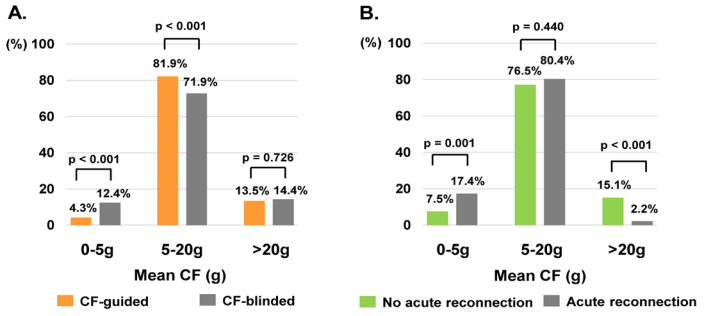

Figure 2: **Distribution of mean CF of segments based on CF-guided strategies (A) and acute PV reconnection (B) .**

*Denotes statistical significance p <0.05. All values are absolute.

CF blindness to avoid the effect of prerequisite learning of CF. The aim of this study, therefore, was to evaluate in a randomized fashion within the same patient with AF, the relationship between CF and acute PVR during catheter ablation.

Methods

This study is a multicenter prospective randomized controlled trial (NCT02924181). Four experienced electrophysiologists in 3 tertiary hospitals performed the procedure. Drug refractory symptomatic AF patients aged between 20 and 80 years were consecutively enrolled. Patients who had undergone previous PVI for AF were excluded. Patients with left atrium (LA) diameter > 50 mm were also excluded. The study protocol was approved by the institutional review boards at each institution (1505-020-669), and informed consent was obtained from all individual participants included in the study. 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 (as revised in Fortaleza, Brazil, October 2013) or comparable ethical standards.

Pulmonary vein isolation procedure

Under conscious sedation, we performed double transseptal puncture and introduced two non-steerable long sheaths (SL1) into the LA Steerable sheath was not used in this study. Three-dimensional electroanatomic mapping of the LA and PVs was performed using the CARTO 3 system (BiosenseWebster, Inc., Diamond Bar, CA, USA). Using a Thermocool SmartTough irrigated CF-sensing RF ablation catheter (BiosenseWebster, Inc., Diamond Bar, CA, USA), a circumferential lesion set was created for PVI. Power was limited to 25 to 35 W at anterior and 20 to 30 W at posterior sites, and minimum ablation time per point was 20 seconds. Among different centers and operators, general procedure characteristics were applied in the same manner. Steerable sheath was not used in this study.

Study design and primary outcomes

To compare the CF-guided and CF-blinded ablation purer, we randomized two different strategies within each patient. Left or right PVs were randomized to either CF-guided or blinded, and the order of CF blindness was also randomized. Therefore, 4 different PVI protocols were identified: CF-guided left PV/CF-blinded right PV, CF-blinded left PV/CF-guided right PV, CF-guided right PV/CF-blinded left PV, and CF-blinded right PV/CF-guided left PV (Figure 1). Each patient received PVI according to the order of randomization. After 30 minutes observation after PVI, spontaneous early reconnection (ER) of the LA to PV was evaluated. If there was ER, additional ablation was performed. In the absence of ER, dormant conduction (DC) was assessed by intravenous adenosine bolus injection (6 to 12 mg intravenous bolus). If there was DC, additional ablation was performed. The site of ER and DC was identified by 18 predefined segments (Supplementary Figure 1). Then, we performed an AF induction test with high-dose isoproterenol and ended the procedure or performed additional linear ablation in patients with persistent AF. The primary outcome was acute PVR including ER or DC in each segment.

Safety outcome and long-term success during follow-up

The safety endpoint was defined as any procedure-related serious adverse events (e.g., tamponade, pericarditis, pericardial effusion, and perforation), which occurred during procedure or within 7 days following the index procedure or PV stenosis or atrioesophageal fistula which occurred >7 days post-procedure. Patients were followed up and evaluated with outpatient visits at 1, 3, 6, 9, and 12 months after the index ablation. Long-term ablation success was defined as freedom from recurrence of AF, atrial tachycardia (AT), or atrial flutter (AFL) at 12 months after the index procedure with the exclusion of the 3-month blanking period.

CARTO Visitag module

During CF-guided ablation, the CARTO Visitag module (Biosense Webster, Diamond Bar, CA, USA) displayed real time ablation parameters including power, impedance, ablation time, and CF at each ablation location, and operators targeted the CF from 10 to 20 g. Only CF information was not provided during CF-blinded ablation. Each ablation point was marked automatically on the 3-dimensional LA map with the following configuration: in the CF-guided PVs, a minimum of 7 seconds, stability of 2.5 mm, and 50% of ablation time higher than 7 g of force, in the CF-blinded PVs, only the stability and time criteria were applied. The maximal interlesion

Table 1: Baseline characteristics of the study patients and procedural parameters

	Total (n=60)	Group 1 (n=15)	Group 2 (n=15)	Group 3 (n=15)	Group 4 (n=15)	p-value
Age (years)	58.1±8.6	56.2±7.9	58.8±10.5	56.4±8.3	61.1±6.9	0.216
Gender (men)	37 (61.7)	8 (53.3)	13 (86.7)	11 (73.3)	5 (33.3)	0.014
Body mass index (kg/m²)	25.1±2.7	24.7±3.2	25.1±2.4	24.3±2.4	26.3±2.7	0.273
Paroxysmal AF	44 (73.3)	11 (73.3)	11 (73.3)	8 (53.3)	14 (93.3)	0.154
Hypertension	19 (31.7)	5 (33.3)	5 (33.3)	6 (40.0)	3 (20.0)	0.644
Diabetes	8 (13.3)	3 (20.0)	1 (6.7)	0 (0)	4 (26.7)	0.120
History of stroke	2 (3.3)	0 (0)	0 (0)	2 (13.3)	0 (0)	NA*
CHA_2DS_2-VASc score	0.9±0.9	0.8±1.0	0.7±0.7	0.9±1.1	1.0±0.9	0.796
LVEF (%)	61.0±5.9	61.1±6.4	61.1±7.5	61.7±4.2	60.0±5.5	0.941
LA size (mm)	42.2±4.4	41.1±3.6	43.2±4.0	41.5±5.6	43.0±4.1	0.353
Number of ablation points for PVAI	180.0±42.7	182.7±47.6	192.0±47.1	179.2±41.3	166.1±33.8	0.552
Additional ablation						
Cavo-tricuspid isthmus	16 (26.7)	4 (26.7)	5 (33.3)	4 (26.7)	3 (20.0)	0.958
LA roof line	9 (15.0)	3 (20.0)	3 (20.0)	2 (13.3)	1 (6.7)	0.808
LA anterior line	1 (1.7)	0 (0)	0 (0)	1 (6.7)	0 (0)	NA*
RA superolateral focal	1 (1.7)	0 (0)	0 (0)	0 (0)	1 (6.7)	NA*
Total procedure time (minutes)	237.0±67.6	251.6±63.0	268.0±87.1	200.7±40.1	227.9±57.7	0.082
Ablation time (minutes)	81.5±28.2	89.8±35.6	85.5±25.9	76.6±23.2	74.0±26.1	0.606
Fluoroscopic time (minutes)	28.3±12.3	31.1±17.8	30.5±12.4	28.2±8.5	23.5±7.3	0.239

Continuous variables, mean ± standard deviation, Categorical variables, n (%)
* P-value calculation was not available due to small number.
Abbreviation: AF, atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; NA, not applicable; PVAI, pulmonary vein antrum isolation; RA, right atrium.

Table 2: Comparison of ablation parameters between CF-guided and CF-blinded segments

Ablation parameters	CF-guided segments (n=540)	CF-blinded segments (n=540)	p-value †
Number of ablation points	10.4±6.6	9.6±5.8	0.120
Minimum force (g)	7.4±4.8	7.3±5.4	0.812
Maximum force (g)	20.5±9.3	21.4±14.2	0.313
Mean force (g)	12.7±6.0	12.7±7.1	0.942
5g>	23 (4.3%)	67 (12.4%)	
5-20g	442 (81.9%)	388 (71.9%)	<0.001
20g<	73 (13.5%)	78 (14.4%)	
Minimum FTI (gs)	98.4±85.1	100.3±86.2	0.829
Maximum FTI (gs)	456.9±307.9	457.5±337.8	0.995
Mean FTI (gs)	228.5±139.0	224.9±149.1	0.804
Impedance drop (ohm)	8.5±4.1	8.4±4.2	0.687
Temperature (°C)	37.8±2.4	37.9±2.5	0.484
Ablation time by each point (sec)	18.2±7.1	18.2±6.7	0.983
Total ablation time (sec)	186.9±142.9	174.9±115.9	0.215

Mean ± standard deviation
†P-value by generalized linear mixed model

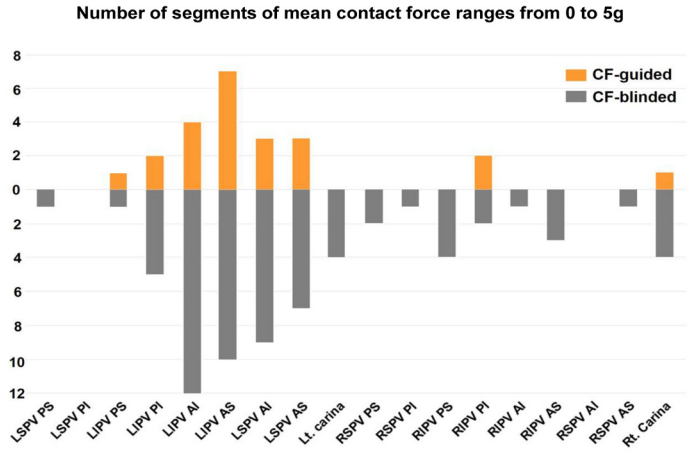

Figure 3: Distribution of segments with mean CF value less than 5 g according to CF-guided or CF-blinded ablation

distance between neighboring lesion was ≤4 mm. Retrospectively, the ablation parameters were extracted for analysis at each ablation point, including average CF, force time integral (FTI), ablation time, temperature, power, and delta impedance. Ablation parameters were analyzed by each predefined PV segment.

Statistical analysis

Categorical variables were presented as proportions and compared using Fisher's exact chi-square test. The Kolmogorov-Smirnoff test was performed to evaluate normal distribution for continuous variables. Normally distributed continuous variables were presented as mean ± standard deviation (SD) and compared using the independent t-test. Variables with non-normal distributions were compared with the Kruskal-Wallis test. We applied generalized linear mixed models for binary outcome (reconnected and non-reconnected) to compare the effect of ablation strategies (CF-guided and CF-blinded) and ablation parameters.[9] A two-tailed P<0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 20, IBM SPSS Statistics, IBM Corp, Armonk, NY).

Results

Baseline characteristics of study populations and procedural parameters

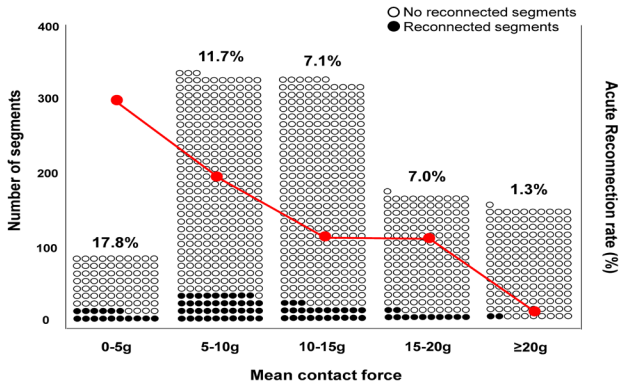

Figure 4: Distribution of segments according to mean CF and acute reconnection

From September 2015 to October 2016, a total of 60 patients (62% men; mean age 58 ± 9 years) were included in the analysis. Thirty patients were allocated to left PVs CF-guided and right PVs CF-blinded groups and 30 patients were allocated to right PVs CF-guided and left PVs CF-blinded groups. Baseline characteristics are summarized in Table 1. All PVs were completely isolated during the procedures.

Comparison of the ablation parameters, differences in contact force-guided versus contact force-blinded segments

Overall, CF-guided segments did not show significant differences in the CF parameters, the impedance drop, and total ablation time compared to CF-blinded segments (Table 2). However, CF-guided segments showed fewer segments with mean CF value less than 5 g than CF-blinded segments (4.3% vs. 12.4%, p<0.001) (Figure 2A). The distribution of segments with mean CF value less than 5 g according to CF-guided or CF-blinded ablation is summarized in Figure 3. Left inferior PV (LIPV) anterior and left superior PV (LSPV) anterior showed higher incidence of segments with mean CF value less than 5 g in CF-blinded group compared to CF-guided group (16.7% vs. 6.7%, p=0.016). For each segment, the mean and minimum CF, mean FTI, and ablation time are shown in Supplementary Figures 2 and 3.

Acute pulmonary vein reconnection

Forty-two patients (70%) demonstrated at least one ER or DC. Acute reconnection was observed in 92 segments of total 1080 segments (8.5%): ER in 55 segments (5.1%), DC in 28 segments (2.6%) and both ER and DC in 9 segments (0.8%). CF-guided segments showed a significantly lower acute reconnection rate compared to CF-blinded segments (5.9% vs. 11.1%, p=0.011). The CF-blinded group showed higher acute reconnection in RIPV PS segment compared to CF-guided group (20% vs. 0%, p=0.024). Acute PVR was more frequently observed in superior ridge (LSPV AI and LSPV AS) and left carina compared to other segments (16.7% vs. 6.9%, p<0.001). The distribution of acute reconnection by different regions according to CF-guided or CF-blinded is presented in Supplementary Figure 4.

Effect of contact force learning and the order of PV antrum isolation on contact force parameters and acute reconnection

We analyzed the segments ablated by CF-blinded according to CF learning: group A with CF-blinded ablation after CF-guided ablation (groups 1 and 3), and group B with CF-blinded ablation before CF-guided ablation (groups 2 and 4). There was no significant difference in CF parameters between the two groups except for ablation time (Supplementary Table 2). The mean ablation time per point in group A was longer than that in group B (18.8 vs. 17.5 sec, p=0.032). The proportion of segments with less than 5 g was not different between two groups (14.1% vs. 10.7%, p=0.296). There was no significant difference in acute reconnection rate during CF-blinded ablation between CF experienced and non-experienced group (13.3% vs. 8.9%, p=0.100).

We analyzed the effect of the order of PVI on CF parameters and acute reconnection. Groups 1 and 2 had started PV ablation from left

sided PV, whereas groups 3 and 4 had started from right sided PV ablation first. There was no significant difference in CF parameters between right side first and left side first groups. Also, there was no significant difference in the acute reconnection between right side first and left side first groups (7.4% vs. 9.6%, p=0.230).

Determinants of acute pulmonary vein reconnection, differences between "non- reconnected" and "reconnected" segments

We compared the ablation parameters between segments with and without reconnection (Supplementary Table 1). The mean CF was significantly lower in segments with acute reconnection compared to those without reconnection (9.7 ± 4.9 vs. 13.0 ± 6.6 g, p<0.001). Reconnected segments showed lower mean impedance drop and longer total ablation time compared to those without reconnection. Reconnected segments showed a higher incidence of segments with mean CF values less than 5 g than those without reconnection (17.4% vs. 7.5%, p=0.001, Figure 2B). The distribution of segments according to mean CF are depicted in Figure 4. Also, the acute reconnection rate according to the mean CF of each segment is summarized. The most common mean CF was 5 to 10 g (333 segments, 31%), followed by a mean CF of 10 to 15 g (326 segments, 30 %). Segments with a mean CF less than 5 g were least common, but the acute reconnection rate in this group was the highest (17.8%), whereas the segments with mean CF more than 20 g showed the lowest acute reconnection rate (1.3%). We found that there was an inverse relationship between the mean CF and acute reconnection rate.

Safety outcome and long-term success during follow-up

There were no procedure-related adverse events during study period. There was no pericardial effusion, cardiac tamponade, deaths, cerebrovascular accident, thromboembolism, atrioesophageal fistula, myocardial infarction, or PV stenosis that occurred within the study period. Overall, the 1-year freedom from AF/AT/AFL after a single procedure was 68.3%. Nineteen patients (32%) showed late recurrence after the 3-month blanking period. Group 1 showed the highest recurrence of AF/AT/AFL, but there was no significant difference in late recurrence among the 4 groups (46.7% in group 1, 33.3% in group 2, 13.3% in group 3, and 33.3% in group 4, log-rank p=0.337, Figure 5). Also, there was no significant difference in the recurrence of AF/AT/AFL according to the order of ablation (left PV first or right PV first) or the order of blindness (CF-guided first or CF-blinded first).

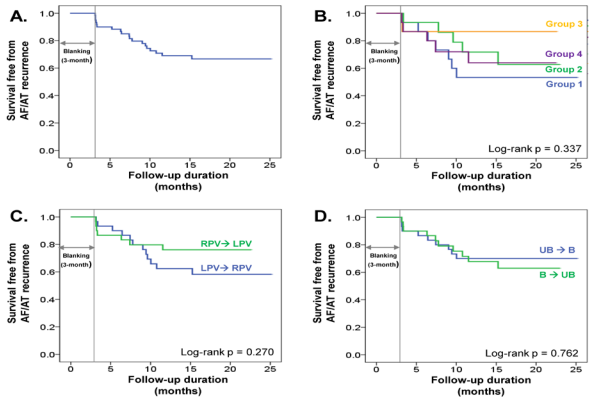

Figure 5: AF/AT free survival according to ablation strategies

A, Total population. B, 4 groups according to randomization. C, order of ablation of right-sided or left-sided PV first. D, order of ablation of CF blindness

Discussion

This was a prospective randomized clinical study to compare the impact of CF monitoring on CF parameters and acute PVR in patients with drug-refractory AF. We found that (1) CF-guided PV isolation did not improve the average CF parameters, but showed fewer segments with mean CF less than 5 g, which resulted in having less acute reconnection than that in the CF-blinded group; (2) the prerequisite learning of real time CF did not have a significant impact on the CF-blinded ablation; and (3) there was an inverse relationship between the mean CF and the acute reconnection rate.

Previous studies reported diverse rates of acute PVR from 33 to 93%, and the importance of detecting acute PVR and re-isolation of reconnected segments to reduce AF recurrence.[12-14] The mechanism of PVR is suggested to be associated with non-permanent myocardial lesion formation, mainly related to tissue edema.[15] Therefore, it is important to deliver enough energy during the first time RF application to minimize the effect of tissue edema. Contact between the ablation catheter and tissue might be the key factor affecting the lesion size, because the passage of current into the target tissue would be influenced by this contact.[16] The real-time feedback of CF information is also important to physicians from the perspective of safety, because it could reduce the risk of perforation by avoiding involuntary overcontact.

Contact force-guide ablation strategy and acute pulmonary vein reconnection

The result of this study, that CF-guided PVAI reduced the incidence of acute PVR, is in line with that of previous clinical studies.[7,9,10,17] The reduction of acute PVR in the CF group might be due to the higher mean CF of the CF-guided group than that of the blinded group.[11] It is well known that acute PVR has an inverse correlation with the CF values.[9,18] However, the average CF of experienced operators who are blinded to real time CF values might not be lower because of the tactile feeling and movement on fluoroscopy, which could also give information related to tissue contact to the operators. In contrast to previous papers, the blindness of real time CF does not seem to affect the average of CF of the total ablation procedure. However, we found that the CF-guided ablation showed a lower incidence of segments with less than 5 grams of CF, which has close relationship with acute PVR. Although the optimal CF value to prevent acute PVR has not been standardized, recent guidelines recommend a minimal targeted CF of 5 to 10 g as reasonable, which is consistent with our study results.[19]

Learning effect on contact force parameters during contact force blinded ablation

In this study, prerequisite learning of CF values before CF-blinded ablation was not associated with lower acute PVR rate, since there was no significant difference in CF parameters between CF-blinded segments with and without CF learning. For experienced operator, CF learning immediate before CF-blinded ablation might not

affect procedure characteristics and acute outcome. Previous studies reported that the mean CF values of the right PV were usually higher than those of the left PV, so the order of ablation of the PV might have some confounding effects of next ablation of the PV on the CF parameters. However, we found that the CF parameters were not affected by the order of ablation of the PV.

Sites of acute pulmonary vein reconnection

The common sites of PVR were carina of right PV and ridge of left PV.[9,13,20] These results are consistent with our study results that right and left carina, LSPV AS and AI segments were the common sites of acute PVR. The ridge is known to have a tendency of catheter instability resulting in low CF, which might explain higher incidence of acute PVR than other regions. The optimal CF values to prevent PVR would have regional difference, highest at the bottom of the right PV and posterosuperior right PV segments (22 g) and lowest in the posteroinferior right PV segment.[18] In our study, the segments with less than 5 g were distributed in the left and right carina, and the ridge of left PV. Interestingly, we found that CF-guided ablation could reduce the number of segments with mean CF values less than 5 g, which could improve the acute outcomes of AF ablation.

Effects of contact force on recurrence of atrial fibrillation

In this study, all patients achieved acute procedural success with 100% of targeted PV being successfully isolated during index ablation procedure. After the 3-month blanking period, the 1-year AF/AT free survival was 68.3%, which is in line with previous studies using CF-catheters.[8] Although the acute PVR was reduced in the CF-guided ablation group, clinical outcomes did not significantly improve in the CF-ablation group compared to the blinded group.[11] TOCCASTAR study did not show a benefit on AF-free survival following CF-guided ablation compared to non-CF ablation.[8] However, those who met optimal CF (≥90% ablations with ≥10 g) showed better AF free survival than those who do not (75.9% vs. 58.1%, p=0.018). In this study, we could not evaluate the impact of CF on the recurrence of AF but found that the order of PV isolation and prerequisite learning of CF did not have significant impact of the results of AF ablation.

Study Limitations

First, although we found that the segments with CF-guided ablation showed significantly better outcomes in acute PVR compared to those with CF-blinded ablation, this study included only a small number of patients. Further larger size studies are needed to confirm whether CF-guided PVI shows consistently better efficacy and safety than CF-blinded PVI and to find which factors mostly affect these results. Second, although we randomized the PV, not the patients, to reduce the risk of patient bias, there is still a potential bias of anatomical difference of the left and right PV. However, we also randomized the order of ablation on right-side or left-side PV, and the CF-guided or CF-blinded ablation to reduce the risk of prerequisite learning of CF and anatomical differences of right and left PV. Third, operator bias would be another limitation of this study. We found the experienced operators would be influenced less by the real-time CF feedback. Also, they tried to avoid contacting less than 5g, which did not affect the mean value of CF. We speculate that CF-guided ablation might be more beneficial in less experienced operators. Fourth, according to previous study, larger interlesion distance (≥5 mm) also influenced delete acute PVR.[20] In this study, we achieved interlesion distance less than 4 mm by study protocol. Although interlesion distance is a critical factor for acute PVR, we preemptively controlled larger interlesion distance by prespecified study protocol. Mean interlesion distance of segments with acute PVR was 2.9±0.9 mm. Fifth, the additional ablation to eliminate PVR could have affected the long-term outcomes after ablation. We tried to find the impact of CF-guided ablation on acute PVR rather than to find the long-term recurrence of AF. Sixth, the information of CF parameters can be analyzed only if the points met the criteria of Visitag setting. Therefore, our study results are more appropriate for point-by-point ablation rather than the drag ablation technique. Also, the points which did not meet the criteria of Visitag setting could not be included in this analysis, which could also have affected the results of this study. However, we tried to stabilize the catheter as much as possible to reduce the number of points which do not meet the Visitag setting. Lastly, in this study, we could not evaluate the impact of CF on the long-term recurrence of AF because of the inherent limitation of the study design: allocating unilateral PVs in a patient by ablation strategy according to CF-guided or not, rather than allocating patients who applied CF-guided or not. Also, redo procedures were performed only in selected patients (16.7% of the total study population). Thus, the results that there was no significant difference in the rates of PV reconnection between CF-guided and CF-blinded PVs should be cautiously interpreted (Supplementary Results). Despite these limitations, the difference in acute reconnection may not guarantee the long-term outcomes either AF recurrence or PV reconnection in redo procedure.

Conclusions

CF-guided ablation could reduce acute reconnection after PVI in patients with AF by decreasing the number of segments with poor contact. Better contact guided by CF information might help in improving the outcomes of PVI.

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Link for Supplementary Materials

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The Impact of Atrial Fibrillation on In-Hospital Outcomes in Patients With Acute Myocardial Infarction Complicated by Cardiogenic Shock Undergoing Coronary Revascularization with Percutaneous Ventricular Assist Device Support

Sonu Gupta[1], Rupak Desai[2*], Bishoy Hanna[1]; Abhishek Deshmukh[3], Gautam Kumar[4], Rajesh Sachdeva[1,2,5], Adam E Berman[5]*

[1]Division of Cardiology, Morehouse School of Medicine, Atlanta, GA, USA.
[2]Division of Cardiology, Atlanta VA Medical Center, Decatur, GA, USA.
[3]Division of Cardiology, Mayo Clinic, Rochester, MN, USA.
[4]Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA.
[5]Division of Cardiology, Medical College of Georgia, Augusta University, Augusta, GA,USA.
*Authors share equal contribution to the manuscript.

Abstract

Background: Atrial fibrillation (AF) is common in acute myocardial infarction complicated by cardiogenic shock (AMI-CS) requiring percutaneous ventricular assist device (pVAD-Impella®) support during percutaneous coronary interventions (PCI). We evaluated the effects of a coexistent diagnosis of AF on clinical outcomes in patients with AMI-CS undergoing PCI with pVAD support.

Methods: The National Inpatient Sample (2008-2014) was queried to identify patients with AMICS requiring PCI with pVAD support and had a concomitant diagnosis of AF. Propensity-matched cohorts (AF+ vs AF-) were compared for in-hospital outcomes.

Results: A total of 840 patients with AMICS requiring PCI with pVAD support (420 AF+ vs 420 AF-) were identified in the matched cohort. Patients with AF were older (mean 69.7±12.0 vs 67.9±11.3 yrs, p=0.030). All-cause in-hospital mortality rates between the two groups were similar (40.5% vs 36.7%, p=0.245); however, higher postprocedural respiratory complications (9.5% vs 4.8%, p=0.007) were seen in AF+ group. In-hospital cardiac arrests were more frequent in the AF- group (32.0% vs 19.2%, p<0.001). We examined the length of stay (LOS), transfer to other facilities, and hospital charges as metrics of health care resource consumption and found that the AF+ cohort experienced fewer routine discharges (13.1% vs 30.2%), more frequent transfers to other facilities including skilled nursing facilities or intermediate care facilities (27.3% vs 17.8%; p<0.001), more frequently required the use of home health care (14.3% vs 7.1%; p<0.001). The mean LOS (11.9±10.1 vs 9.11±6.8, p<0.001) and hospital charges ($308,478 vs $277,982, p=0.008) were higher in the AF+ group.

Conclusion: In patients suffering AMICS requiring PCI and pVAD support, a coexistent diagnosis of AF was not associated with an increase in all-cause in-hospital mortality as compared to patients without AF. However, healthcare resource consumption as assessed by various metrics was consistently greater in the AF+ group.

Introduction

Atrial fibrillation (AF) is the most prevalent supraventricular arrhythmia observed in the general population [1]. Advanced age is the most common risk factor, with a lifetime risk of developing AF >10% after the age of 55 years [2]. Prior studies have demonstrated that the presence of AF portends a worse outcome in patients with AMI and may serve as an independent predictor of mortality [3-6].

AF is a common pre-existing comorbidity in patients with AMI, but it may also develop de novo owing to the acute hemodynamic insult to the atria in the setting of AMICS, where acute ventricular pump dysfunction leads to an acute increase in intracardiac pressures and mechanical distention of the atria. These hemodynamic and structural changes to the atria result in electrophysiologic derangements that may lead to AF, the development of which can result in further hemodynamic compromise.

Key Words

Acute Myocardial Infarction; Cardiogenic Shock; Atrial Fibrillation; Arrhythmia; Percutaneous Ventricular Assist Device (Pvad); Impella; Outcomes; All-Cause Mortality

Corresponding Author
Adam E Berman, MD, MSc, MPH
Division of Cardiology, Medical College of Georgia, Augusta University,
1120 15th Street, BBR6518A, Augusta, GA 30912, USA,

Hemodynamic support devices have often been utilized to bridge recovery in patients with acute myocardial infarction complicated by cardiogenic shock (AMICS) undergoing percutaneous coronary intervention (PCI). Owing to its favorable outcomes and relatively noncomplex procedural deployment, pVAD devices, particularly the Impella® device (Abiomed, Danvers, MA), are increasingly utilized. Based on studies [7-10] suggesting the possibility of improved survival outcomes with the use of pVAD for protected PCI, the Impella ® has found increasing use in clinical practice in the setting of AMICS [11]. Considering the previously demonstrated association of worse clinical outcomes in AMI patients with AF, we performed a propensity-matched analysis investigating the impact of AF on in-hospital outcomes in patients with AMICS requiring pVAD support for revascularization using a large national inpatient database.

Methods

We conducted a retrospective observational study utilizing the US National Inpatient Sample (NIS) database from 2008 through 2014. The Agency for Healthcare Research and Quality (AHRQ) as a part of the Healthcare Cost and Utilization Project (HCUP) keeps a record of NIS, which nearly depicts data from an estimated 35 million weighted discharges annually [12]. The NIS embodies a stratified 20% section of hospital records from community hospitals across 44 states, representative of over 95% of the US population. The NIS database includes up to 25 discharge diagnoses, along with on admission comorbidities, up to 15 inpatient records of procedures, and documented complications during a hospital stay. Sampling design and discharge weights (DISCWT) provided in the database were incorporated to appraise national estimates. The information on the self-weight design of the database is detailed online [12]. The International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9 CM) codes were utilized to identify the diagnoses of interest, comorbidities and primary endpoints. Informed consent and institutional review board approval for this study were not required owing to the de-identified data source.

Adult hospitalizations with a principal diagnosis of AMI complicated by CS were identified from January 2008 through December 2014. Of the AMICS encounters queried, those in which the patient required PCI with pVAD support were further identified using ICD-9 CM codes. Inpatient encounters in which other mechanical hemodynamic support devices were utilized [e.g. LVAD, intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO)] or those with missing data were excluded. Eligible hospitalizations were then further stratified into two study cohorts, AF+ vs. AF-, using the ICD-9 CM code 427.31. The study population was identified using an algorithm as shown in Figure 1.

Baseline demographics, hospital characteristics, medical comorbidities, and complication rates were compared between the AF+ and AF- groups. Patient-level sociodemographic and hospital-level attributes were directly drawn out as provided, whereas the AHRQ comorbidity indicators were employed to identify on admission comorbid disorders using apposite ICD-9 CM codes as detailed earlier [13, 14]. We queried the AMICS cases for in-hospital complications using the validated diagnostic codes present among the secondary diagnoses fields (Supplementary Table S1).

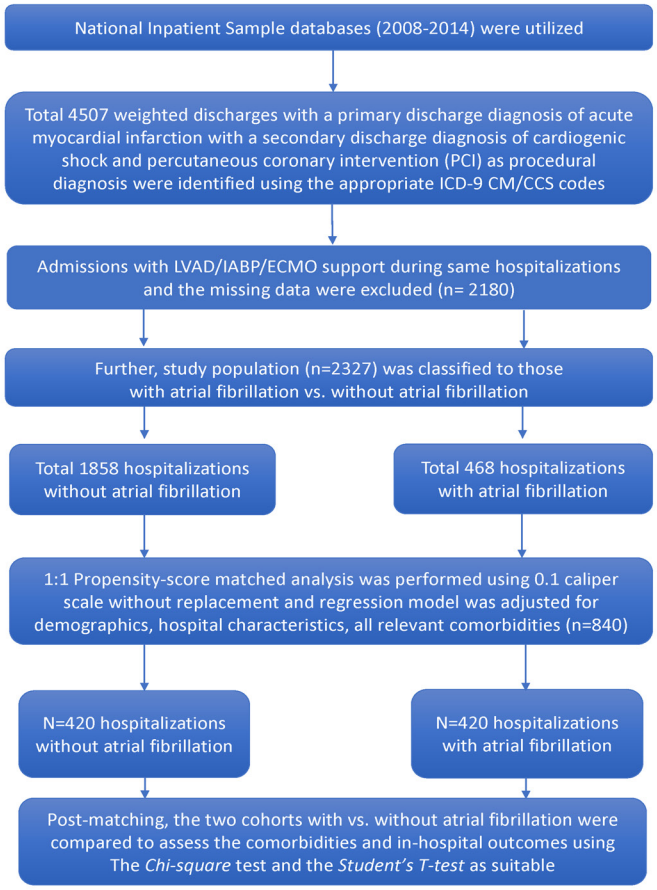

Figure 1: **Study population selection algorithm**

The primary outcomes were all-cause in-hospital mortality and the development of complications, including cardiac arrest, post-procedural hemorrhage, respiratory complications, acute kidney injury (AKI) requiring dialysis, infection and septic shock. The secondary outcome was the economic burden of disease, as measured by the length of stay (LOS, in days), discharge disposition and the total cost of the inpatient encounter (in US dollars).

Categorical variables were represented as numbers and proportions and assessed with the Chi-Square test. Continuous variables were reported as the mean and standard deviation and were matched using Student's t-test. Discharge weights with strata and cluster designs provided by the HCUP were accounted for using complex modules to appraise nationwide assessments. To control the existent selection bias in the unmatched cohort, a propensity score-matched analysis of the AF+ vs. AF- AMICS patients' cohort was accomplished. We performed a multivariable logistic regression model after adjusting for demographics, hospital-level elements and all relevant cardiovascular comorbidities present on admission to calculate a propensity score for each discharge record. The subsequent individually matched propensity score was used for the nearest neighbor matching of both groups (AF+ vs. AF-) with a caliper width tolerance of 0.01. Later, we compared and tabulated AMICS encounters requiring PVAD and the PCI outcomes between both AF and non-AF groups in the propensity score-matched cohort. Absolute standardized differences

Table 1: . Study Population Undergoing Coronary Revascularization with PVAD (Impella®) Support Following Acute Myocardial Infarction Complicated by Cardiogenic Shock With vs. Without Atrial Fibrillation

Variables	Before Matching (weighted N=2327)			After Matching (weighted N=840)		
	No AF (n=1,858)	AF (n=468)	P	No AF (n=420)	AF (n=420)	P
Age (yrs) at hospitalization						
Mean age (Mean±SD)	63.7 ± 12.5	70.7 ± 11.8	<0.001	67. 9 ± 11.3	69.7 ± 12	0.030
18-44	7.0%	3.1%		*	3.5%	
45-64	45.9%	27.9%	<0.001	34.7%	31.2%	0.368
≥65	47.2%	69.0%		62.9%	65.3%	
Sex			0.888			0.020
Male	71.1%	71.5%		78.6%	71.6%	
Female	28.9%	28.5%		21.4%	28.4%	
Race			<0.045			0.964
White	70.0%	72.2%		73.8%	74.9%	
American African	9.7%	6.4%		6.0%	4.8%	
Hispanic	9.9%	11.7%		9.4%	9.6%	
Asian and Pacific Islander	3.5%	*		*	*	
Native American	*	*		*	*	
Others	6.4%	7.5%		8.4%	8.4%	
Admission day			0.022			0.593
Weekend	78.1%	82.9%		82.3%	80.9%	
Weekday	21.9%	17.1%		17.7%	19.1%	
Type of Admission			0.806			1.000
Non-elective	93.3%	93.6%		95.1%	95.2%	
Elective	6.7%	6.4%		4.9%	4.8%	
Primary Payer			<0.001			0.002
Medicare	49.7%	61.6%		59.2%	60.7%	
Medicaid	8.4%	4.3%		8.5%	4.8%	
Private including HMO	30.7%	30.9%		26.3%	31.0%	
Self-pay/no charge/other	11.1%	3.2%		32.3%	34.6%	
Hospital characteristics						
Median household income quartile as per patients' zip codex			<0.001			0.071
0-25th	**31.5%**	**23.5%**		**20.2%**	**25.1%**	
26-50th	**31.4%**	**24.6%**		**21.4%**	**23.9%**	
51-75th	**20.3%**	**28.6%**		**28.6%**	**28.5%**	
76-100th	**16.9%**	**23.3%**		**29.7%**	**22.5%**	
Hospital bed size¥			0.004			0.283
Small	**5.0%**	**8.5%**		**10.6%**	**8.3%**	
Medium	**22.3%**	**17.9%**		**14.3%**	**17.7%**	
Large	**72.7%**	**73.6%**		**75.1%**	**74.1%**	
Hospital location/teaching status			**0.010**			**0.920**
Rural	**4.5%**	*		*	*	
Urban non-teaching	**30.4%**	**26.5%**		**27.1%**	**28.4%**	
Urban teaching	**65.1%**	**71.4%**		**70.5%**	**69.2%**	
Hospital region			**0.006**			**0.886**
Northeast	**15.2%**	**14.9%**		**16.5%**	**15.5%**	
Midwest	**14.2%**	**18.0%**		**15.3%**	**15.5%**	
South	**49.6%**	**41.3%**		**46.5%**	**45.0%**	
West	**21.0%**	**25.7%**		**21.7%**	**24.0%**	

P<0.05 (bold) indicates statistical significance.
AF=Atrial Fibirllaion, PVAD=Percutaneous Ventricular Assist Device, HMO=Health Maintenance Organization
xRepresents a quartile classification of the estimated median household income of residents in the patient's ZIP Code. Derived from https://www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nisnote.jsp
¥ The bed size cut off points divided into small, medium, and large have been derived from https://www.hcup-us.ahrq.gov/db/vars/hosp_bedsize/nisnote.jsp
*Cell counts <11 could not be reported as per the privacy guidelines by HCUP (https://www.hcup-us.ahrq.gov/db/publishing.jsp).

Table 2: Comorbidities in Study Population Undergoing Coronary Revascularization with PVAD (Impella®) Support Following Acute Myocardial Infarction Complicated by Cardiogenic Shock With vs. Without Atrial Fibrillation

Comorbidities (%)	Before Matching (weighted N=2327)			After Matching (weighted N=840)		
	No AF (n=1858)	AF (n=468)	P	No AF (n=420)	AF (n=420)	P
Alcohol abuse	2.4%	3.2%	0.342	*	3.5%	0.307
Deficiency anemias	15.7%	33.7%	<0.001	29.6%	28.2%	0.663
Congestive heart failure	3.2%	4.3%	0.241	*	4.8%	0.062
Chronic pulmonary disease	17.2%	15.9%	0.484	13.1%	17.7%	0.067
Coagulopathy	23.4%	22.2%	0.574	28.6%	20.0%	0.004
Diabetes, uncomplicated	30.4%	29.9%	0.823	32.2%	28.6%	0.270
Diabetes with chronic complications	5.6%	8.5%	0.018	5.9%	7.2%	0.480
Dyslipidemia	43.5%	47.9%	0.085	50.2%	46.5%	0.284
Drug abuse	3.2%	3.2%	0.973	6.1%	3.5%	0.079
Hypertension	58.6%	63.8%	0.040	54.9%	61.9%	0.042
Fluid and electrolyte disorders	53.5%	56.1%	0.307	47.8%	55.7%	0.025
Smoking	35.9%	32.0%	0.119	34.5%	33.4%	0.734
Obesity	15.3%	16.0%	0.016	15.7%	14.4%	0.572
Obstructive sleep apnea	3.8%	4.3%	0.612	7.2%	4.8%	0.145
Peripheral vascular disorders	15.3%	16.0%	0.724	16.6%	14.3%	0.348
Renal failure	23.3%	34.2%	<0.001	24.8%	30.0%	0.095
Hemodialysis status	8.8%	15.0%	<0.001	14.1%	10.8%	0.142
Previous MI/PCI/CABG	17.8%	19.1%	0.527	20.4%	16.5%	0.135
Multivessel PCI	27.5%	36.2%	<0.001	28.3%	31.0%	0.393
Prior TIA/Stroke	3.0%	4.3%	0.151	4.8%	3.6%	0.392
Pacemaker status	1.1%	3.2%	0.001	*	*	*
ICD status	2.2%	3.2%	0.181	*	3.6%	0.307
Ventricular tachyarrhythmias	42.3%	39.5%	0.262	40.3%	40.6%	0.921

P<0.05 (bold) indicates statistical significance, AF= Atrial Fibrillation, PVAD=Percutaneous Ventricular Assist Device, MI=Myocardial Infarction, PCI=Percutaneous Coronary Intervention, CABG=Coronary Artery Bypass Grafting, TIA=Transient Ischemic Attack, ICD=Implantable Cardioverter-defibrillator.
* Cell counts <11 could not be reported as per the privacy guidelines by HCUP (https://www.hcup-us.ahrq.gov/db/publishing.jsp).

Table 3: Outcomes and Complications of Coronary Revascularization with PVAD (Impella®) Support Following Acute Myocardial Infarction Complicated by Cardiogenic Shock With vs. Without Atrial Fibrillation (After Propensity-score Matching)

Complications	1:1 Propensity-Matched Cohorts		P
	No AF (n=420)	AF (n=420)	
All-cause in-hospital mortality	154 (36.7%)	170 (40.5%)	0.245
Hemorrhage or hematoma complicating a procedure	30 (7.1%)	20 (4.8%)	0.147
In-hospital cardiac arrest	245 (32.0%)	181 (19.2%)	<0.001
Perioperative stroke	<11*	40 (9.5%)	<0.001
Postoperative respiratory complications	20 (4.8%)	40 (9.5%)	0.007
Postoperative AKI requiring dialysis	24 (5.8%)	20 (4.7%)	0.536
Postoperative infection	65 (15.5%)	75 (17.9%)	0.347
Septic shock	25 (6.0%)	35 (8.4%)	0.177
Disposition			<0.001
Routine	133 (30.2%)	75 (13.1%)	
Transfer to short term hospital	54 (8.3%)	45 (4.7%)	
Other transfers including SNF, ICF & others	164 (17.8%)	173 (27.3%)	
Home health care	44 (7.1%)	91 (14.3%)	
Mean Length of stay Mean (±SD)	9.1 (± 6.8) days	11.9 (± 10.1) days	<0.001
Mean hospital charges	$277,982	$308,478	0.008

P-values <0.05 (bold) indicates clinical significance, AF= Atrial Fibrillation, pVAD=Percutaneous Ventricular Assist Device, AF=Atrial Fibrillation, AKI=Acute Kidney Injury, SNF=Skilled Nursing Facility, ICF=Intermediate Care Facility
Note: Cell counts <11 are not reported as per the privacy guidelines by HCUP.

between pre-matched and post-matched cohorts were compared to assess the residual imbalances (Supplementary Figure 1). A greater than five percent post-matching difference between the two groups (AF and non-AF) was considered as statistical significance. IBM SPSS version 24.0 (IBM Corp., Armonk, NY) was used to conduct the statistical analyses.

Results

A total of 2326 encounters with a principal diagnosis of AMI complicated by CS requiring PCI with pVAD support were identified during the study period. 20.1% of these encounters also featured a concomitant diagnosis of AF. The study cohort was comprised of 468 AF+ vs 1,858 AF- patients. AMICS patients with AF who required pVAD support were significantly older (70.7± 11.8 vs 63.7±12.5, p <0.001) and more often white (72.2% vs 70 %, p <0.045) males. Compared to the AF- cohort, the unmatched AF+ cohort consisted of older (age >65yrs; 69% vs 47.2%, p <0.001), Hispanic (11.7 % vs 9.9%, p <0.045), non-electively admitted (93.6% vs 93.3%, p =0.806), Medicare (61.6% vs 49.7%, p <0.001) enrollees with higher income quartiles (23.3% vs 16.9%, p <0.001) and were admitted to small as well as large urban teaching and non-teaching hospitals (Table 1). There was a higher proportion of males in both cohorts (71.6 % vs 78.6 %), though the proportion of females was higher in the AF+ group (28.4% vs 21.4%) (p=0.020). After propensity matching, a cohort of 420 AF and non-AF patients were comparable regarding race, admission day, type of admission, median household income, hospital bed size, location and region with a standardized difference of <10% between both groups.

After propensity-matching, a remarkably higher number of comorbidities in the AMICS AF+ group disappeared, but the proportion of patients with hypertension (61.9% vs 54.9%, p=0.042) and fluid electrolyte disorder (55.75 vs 47.8%, p = 0.025) remained higher in patients with AF. The proportion of patients with coagulopathy was significantly lower in the AF+ group after propensity matching (20.1% vs 28.6%, p = 0.004). Cardiovascular comorbidities were similar in both groups following propensity matching (Table 2).

No difference was seen in all-cause in-hospital mortality in AF+ vs AF- (40.5% vs 36.7%, p=0.245) patients (Table 3). Additionally, no dissimilarities were noted between the groups in the rates of post-procedural hemorrhages, infection, AKI requiring dialysis, and septic shock in AF in the matched cohort. Interestingly, in-hospital cardiac arrest was remarkably higher in the AF- group (32% vs 19.2%, p<0.001). Postoperative respiratory complications were seen more often in AF+ patients (9.5% vs 4.8%, p = 0.007). Indices of healthcare/economic burden were universally higher in the AF+ group, as assessed by less number of routine discharges (13.1% vs 30.2%), the higher number of transfers to other facilities (27.3% vs 17.8%), greater utilization of home health care (14.3 % vs 7.1%) (p<0.001), a greater mean length of stay (11.9 ± 10.1 vs 9.11 ± 6.8 days, p <0.001) and greater hospital charges ($308,478 vs. 277,982, p=0.008) as compared to the AF- cohort.

Discussion:

To the best of our knowledge, this is the first study to analyze the impact of a concomitant AF on the outcomes of AMICS patients undergoing PCI with pVAD support as assessed with a large national inpatient database. Importantly, there was no difference in all-cause in-hospital mortality in the AF+ and AF- cohorts. While a cardiac arrest was significantly more common in AF- patients, AF+ patients were more likely to experience postoperative respiratory complications. Finally, the economic burden of disease was significantly higher when AF was present, as demonstrated by an increased prevalence of non-routine disposition, increased utilization of home health care services, greater LOS, and increased hospital charges.

AF has traditionally been associated with higher morbidity and mortality in the general population, which is generally attributed to the higher prevalence of comorbid conditions and advanced age in these patients [15, 16]. In keeping with prior studies, AF+ patients tended to be older and male in our analysis [17]. Prior studies have suggested that patients with AMI who were hemodynamically stable and developed AF had greater morbidity and mortality [3, 4] which persisted even after adjustment for baseline characteristics. In the same vein, Sakata et al showed patients with new-onset AF in the setting of AMI had higher mortality [18], and Crenshaw et al also demonstrated an independent effect of AF on 30-day mortality in post-MI patients [19]. The presence of AF in the setting of acute ventricular dysfunction may further exacerbate these patients' hemodynamic compromise, accounting for the worse outcome in these patients. While the literature remains contentious regarding AF being an independent predictor of AMI-related mortality, it is notable that the presence of AF was not associated with an increase in all-cause in-hospital mortality in our study population [2, 20, 21].

Clinical outcomes in patients with AMICS may be influenced by multiple factors, including a deranged systemic inflammatory response, and treatment success is not merely dependent on the restoration of cardiac output [22]. In our study, we found no statistical difference in in-hospital all-cause mortality between AF+ and AF- patients with AMICS undergoing PCI with pVAD support, in keeping with a recent sub-study of the IABP-SHOCK trial that investigated the impact of AF on AMICS [23]. In the sub-study, the presence of AF was not associated with early or late mortality in patients with AMICS. Furthermore, there was no increase in mortality in patients who presented with AF or developed AF in-hospital as compared to patients without AF. Also noted were similar occurrences of non-fatal events and functional outcomes in both groups. Interestingly, these investigators also observed that AF loses its prognostic significance with increasing severity of sickness . Hickey et al studied the impact of AF on patients with end-stage heart failure requiring LVAD support and found that the presence of AF was not associated with increased mortality [24]. Similarly, Stulak et al observed that AF did not portend higher mortality in LVAD use in heart failure [25]. Our findings are in keeping with these studies.

Surprisingly, the rate of cardiac arrest was higher in AF- patients in our study cohort. Several hypotheses may be advanced to explain this observation. It is possible that this observed difference can be due to the higher use of anti-arrhythmic and anticoagulant medications in AF+ patients, thereby affording a protective effect on the AF+ group. However, owing to the retrospective nature of this analysis and a lack of information regarding medication use, we cannot further explore

this possibility.

From a health economics perspective, the presence of AF resulted in significantly greater indices of economic burden and health care resource consumption, as demonstrated by a greater length of stay, higher total hospitalization costs, and a higher acuity of discharge disposition in the AF+ group. One possible explanation for this finding is the higher incidence of respiratory complications noted in the AF+ group, which may have led to increased use of long periods on mechanical ventilation.

The present study should be interpreted within the context of numerous limitations. The NIS is a retrospective database, so we cannot reliably comprehend the time duration and type of AF occurrence with a clear differentiation between a new-onset AF and a pre-existing AF. Information regarding medication use, laboratory studies, and other clinical variables is unavailable, a limitation inherent to NIS data. Propensity matched analysis was done to minimize selection bias. Despite these measures, it is impossible to control for all potential confounders and residual imbalances between the groups. Long-term outcomes cannot be evaluated using the NIS databases due to a lack of follow-up data. As there are no separate ICD-9 codes available to differentiate between Impella® and Tandem heart®, the results of our analysis cannot be individualized towards any single PVAD device. However, since 2013 most of the growth in PVAD use has occurred with the use of Impella® especially in AMI [26] and the use of Tandem heart is in semi-urgent situations as this involved trans septal puncture. Despite these limitations, a large sample size and comprehensive propensity-score matching enabled us to perform this unique analysis.

In conclusion, the presence of a concomitant diagnosis of AF in the setting of AMI complicated by cardiogenic shock in patients undergoing PCI with the use of pVAD is not associated with an increase in all-cause mortality. Importantly, the presence of AF was associated with a greater economic burden of disease, as demonstrated by significantly higher hospitalization costs, greater LOS, and a greater proportion of non-routine discharges, possibly owing to the higher rate of respiratory complications observed in this group.

Conclusions:

In patients suffering AMICS requiring PCI and pVAD support, a coexistent diagnosis of AF was not associated with an increase in all-cause in-hospital mortality as compared to patients without AF. However, healthcare resource consumption as assessed by various metrics was consistently greater in the AF+ group.

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Supplementary Table

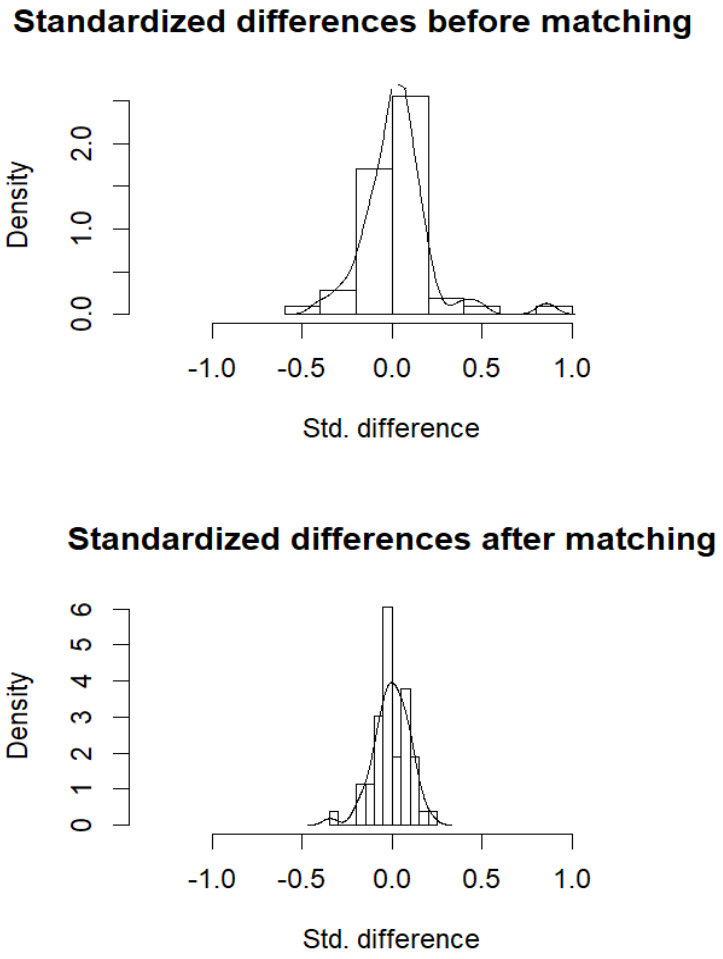

Figure 1: Absolute standardized differences before propensity-score matching vs. after propensity-score matching

Supplementary Table 1: **ICD-9 CM and CCS Codes Used to Identify Comorbidities and Procedural Complications**

Comorbidities/Complications	ICD-9 CM/CCS	Codes (Diagnostic/ Procedural)
Acute Myocardial Infarction	CCS	100
Atrial fibrillation	ICD-9 CM	427.31
Cardiogenic shock	ICD-9 CM	785.51
Multivessel percutaneous coronary intervention	ICD-9 CM	00.41 00.42 00.43
Hemodialysis	ICD-9 CM	39.95 V45.1
Status pacemaker	ICD-9 CM	V45.01
Smoking	ICD-9 CM	305.1, V15.82
Dyslipidemia	CCS	53
Implantable Cardioverter Defibrillator status	ICD-9 CM	V45.02
Ventricular tachyarrhythmia	ICD-9 CM	427.1, 427.41, 427.42
Prior transient ischemic attack/stroke	ICD-9 CM	V12.54
Percutaneous ventricular assist device (Impella®)	ICD-9 CM	37.68
Intraaortic balloon pump	ICD-9 CM	37.61
Extracorporeal membrane oxygenation	ICD-9 CM	39.65
left ventricular assist device	ICD-9 CM	37.66
Hemorrhage or hematoma complicating a procedure	ICD-9 CM	998.1, 998.11, 998.12 998.13
Perioperative autologous transfusions of whole blood or blood components	ICD-9 CM	V58.2, 99.00
In-hospital cardiac arrest	ICD-9 CM	427.5
Postoperative myocardial infarction	CCS	100
Postoperative stroke	ICD-9 CM/CCS	997.02, 109
Post procedural respiratory complications	ICD-9 CM	997.3 997.31 997.32 99739
Acute kidney injury + dialysis	ICD-9 CM	584.9+39.95
Postoperative infection	ICD-9 CM	998.5, 998.51, 998.59, 999.3, 038.0, 995.91, 995.92
Septic shock	ICD-9 CM	785.52

ICD-9 CM = The International Classification of Diseases, Ninth Revision, Clinical Modification
CCS = Clinical Classifications Software, https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp

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Clinical Discussions in Antithrombotic Therapy Management : A Delphi Consensus Panel

Gabriello Marchetti [1], Emanuele Bertaglia[2], Alberto Camerini[3], Giuseppe De Angelis[4], Lucia Filippucci[5], Antonio Maggi[6],Sebastiano Marra[7], Carlo Racani[8], Carlo Serrati[9]

[1]Cardiologia, Ospedale Bellaria, Bologna.
[2]Azienda Ospedaliera di Padova.
[3]Ospedale Antero Micone Sestri Ponente, Genova.
[4]UOC Cardiologia, ASST-RHODENSE, Ospedale di Rho (MI).
[5]U.O. Cardiologia Riabilitativa e Prevenzione Patologie Cardiovascolari, USL Umbria 1,Perugia.
[6]Fondazione Poliambulanza Istituto Ospedaliero, Brescia.
[7]AOU Città della Saluta e Scienza, Torino.
[8]Direzione Airport Management, OPR / OAP - Pronto Soccorso, Aeroporti di Roma, Roma.
[9]IRCCS AOU S. Martino, Genova.

Abstract

For some years now, direct-acting oral anticoagulants (DOACs) have entered the clinical practice for stroke prevention in non-valvular atrial fibrillation (NVAF) or prevention and treatment of venous thromboembolism (VTE). However, there is uncertainty on DOAC use in some clinical scenarios not fully explored by clinical trials, but commonly encountered in the real world.

We report a Delphi Consensus on DOAC use in NVAF and VTE patients. The consensus dealt with 16 main topics: (1) clinical superiority of DOACs compared to VKAs; (2) DOACs as a first-line treatment in patients with AF; (3) therapeutic options for patients undergoing electrical cardioversion; (4) selection of patients suitable for switching from VKAs to DOACs; (5) and (7) role of general practitioners in the follow-up of patients receiving a DOAC; (6) duties of Italian oral anticoagulation therapy centers; (8) role of therapy with DOACs in oncological patients with NVAF; (9) role of DOACs in oncological patients with VTE; (10) methods for administration and therapy compliance for DOACs; (11) drug interactions; (12) safety of low doses of DOACs; (13) therapeutic management of frail patients with NVAF; (14) therapeutic management of NVAF patients with glomerular filtration rate <30 ml/min (15); advantages of DOACs for the treatment of frail patients; (16) limitations on therapeutic use of DOACs.

Sixty-two cardiologists from Italy expressed their level of agreement on each statement by using a 5-point Likert scale (1: strongly disagree, 2: disagree, 3: somewhat agree, 4: agree, 5: strongly agree). Namely, votes 1-2 were considered as disagreement while votes 3-5 as agreement. Agreement among the respondents of ≥66% for each statement was considered consensus. A brief discussion about the results for each topic is also reported.

Introduction

For some years now, direct-acting oral anticoagulant non-vitamin K antagonists (DOACs) have entered the clinical practice of a large group of specialists such as cardiologists, internists, angiologists, neurologists, hematologists, and geriatricians to reduce the thromboembolic risk associated with atrial fibrillation (AF) or to prevent or treat venous thromboembolism (VTE).

Key Words

atrial fibrillation; consensus; Delphi; direct oral anticoagulants; venous thromboembolism; vitamin K antagonists.

Corresponding Author
Gabriello Marchetti
Cardiologia , Ospedale Bellaria, Bologna
Address: Via Altura 3 Bologna 40100, Italy

In many cases, the centers that historically managed anticoagulation by means of vitamin K antagonists (VKAs) (i.e., oral anticoagulation therapy centers, named TAO centers in Italy) have taken over prescription and renewal of therapeutic plans. Superiority or safety of DOACs compared to VKAs, both in pharmacoeconomic terms and in management of follow-up have been evaluated. Economic sustainability has been assessed.

General practitioners (GPs) and other specialists (i.e., cardiologists not working in a TAO center in some regions) cannot prescribe DOACs, manage patients that need a change in their treatment regimen from warfarin to DOAC or need to begin a treatment with a DOAC.

A consensus conference focused on these issues from different

points of view has been realized with the aim of discussing on these topics.

Material and methods

The Delphi method is frequently used in scientific and medical settings with the aim of reaching consensus within a group of experts, when scientific evidence is absent or conflicting [1-3]. In this paper, Delphi method was used to evaluate the consensus on clinical management of DOACs in patients with AF.

The process has been structured into four phases. In the first phase (June-December 2017) nine regional round tables were organized. Participants involved in the treatment of AF (cardiologists, neurologists, hematologists, and internal medicine specialists), discussed on the following main issues on DOACs: clinical experience and physicians perception of DOACs, safety and handling, use of low doses and management in frail patients. In the second phase (January-February 2018), a scientific board of nine experts were identified as representative of clinical specialties involved in the treatment of patients with AF. This scientific board identified a list of statements arose from the nine round table discussions. During the third phase (March 2018) the list of statements was administered online to the 62 clinicians, participated in the regional round tables. Survey was performed online on a secured survey website (first round), by using a web-based survey platform (http://www.consensusdelphinao.it/). The results were evaluated by the scientific board.

The responses of participants were collected and analyzed prior to the final consensus meeting (second round, fourth and last phase of the process) held in Milan, Italy (June 2018). Results from the first-round vote were presented by the scientific board and a second-round vote was performed (62 participants) in order to estimate consensus on the statements that were more controversial in the first round. Both rounds of vote were blinded.

Delphi statements

The scientific board defined 60 statements divided into the following 16 main topics: (1) clinical superiority of DOACs compared to VKAs; (2) DOACs as a first-line treatment in patients with AF; (3) therapeutic options for patients undergoing electrical cardioversion (ECV); (4) selection of patients suitable for switching from VKAs to DOACs; (5) and (7) role of GPs in the follow-up of patients receiving a DOAC; (6) duties of Italian TAO centers; (8) role of therapy with DOACs in oncological patients with non-valvular AF (NVAF); (9) role of DOACs in oncological patients with VTE; (10) methods for administration and therapy compliance for DOACs; (11) drug interactions; (12) safety of low doses of DOACs; (13) therapeutic management of frail patients with NVAF; (14) therapeutic management of NVAF patients with glomerular filtration rate (GFR) <30 ml/min (15); advantages of DOACs for the treatment of frail patients; (16) limitations on therapeutic use of DOACs.

	1	2	3	4	5	TOT
1.1 In terms of efficacy	2	6	14	17	23	62
	13%		87%			100%
1.2 In terms of efficacy and safety	1	4	6	14	37	62
	8%		92%			100%
1.3 In terms of efficacy but not safety	26	26	5	3	2	62
	84%		16%			100%
1.4 In terms of safety but not efficacy	17	15	9	17	4	62
	52%		48%			100%
1.5 In terms of handling	1	1	3	10	47	62
	3%		97%			100%

Table 1: **Statement 1: DOACs are superior to VKAs**

	1	2	3	4	5	TOT
2.1 In all patients with no contraindications	0	0	3	10	49	62
	0%		100%			100%
2.2 Only in patients with high hemorrhagic risk	21	23	8	6	4	62
	71%		29%			100%
2.3 Only in patients with high thromboembolic risk	23	25	5	6	3	62
	77%		23%			100%
2.4 Never	53	9	0	0	0	62
	100%		0%			100%

Table 2: **Statement 2: DOACs are the first-choice option for treatment of NVAF**

Participants expressed their level of agreement on each statement by using a 5-point Likert scale (1: strongly disagree, 2: disagree, 3: somewhat agree, 4: agree, 5: strongly agree).

Agreement among the respondents of ≥66% for each statement was considered consensus. Namely, votes 1-2 were considered as disagreement while votes 3-5 as agreement.

Results and Discussion

The overall response rate of Delphi first round was 100% (62 responding participants out of 62 total panelists) and that of second round was 100% (62 out of 62).

Of the total of 65 items, 37 reached a positive consensus (agreement), 14 reached a negative consensus (disagreement) and 14 did not reach a consensus. The group of experts therefore decided to undergo a second vote. In particular, the statements 7, 9, 10 (items 10.4 to 10.8) and 13 were revised. Among these, only point 7.2 reached a different consensus than the first vote. For narrative reasons the topics have been organized and discussed in 7 scenarios.

Scenario 1. DOACs versus VKAs (topics 1, 2 and 4)

Participants expressed agreement on the superiority of DOACs compared VKAs both in terms of efficacy (87%) and efficacy and safety (92%) (Table 1, statements 1.1, 1.2). Clear disagreement on statement 1.3 (84%), showed that according to the experts' opinion, effectiveness of DOACs does not compromise the safety (Table 1, statement 1.3). The consensus on superiority in terms of safety alone was more articulated and less compact (Table, 1, statement 1.4), thus emphasizing the importance of the "net clinical benefit" while assessing impact of DOACs. On the other hand, consensus on the greater handling of the DOACs compared to the VKAs was almost unanimous (97%) (Table 1, statement 1.5).

Participants expressed maximum agreement to consider DOACs as the first choice compared to VKAs, not only in patients with high thromboembolic or hemorrhagic risks, but in all patients. This position is also in line with the latest European guidelines on AF [4] (Table 2, item 2.1).

Appropriateness of the switch from AVKs to DOACs obtained the maximum consensus in cases of failure to INR (International Normalized Ratio) control or in any case of practical difficulty in performing close sampling (Table 3, items 4.1-4.2). In case of INR stability (i.e., adequate time in therapeutic range, TTR) there was no consensus to switch. As well as no consensus was reached on indiscriminate switch to DOACs for all patients treated with AVKs who have no contraindications to treatment with DOACs themselves (Table 4, items 4.3-4.4).

A meta-analysis of the results of four pivotal trials for the use of DOACs in patients with NVAF was performed to evaluate ischemic and hemorrhagic stroke, systemic embolism, all-cause mortality, myocardial infarction and major bleeding events [5-8]. The results showed that DOACs significantly reduced systemic stroke/embolism events by 19% compared to warfarin (RRR 0.81, 95% CI 0.73-0.91; p <0.0001), markedly reduced the hemorrhagic stroke (RRR 0.49, 95% CI 0.8-0.64; p <0.0001) and significantly reduced all-cause mortality (RRR 0.90, 95% CI 0.85-0.95; p = 0.0003) [9].

Similar meta-analyses performed by Renda et al. [10,11], evaluating the net clinical benefit by a cumulative examination of endpoints analysis, demonstrated the clear superiority of DOACs compared to warfarin in terms of the composite endpoint of disabling stroke and life-threatening bleeding. On the contrary, compared to warfarin, only dabigatran and apixaban showed a significant reduction in the disabling stroke and life-threatening bleeding composite endpoint. Moreover, only edoxaban (at both recommended doses) was superior to warfarin in the cumulative evaluation of ischemic/hemorrhagic stroke/acute myocardial infarction/systemic embolism and major bleeding [12].

	1	2	3	4	5	TOT
4.1 In not-controlled patients via AVKs	0	0	0	8	54	62
	0%		100%			100%
4.2 In well controlled patients with difficulty in monitoring the INR and adhering to the therapy	0	0	3	12	47	62
	0%		100%			100%
4.3 Never if patient is stable while on AVK therapy	5	29	19	9	0	62
	55%		45%			100%
4.4 Always in the absence of contraindications	5	22	13	9	13	62
	44%		56%			100%

Table 3: **Statement 4: The switch from VKAs to DOACs is appropriate**

	1	2	3	4	5	TOT
3.1 DOACs are always the first-choice therapy	1	5	8	16	32	62
	10%		90%			100%
3.1 DOACs are a valid alternative to VKAs	3	2	14	19	24	62
	8%		92%			100%
3.3 VKAs are the first-choice therapy	24	32	4	2	0	62
	90%		10%			100%
3.4 DOACs should not be used	56	5	0	1	0	62
	98%		2%			100%

Table 4: **Statement 3 on the use of DOACs in patients undergoing ECV**

Regarding the safety endpoint of DOACs compared to warfarin, in addition to the strong reduction in brain hemorrhage of 50% in all studies, the sub-analysis of the ENGAGE AF-TIMI 48 study demonstrated a significant reduction in fatal bleeding at both recommended doses of edoxaban, compared to warfarin [6].

In parallel, a meta-analysis of randomized clinical studies reported that DOACs significantly reduced major bleeding compared to warfarin, when the TTR was <66% (p <0.02), even if intestinal bleeding was slightly increased (RR 1.25, p = 0.04) [13].

Several real-world studies support the importance of examining the net clinical benefit in the elderly before establishing a therapy because the risk of thromboembolic and hemorrhagic events in patients with AF increases with age. In this regard, some researchers aimed at comparing DOACs with VKAs in terms of the 1-year clinical outcome in elderly (≥75 years) patients with AF enrolled in a prospective European Registry. The data obtained in 3,852 elderly patients were assembled by the PREFER in AF registry [14] and in AF-PROLONGATION (the data of this registry are still unpublished). The primary outcome was the incidence of the composite endpoint, including major hemorrhagic and ischemic events, during the treatment with DOACs (N = 1,556) compared to VKAs (N = 2,269). The percentage of the composite endpoint was 6.6%/year with DOACs versus 9.1%/year with VKAs (adjusted OR 0.64, 95% CI 0.48-0.86, p = 0.003). The treatment with a DOAC was associated with a lower bleeding rate compared to VKA treatment (adjusted OR 0.52, 95% CI 0.33-0.83, p = 0.006). Moreover, the number of ischemic events was lower (OR adjusted 0.71, 95% CI

0.50-0.99, p = 0.048). The difference in major bleeding associated with DOACs compared to patients treated with VKAs was even greater in elderly patients with low body mass index (BMI, adjusted OR 0.40), and in patients aged ≥85 (adjusted OR 0.33) [14].

Participants of this consensus expressed agreement on the superiority of DOACs compared VKAs both in terms of efficacy, safety and handling. Consequently, DOACs can be considered as first-choice option for thromboprophylaxis in patients with NVAF and no contraindications to them.

Scenario 2. DOACs use in patients undergoing ECV (topic 3)

The panel agreed in considering DOACs as first therapeutic choice also in the setting of patients undergoing ECV [Table 4], according to the results of recent trials and based on greater safety, manageability and quick action compared to VKAs [15-17].

ECV is a valid alternative for restoring sinus rhythm in patients with AF [18]. The need for anticoagulation for the prevention of thrombotic events in patients with AF undergoing ECV is entirely empirical, even if it was further validated by studies using transesophageal echocardiography (TEE) in the 1990s [18].

The current mainstay is the use of a VKA for at least 3 weeks prior to ECV and for the following 4 weeks. Furthermore, the patient should have INR values in the range of 2.0- 3.0 in the 3 weeks before the procedure. The duration of anticoagulant therapy preceding ECV may be less than three weeks, if ECV is anticipated by a negative TEE. This approach results in thromboembolic rates lower than 1% within 30 days [19].

Since the marketing of DOACs, the scenario of the prevention of thromboembolism in the AF has changed. This certainly also extends to the subgroup of patients who are candidates for ECV [19]. During the pivotal studies, efficacy and safety were demonstrated for all DOACs, even in patients who underwent ECV during the anticoagulant treatment. Prospective studies focused on patients undergoing ECV have also validated the possibility of using the DOACs in this setting, both for the classic anticoagulation (late ECV) scheme for 3 weeks before and 4 weeks after ECV, and for early ECV (TEE-guided).

Subgroup analyses followed the publication of the results of the related main studies (RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TMI 48) [5-8]. The largest sub-analysis is that of the RE-LY study regarding 1,983 ECV in 1,270 patients (647, 672, and 664 patients respectively in each of the dabigatran 110 mg, dabigatran 150 mg, and warfarin arms) [20]. TEE was performed in about 25% of the dabigatran groups versus 13.3% in the warfarin group. No difference was observed for the incidence of spontaneous left atrial echo contrast or auricular thrombus (ranging from 1.1% with warfarin to 1.8% with dabigatran 110 mg). The main results of an intention-to-treat analysis showed a low rate of events (<1%) 30 days after ECV and no statistical difference was found among the three groups [20].

In a post-hoc analysis of the ARISTOTLE study on apixaban and ECV, 743 ECVs were performed in 540 patients [21], 265 ECVs in patients allocated to the apixaban arm, and 275 in patients assigned to warfarin. In the 30-day follow-up period no ischemic stroke or systemic embolism occurred in either groups. Major bleeding occurred in 1 patient (0.2%) treated with warfarin and in 1 patient treated with apixaban (0.3%). TEE was performed in 171 patients (203 ECVs): 86 patients (97 ECVs) assigned to the apixaban arm, and 85 patients (106 ECVs) assigned to the warfarin arm. In none of the patients a left atrial thrombus occurred, while 4 patients (1 for apixaban and 3 for warfarin) had evidence of spontaneous echo contrast. For apixaban, the EMANATE trial in 1,038 patients undergoing ECV and 300 spontaneous cardioversions showed that there were 0/753 vs. 6/747 strokes [relative risk (RR) 0; 95% confidence interval (95% CI) 0-0.64; nominal P = 0.015], no systemic embolism, and 2 vs. 1 deaths (RR 1.98; 95% CI 0.19-54.00; nominal P > 0.999). Moreover, there were 3/735 vs. 6/721 major (RR 0.49; 95% CI 0.10-2.07; nominal P = 0.338) and 11 vs. 13 clinically relevant non-major bleeding events (RR 0.83; 95% CI 0.34-1.89; nominal P = 0.685). In summary, rates of stroke, embolic events, deaths and bleedings were low for both apixaban and heparin/VKA in patients with AF undergoing cardioversion [17,21].

Two studies examined rivaroxaban in this context. In the post-hoc analysis of the ROCKET AF study [22] in 14,264 patients only 143 patients underwent 181 electrical ECVs. This number was small because, according to the protocol, the patients for whom an ECV was planned, were excluded from the trial. Because of this small number, the patients undergoing ECV, pharmacological cardioversion, and transcatheter ablation were analyzed together. There were 2 thromboembolic events in the rivaroxaban group (1.64%) and 3 in the warfarin group (2.48%).

Rivaroxaban was compared to warfarin in the prospective randomized X-VeRT study specifically focused on ECV [15], where 1,504 patients with hemodynamically stable NVAF were randomized in a 2:1 ratio to receive rivaroxaban once daily (20 mg/day, or 15 mg/day in patients with creatinine clearance [CrCl] 30-49 ml/min), or VKAs. Patients were also randomized to either early strategy or delayed strategy for ECV. For early ECV, rivaroxaban or VKA were administered for a period of 1-5 days prior to ECV, and for 6 weeks after the procedure. For late ECV, patients received rivaroxaban or a VKA for 3-8 weeks before ECV and for further 6 weeks. Interestingly, among patients assigned to late ECV, 77% of the rivaroxaban group and only 36.3% of the VKA group underwent ECV within the expected period (p <0.001). The main reason for postponing the procedure in the patients treated with VKAs was the failure to achieve adequate anticoagulation with weekly INRs within the range 2.0-3.0. The primary efficacy outcome was the composite of stroke, transient ischaemic attack, peripheral embolism, myocardial infarction, and cardiovascular death. The primary efficacy outcome occurred in 5 (two strokes) of 978 patients (0.51%) in the rivaroxaban group and in 5 (two strokes) of 492 patients (1.02%) in the VKA group [risk ratio 0.50; 95% confidence interval (CI) 0.15-1.73]. The primary safety outcome was major bleeding. Major bleeding occurred in 6 patients (0.6%) in the rivaroxaban group and 4 patients (0.8%) in the VKA group (risk ratio 0.76; 95% CI 0.21-2.67) [15]. Consequently, rivaroxaban can be considered an effective and safe alternative to VKAs.

	1	2	3	4	5	TOT
5.1 Manage follow-up and intermediate controls	2	3	20	18	19	62
	8%		92%			100%
5.2 Manage temporary suspension of anticoagulation therapy prior to invasive diagnostics and interventions, as well as in case of minor bleeding	6	10	18	17	11	62
	26%		74%			100%
5.3 Manage potential adverse events	7	17	15	14	9	62
	39%		61%			100%
5.4 Not to be involved in the management of patients treated with DOACs	36	18	5	2	1	62
	87%		13%			100%

Table 5: **Statements 5 on GPs role in the management of patients treated with DOACs**

The post-hoc analysis of the ENGAGE AF-TIMI 48 trial regarded a total of 632 ECV attempts performed while on study drug in 365 patients [23]. In the 30 days after ECV, stroke or systemic embolism occurred in 2 patients on the lower-dose edoxaban regimen; none occurred with warfarin or higher-dose edoxaban. There were no major bleeding events and 1 death (higher-dose edoxaban) in the same timespan. Consequently, thromboembolic and major bleeding events post ECV were infrequent and similar with edoxaban and warfarin in the ENGAGE AF-TIMI 48 trial [23]. The ENSURE-AF study is the largest randomized clinical trial comparing a DOAC agent and VKAs in patients with NVAF undergoing ECV [16]. The study enrolled 2,199 patients and compared in a 1:1 fashion edoxaban mono-therapy daily with the enoxaparin/warfarin treatment with a mean TTR (INR 2.0-3.0) of 70.8%. The primary efficacy endpoint was a composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality, analysed by intention to treat. It occurred in 5 (<1%) patients in the edoxaban group versus 11 (1%) in the enoxaparin-warfarin group (odds ratio [OR] 0.46, 95% CI 0.12-1.43). The primary safety endpoint was major and clinically relevant non-major bleeding. It occurred in 16 (1%) of patients given edoxaban versus 11 (1%) of patients given enoxaparin-warfarin (OR 1.48, 95% CI 0.64-3.55). The results were independent of the TEE-guided strategy and anticoagulation status. Edoxaban was shown as a valid alternative to warfarin in subjects undergoing both TEE-guided ECV or late ECV [16].

The results of this consensus were totally convergent in deeming the treatment with DOACs as first choice compared to VKAs also in patients who undergo ECV.

Scenario 3. Role of GPs and TAO centers (topics 5, 6 and 7)

According to the expert panel, GPs should manage the follow-up and the intermediate controls, monitoring renal function and blood count. Moreover, GPs could indicate temporary suspension of anticoagulation therapy prior to invasive diagnostics and interventions, as well in case of minor bleeding (Table 5, items 5.1-5.2). This scenario is also suggested by the European Heart Rhythm Association (EHRA) Practical Guide for the use of anticoagulants in patients with AF [24]. There was no consensus on the exclusive role of GPs in control and management of any adverse events, which should - at least in selected cases - be prerogative of the specialist (namely, Centro Prescrittore in Italy) (Table 5, item 5.3). The consensus was broad on the involvement of GPs in the management of patients treated with DOACs (Table 5, item 5.4). However, the panel highlighted operative issues as the number of therapeutic plans with DOACs is constantly increasing (e.g., in Lazio Region, about 3,000 new therapeutic plans/month are recorded). In this setting, service providing for the subsequent year is overflowing. A further problem raised by the panel is related to patients who do not have the clinical documentation suitable for follow-up visits (echocardiogram and updated biochemical tests).

Consensus was reached on the control and management of adverse events, as well as renewal of therapeutic plan and start of therapy with DOACs, performed by TAO centers (Table 6, items 6.1-6.5).

TAO centers should continue managing patients for whom AVKs is the only therapeutic option. Namely: carriers of mechanical valve prostheses, patients with moderate-severe rheumatic mitral stenosis, patients with diseases affecting the factors of coagulation (e.g., anti-phospholipid antibodies) and patients with stable INR not switched to treatment with DOACs.

The panel evaluated the possibility of converting TAO centers into DOAC centers, for i) better management of the switch from AVKs to DOACs, ii) therapy with DOACs in naïve patients, iii) managing follow-up visits and renewals of therapeutic plans and iv) the

	1	2	3	4	5	TOT
6.1 Adverse events could be monitored and managed in TAO centers	3	5	20	14	20	62
	13%		87%			100%
6.2 Therapeutic plans for DOACs could be renewed in TAO centers	5	5	12	15	25	62
	16%		84%			100%
6.3 DAOCs treatment in naïve patients could be start in TAO centers	7	9	16	12	18	62
	26%		74%			100%
6.4 Follow-up vistits could be managed in TAO centers	4	13	23	12	10	62
	27%		73%			100%
6.5 Potential switch from VKAs to DOACs could be evaluated in TAO centers	4	7	18	14	19	62
	18%		82%			100%

Table 6: **Statements 6 on the role of TAO centers**

	1	2	3	4	5	TOT
7.1 GPs can replace TAO centers and/or specialists in prescribing therapy and managing follow-up visits for patients treated with DOACs	11	17	15	9	10	62
	45%		55%			100%
7.2 GPs can replace TAO centers and/or specialists in renewing therapeutic plans with DOACs	18	16	7	10	11	62
	55%		45%			100%
7.3 GPs can manage minor side effects of therapy with DOACs	1	5	19	28	9	62
	10%		90%			100%
7.4 GPs can prescribe DOACs in naïve patients	27	23	8	3	1	62
	81%		19%			100%
7.5 GPs should not be involved in the monitoring of patients treated with DOACs	38	14	7	1	2	62
	84%		16%			100%

Table 7: **Statements 7 on GPs role in the management of therapy with DOACs**

management of side effects. However, this scenario would perpetrate some territorial disparities due to lack of equality of the distribution of TAO centers in the Country and within Regions.

Clinicians (such as cardiologists, internists, neurologists) could manage prescription of DOACs in naïve patients and switch from treatment with AVKs to DOACs in patients with low TTR.

No consensus was reached on the hypothesis that the GPs can replace TAO/DOAC centers neither in prescription and management of DOAC-based therapy nor in the renewal of the therapeutic plan (Table 7, statements 7.1 and 7.2). Although GPs should not prescribe DOACs in naïve patients (Table 7, statement 7.4), they should be involved in the monitoring of patients treated with DOACs (Table 7, statement 7.5), being in charge of the management of DOACs minor side effects (Table 7, statement 7.3).

Regarding the involvement of the GPs, the panel expressed a negative consensus on the possibility that the GPs will carry out the first prescription of a DOAC or renew the treatment plan when expired. It was agreed instead that the GPs shall manage the follow-up and the intermediate controls in patients treated with DOACs. This position is also suggested by a European consensus document [24].

Nevertheless, according to the expert panel, the TAO centers will continue managing patients who have unique indications to VKAs, such as patients with mechanical prostheses, rheumatic mitral stenosis, single coagulation factor disorders (e.g., anti-phospholipid antibodies), and with stable INR.

Converting TAO centers into DOAC centers may be envisioned, with the specific aim of optimizing the management of VKA to DOAC transition, the referral of naïve patient to DOAC therapy, the intermediate controls, and the restorations of therapeutic plans, as well as the management of adverse events. However, this transformation in principle may introduce the risk of regional disparities. The prescription of DOACs in naïve patients and the transition from VKAs to DOACs in patients with low TTR, should be managed by the specialist (cardiologist, internist, neurologist) who can follow the patient directly. There was no consensus in the panel on the control and management of the possible adverse events by the GP.

The panel debated the operational weaknesses related to the TAO to DOAC centers, as the number of DOAC therapeutic plans is constantly increasing (e.g., according to data provided by the Lazio region, around 3,000/month new DOAC therapy are currently established), leading to saturation of the planning of health services in the following year [25].

A further issue discussed by the panel is the lack of clinical documentation (echocardiogram or updated biochemical tests) suitable for the follow-up visits of the patient at the referral center, as suggested by guidelines and consensus papers [4,24,26].

In August 2018, a consensus document from SIMG-FCSA (Società Italiana di Medicina Generale e delle cure primarie – Federazione Centri per la diagnosi e la Sorveglianza delle terapie Antitrombotiche) was issued on the correct anticoagulation procedures, gathering the opinions of different experts on the theme of clinical/organizational course for an integrated management of DOAC [27]. This document highlights that DOACs represent therapeutic agents of great social impact (improving the quality of life of patients), and underscores that their use must be managed appropriately and dutifully, by exploiting the collaboration among all the health Tables involved, to improve drug effectiveness and safety. Therefore, it is proposed a model of shared and integrated management also for DOACs, which includes a close, collaborative, and interactive action among GPs, thrombosis centers, and specialists, with the aim of improving the quality of life of patients, and ensuring prescription appropriateness and a level of assistance of high quality with regard to efficacy and safety [27].

The health management of patients treated with DOACs (at first visit and at follow-up) is currently performed by the TAO center, or by the specialist who takes care of the patient, ensuring the required appropriateness and the consequent safety and efficacy of the treatment. Given the strategic role of the GPs in the follow-up of patients treated with DOACs, for ensuring prescription appropriateness, it is proposed to involve GPs in the implementation of an integrated management project, similar to that existing for the management of VKAs.

Scenario 4. Oncological patients with NVAF or VTE (topics 8 and 9)

Participants agreed on the use of therapy with DOACs in oncological patients with NVAF. However, the importance of a careful evaluation of possible interactions with drugs administered in these patients for cancer therapy was underlined (Table 8, statement 8.1, 8.2). This consensus derives from the results of subgroup analyses of patients with cancer enrolled in clinical trials on DOACs therapy in AF, as reported in the results of a sub-analysis on oncological patients cancer in the ENGAGE AF-TIMI 48 study [28], and from the Hokusai VTE Cancer trial, which evaluated safety and efficacy of edoxaban in oncological patients with VTE [29]. Although these data were about patients treated for a different indication (VTE instead of AF), they added important information on safety of edoxaban in cancer patients, given the large number of antineoplastic and chemotherapeutic agents used in the study [29,30].

Based on the recent results of the prospective trial Hokusai VTE Cancer [29], a general consensus was reached on the use of DOACs in the setting of patients with VTE and cancer (Table 9, statement 9.1-9.3.).

Regarding the neoplastic patient, the panel expressed a general consensus on the use of DOACs, following recent studies that demonstrated efficacy, safety, and compatibility with antineoplastic and chemotherapeutic agents [29,30]. However, a drug warning is maintained in the subgroup of patients with gastric and intestinal neoplasms, where a higher degree of bleeding was observed, compared to low molecular weight heparin administered by subcutaneous injection [29]. Until 2017 the guidelines indicated low-molecular weight heparins as the sole treatment available for the secondary prophylaxis of venous thrombosis and pulmonary embolism in cancer patients [31]. At the end of 2017, the Hokusai VTE Cancer study

	1	2	3	4	5	TOT
8.1 DOACs can be administered as in any other patients	3	16	13	19	11	62
	31%		69%			100%
8.2 DOACs can only be administered if they do not interact with anti-cancer treatments	1	1	20	22	18	62
	3%		97%			100%
8.3 DOACs should never be administered	29	30	3	0	0	62
	95%		5%			100%

Table 8: **Statements 8 on DOACs use in oncological patients with NVAF**

	1	2	3	4	5	TOT
9.1 In this kind of patients it is necessary to pay attention to anticoagulant therapy for 6-12 months after detection of VTE, as it is the second cause of death	0	0	15	18	29	62
	0%		100%			100%
9.2 Beacuse of the many interactions between DAOCs, anti-epileptic drugs and antineoplastic drugs, it is necessary to monito the action of DOACs on cytochrome CYP3A4 and on P-glycoprotein (Pgp)	0	9	26	19	8	62
	15%		85%			100%
9.3 Better quality of life associated with treatment with DAOCs compared to low molecular weight heparin in venous secondary prophylaxis is ensured by the handling of DOACs (Hokusai VTE Cancer trial)	1	1	7	16	37	62
	3%		97%			100%

Table 9: **Statements 9 on the use of DOACs in oncological patients with VTE**

compared edoxaban and dalteparin in the secondary prophylaxis of VTE in cancer patients. In the prospective, multicentric study with a PROBE design, edoxaban was shown to be not inferior to dalteparin in the composite endpoint of VTE recurrence and major bleeding [29]. Recurrent VTE was reduced by edoxaban: 7.9% versus 11.3% of the dalteparin group. There was an increase in major bleedings (although not fatal or life-threatening) with the DOAC, with 6.9% versus 4% of the dalteparin group. However, this increase is likely restricted to patients presenting with a randomized gastrointestinal neoplasia. The site affected by the increase in bleeding was that of the upper gastrointestinal tract. A greater proportion of gastric malignancies allocated to the edoxaban arm may have influenced the outcome [29].

Scenario 5. Administration route, adherence to therapy and drug interactions (topics 10 and 11)

The panel expressed broad consensus that mono-administration of DOACs could end-up in greater adherence and better quality of life of patients who are often poly-treated because of co-morbidities (Table 10, statement 10.1, 10.2). However, consensus was not reached on a real impact of the different route of administration of DOACs on adherence in clinical practice.

DOACs interact with commonly used drugs such as antibiotics, antifungals or antiarrhythmics [24]. The panel did not agree on the need for further discussion of the drug interactions of the DOACs, as

	1	2	3	4	5	TOT
10.1 Single administration can advantageous because it promotes adherence to therapy	0	6	20	18	18	62
	10%		90%			100%
10.2 Single administration is preferable because it improves the quality of life of patients	1	9	23	14	15	62
	16%		84%			100%
10.3 There are no differences in terms of adherence to therapy considering the route of administration	9	31	15	6	1	62
	65%		35%			100%
10.4 In clinical practice patients prefer single administration regimen	0	10	31	15	6	62
	16%		84%			100%
10.5 In clinical practice patients prefer double administration regimen	9	43	7	1	2	62
	84%		16%			100%
10.6 If properly treated, patients mantain the reccomended treatment regimen for a long time	3	0	13	30	16	62
	5%		95%			100%
10.7 Seriousness of AF or VTE disease and the possible treatment with anti-coagulants (in particular with DAOCs) should be clearly explained to patients	0	0	8	19	35	62
	0%		100%			100%
10.8 Specific attention should be paid to the undesiderable effects reported by patients	2	0	13	25	22	62
	3%		97%			100%

Table 10: **Statements 10 on the route of administration and therapy adherence**

11.1 Currently, drug interactions with DOACs are poorly known and further information is needed	1	21	16	16	8	62
	35%		65%			100%
11.2 The profile of drug interactions of individual DOACs is a criterion of choice for drugs of this class	0	1	23	26	12	62
	2%		98%			100%
11.3 A better understanding of drug interactions of DOACs would ensure greater safety for patients	0	0	16	20	26	62
	0%		100%			100%

Table 11: **Statements 11 on drug interactions**

no consolidated data are available on this point (Table 11, statement 11.1). However, the interactions profile is standard of choice for the use of a specific DOAC. Participants state that further investigation and deeper knowledge on the interactions of each single DOAC could ensure a better safety for patients (Table 11, statements 11.2, 11.3).

Mono-therapy is certainly recognized as favoring adherence and quality of life, although this is not the main element ensuring consistency of the intake of the anticoagulant. A correct education and motivation by the prescriber of DOAC drugs should promote the patient's awareness of the importance of daily intake of anticoagulant therapy. Adherence to treatment is usually assessed by the percentage of days in the period in which the patient has taken the therapy. An adherence of at least 80% is considered suitable, while lower percentages indicate inadequate adherence. Inconsistent adherence to VKAs were depending on the modalities of monitoring and on health systems, which are often inadequate. It can be expected that the constant dose, the easy intake mode, the modality, and the unneeded periodic controls may ensure a greater adherence to the new DOACs. Some studies on adherence with DOACs or VKAs are already available, while others are ongoing [32,33]. Very interesting results were shown by a recent retrospective study analyzing not only the adherence to both old and new anticoagulants, but also the clinical effect of the insufficient adherence. The study was based on insurance databases that examined 64,661 patients with AF (mean age 73 years, males 56.2%), who initiated the therapy with VKAs (warfarin, 59.1%), or DOACs (dabigatran, 15,8%, rivaroxaban, 19.1%, or apixaban, 6.0%), between 2010 and 2014 [25]. During the median 1.1-year follow-up only 47.5% of patients treated with a DOAC showed adequate adherence (>80% of days with appropriate drug usage), however this fraction was significantly greater than the one of patients treated with warfarin (40.2%, p <0.001). Similarly, data of 7,265 patients from primary care practices across Germany suggest that rivaroxaban and dabigatran have a better persistence than VKA at Day 360 and that rivaroxaban was associated with better persistence and adherence than dabigatran [34,35]. On the contrary, a population-based study in Ontario (n=125,195) recently provided data about warfarin treatment in patients aged more than 65 years: 31.8% discontinued therapy within 1 year, 43.2% discontinued therapy within 2 years, and 61.3% discontinued therapy within 5 years [36]. In conclusion, adherence to anticoagulation was generally modest in the clinical practice, but it was significantly improved by the use of DOACs. The clinical importance of good adherence to anticoagulant therapy in patients with AF was likely greater in patients at increased risk of complications (CHA2DS2-VASc ≥ 2) [37]. The work of Castellucci et al. was aimed at evaluating patient self-reported adherence to anticoagulant treatment at a third-level hemostasis and thrombosis center [38]. This is a cross-sectional observational study in patients receiving oral anticoagulation agents, both VKAs and DOACs (rivaroxaban, dabigatran and apixaban). Adherence to treatment was assessed using the Morisky scale - a questionnaire based on 4 simple questions - and the basic characteristics of the patients were assessed in association with adhesion. Among the 500 patients who completed the questionnaire, 74% were in treatment with VKAs and 26% with DOACs (79% rivaroxaban, 19% dabigatran and 2% apixaban). The 72% of patients were treated for VTE and 18% for AF. Self-reported adherence according to the Morisky scale was 56.2% in patients treated with VKAs and 57.1% in patients treated with DOACs [38]. Age, female gender, and oral intake of other drugs were predictive factors of good adherence to treatment, even after multivariate analysis. The study found that adherence to the oral anticoagulant treatment was similar in patients treated both with VKAs and DOACs. Furthermore, there were no differences in between mono-therapy and dual-therapy. The authors conclude that, as long as adherence laboratory tests to evaluate adherence to treatment with DOACs will not be generally available, the physicians must emphasize with the patient the importance of adherence at each visit. Moreover, the Morisky scale, albeit providing a simple system to evaluate the adherence to anticoagulant treatment, has not yet been validated for this purpose [38].

A retrospective cohort study in patients of the Veterans Affairs (VA) Healthcare System who started pharmacotherapy with dabigatran, rivaroxaban, or apixaban between November 2010 and January 2015 for NVAF with a CHA_2DS_2-VASc score ≥2, showed that adherence, determined using the prescription data and estimated by calculating the proportion of days covered (PDC) during the first year of therapy, was relatively low [39]. Clinical results, including all-cause mortality and stroke, were measured at 6 months from the initiation of therapy and were used to evaluate adherence for each DOAC. A total of 2,882 patients were included. Most were prescribed dabigatran (72.7%), then rivaroxaban (19.8%), or apixaban (7.5%). The mean PDC was 0.84 ± 0.20 for dabigatran, 0.86 ± 0.18 for rivaroxaban, and 0.89 ± 0.14 for apixaban (p <0.01). The percentage of non-adherent patients (PDC <0.80) was 27.6% in general and was variable according to the DOAC administered. Low adherence to dabigatran was associated with a higher risk of mortality and stroke (HR 1.07; 95% CI 1.03-1.12 for a decrease of 0.10 PDC). The study concluded that in a real-life population of patients whom an anticoagulant was prescribed for AF, more than a quarter of patients showed non-optimal adherence [39]. Low adherence was associated with a higher risk of mortality and stroke. Efforts to identify non-adherent patients and adherence interventions are needed to improve outcomes. It should however be emphasized that the impact of mono- or dual-therapy of the DOAC on adherence remains under discussion yet. In a review of 76 studies, compliance with single-dose administration and twice-daily dosing was 79 ± 14% and 69 ± 15%, respectively. Therefore, in absolute terms single-dose administration was more favorable, even if the difference did not reach statistical significance [40]. In addition, data from a national Canadian survey suggest that patients prescribed and taking once daily medications (rivaroxaban or warfarin) show better compliance: approximately 30% of twice daily medications being taken once daily, with significantly more missed doses compared with once daily medications [41]. On the other hand, the EHRA Practical Guidelines clearly state that daily single-dose administration leads to greater adherence compared to twice-daily dosing in patients with cardiovascular disease [24]. When prescribing therapy with DOACs, in order to implement adherence to therapy it is essential: i) to emphasize the value of the dosage regimen in daily mono- or double-fixed-dose, and the importance of adherence to therapy; ii) to underscore that poor adherence is the main cause of ineffective drug therapy, providing simple and clear instructions; iii) to listen to the patient, his needs and hesitations aiming at personalizing the dosage regimen based on the patient's characteristics and wishes.

Scenario 6. Low doses of DOACs, frail patients and chronic kidney disease (topics 12, 13, 14 and 15)

Participants agreed on the need to pay close attention to the use of the appropriate dosage of DOACs. In particular, the use of so-called low doses outside the pre-specified indications for each individual DOAC is strongly discouraged (Table 12, statements 12.1, 12.2). Furthermore, the panel expresses a unanimous consensus against the use off-label of low-dose with the aim of reducing bleeding rates. The available data, in fact, do not support, but rather strongly contrast this attitude (Table 12, statement 12.3).

Participants express preference of the use of DOACs over VKAs in frail patients needing triple therapy for coronary artery disease (CAD) and AF (Table 13, statements 13.1, 13.2).

In patients with GFR <30 ml/min, therapy with VKAs should be used. DOACs may be used only in the presence of specific supporting data in this patient setting (Table 14, statements 14.1 and 14.3).

The population of frail patients is a broad category well represented in clinical trials and real-world evidence. Therefore, convincing data are available on the use of DOACs in these patients. Wide consensus was expressed on the use of DOACs as an advantage for frail patients also in terms of safety (Table 15, statement 15.1), even in the presence of renal disease. Most of all, when DOACs have been specially tested in these settings (Table 15, statements 15.3 and 15.4).

The defensive medicine has probably exceeded in using low dosages beyond the actual indications of the technical data sheets. An improper use of low doses is possibly the consequence of the attempt to further improve the safety of anticoagulant therapy in subgroups of patients who are considered frail. However, the inappropriate use of low dosages can lead to severe consequences on drug efficacy. All DOACs currently on the market have two doses that are indicated for the prevention of ischemic stroke and systemic embolism in patients with NVAF [42]. Although these dosages are generally defined as full dosages and reduced dosages, they exhibit significant differences indeed, both from a pharmacological and clinical point of view. These differences derive mainly from the diverse design of the pivotal studies of the four DOACs.

In the RE-LY study, patients were randomized in open into three homogeneous groups, dabigatran 150 mg bid, dabigatran 110 mg bid, and warfarin with adjusted doses, to maintain INR between 2.0 and 3.0 [5]. In ARISTOTLE, ENGAGE AF-TIMI 48, and ROCKET AF studies, the enrollment included two arms: 1) a warfarin arm with adjusted doses to maintain the INR between 2.0 and 3.0, and 2) an arm with apixaban 5 mg bid, edoxaban 60 mg/day (randomized to another arm receiving edoxaban 30 mg/day which did not reach the first outcome), and rivaroxaban 20 mg/day in the three studies respectively [6-8]. In the DOAC arms, the dose reduction was allowed (to 2.5 mg bid for apixaban, 30 mg/day for edoxaban (or 15 mg/day for the second arm not reaching the first outcome and so not on commerce), and 15 mg/day for rivaroxaban, respectively), based on characteristics differently pre-specified in the three studies (two or more characteristics among age ≥80 years, weight ≤60 kg, and serum creatinine ≥1.5 mg/dl for apixaban; one or more characteristics among creatinine clearance 30-50 ml/min, weight ≤60 kg, and concomitant use of P-glycoprotein inhibitors for edoxaban; creatinine clearance 30-49 ml/min for rivaroxaban). This dose reduction was based on the results of phase II studies on the plasma concentrations of these drugs [43,44]. In practical terms, these results prompt to issue a strong recommendation for the clinician to carefully follow the dose reduction criteria for each factor Xa inhibitor, to ensure the most effective and safe dosage to each patient [24]. To date, the prescriptions for the DOAC category in Italy has exceeded VKAs (corresponding to a market share of 54% versus 46%, according to the IMS Health data of December 2017), in a market steered essentially by drivers on safety, as demonstrated also in the survey produced by ARCA Biopharma [45]. Currently, about 40% of the patients are administered the reduced dosage of factor Xa inhibitors and 60% of patients in treatment with dabigatran take the 110 mg bid dose. The fractions of patients treated with low doses strongly differ from those of the pivotal studies (5% for apixaban 2.5 bid, 25% for edoxaban 30 mg/day and 20% for rivaroxaban 15 mg/day) [6-8]. The overprescribing of low doses for factor Xa inhibitors may be a sign of frequent underdosing of the DOACs, resulting in the exposure of a proportion of patients to a greater risk of brain and systemic embolism. This hypothesis is supported by observational data obtained in the real-world setting that show that the use of reduced doses beyond the pre-specified conditions, may not provide adequate protection against cardioembolic events [37,46].

Statement 14 analyzes the possibility of administering DOACs in patients with NVAF and GFR below 30 ml/min. The expert panel recommend reducing the time interval between renal function controls (although a consensus has not been reached on this point), and reiterates that DOACs can be used in these patients only in the presence of supporting evidence. Chronic kidney disease is common in patients with AF. A European register reported a prevalence of mild and moderate-severe renal failure in 47% and 18% of patients with AF, respectively [47]. Chronic renal failure is also associated with the increased risk of both thrombotic and hemorrhagic events, compared to patients with AF and normal renal function. Since all DOACs are, at least partially, eliminated by the renal route, the prescription of these drugs requires an assessment of renal function before initiating the therapy and regularly during treatment. In this regard, a recent study has shown that, similar to what has already been reported for patients treated with warfarin or aspirin, renal failure increases the risk of bleeding also in patients treated with DOACs [48]. Therefore, it is important to monitor renal function regularly in patients with AF who have been prescribed a DOAC, and to try identifying the patients who may experience worsening of renal function over time (e.g., patients with already reduced renal function, advanced age, heart failure, or contraindicated therapies). In the DOAC pivotal studies, renal function was evaluated using the Cockcroft-Gault equation, which provides an estimate of GFR (eGFR), taking into account the patient's age, sex, weight, and creatinine levels. A recent study by Becattini et al. evaluated 449 patients with NVAF (mean age 79 years) who were followed prospectively from the first prescription of a DOAC [49]. In this study the renal function was evaluated at regular intervals (every 3-6 months or when required by clinical reasons) using the Cockcroft-Gault equation, and was classified into 5 stages: 1.) conserved renal function (eGFR ≥90 ml/min); 2.) slight reduction in renal function (eGFR 60-89 ml/min); 3.) moderate reduction of renal function (eGFR 30-59 ml/min); 4.)

12.1 The off-label use of low doses may increase the risk of ischemic stroke	0	3	13	20	26	62
	5%		95%			100%
12.2 Proper use of low doses does not result in a reduction in efficacy and safety	2	8	21	20	11	62
	16%		84%			100%
12.3. The use of low doses even if off-label may increase safety by reducing the risk of bleeding	16	30	7	8	1	62
	74%		26%			100%

Table 12: **Statements 12 on safety on the use of DOACs at low doses**

	1	2	3	4	5	TOT
13.1 The use of VKAs is preferable in frail patients with NVAF and CAD needing triple therapy	20	35	7	0	0	62
	89%		11%			100%
13.2 The use of DOACs is preferable in frail patients with NVAF and CAD needing triple therapy	0	1	10	29	22	62
	2%		98%			100%

Table 13: **Statements 13 on the use of DOACs in frail patients**

	1	2	3	4	5	TOT
14.1 VKAs might be used	3	12	20	14	13	62
	24%		76%			100%
14.2 DOACs might be used with closer follow-up vistis	10	18	21	29	4	82
	34%		66%			100%
14.3 Only DOACs with available data on low-doses might be used	9	4	24	16	9	62
	21%		79%			100%
14.4 DOACs should be used based on clinical experience and individual patient characteristics	13	15	15	12	7	62
	45%		55%			100%

Table 14: **Statements 14: on the use of DOACs in patients with NVAF and GFR <30 ml/min**

	1	2	3	4	5	TOT
15.1 Yes, beacuse of higher safety	0	2	15	14	31	62
	3%		97%			100%
15.2 No, treatment with VKAs is preferable particularly in frail patients with moderate to severe renal disease	10	37	10	5	0	62
	76%		24%			100%
15.3 Only together with closer follow-up visits	1	14	24	19	4	62
	24%		76%			100%
15.4 Only if DOACs may be used at low doses according to product data sheet	2	18	29	9	4	62
	32%		68%			100%

Table 15: **Statements 15: The use of DOACs is particularly beneficial in frail patients**

	1	2	3	4	5	TOT
16.1 Costs	12	18	11	10	11	62
	48%		52%			100%
16.2 Need for therapeutic plan	9	14	16	11	12	62
	37%		63%			100%
16.3 Insufficient knowledge of the drug by GPs	5	17	20	12	8	62
	35%		65%			100%
16.4 Management of follow-up visits and adherence uncertainty	12	26	14	8	2	62
	61%		39%			100%

Table 16: **Statements 16 on the main limit on DOACs use**

severe reduction of renal function (eGFR 15-30 ml/min); 5.) pre-dialysis (eGFR <15 ml/min). The aim of this study was analyzing the frequency of changes in renal function in patients with AF and the consequence on the hemorrhagic risk during DOAC therapy. A deterioration in renal function causing staging changes occurred in 34% of patients. The advanced age and the presence of heart failure were independent factors associated with the worsening of renal function. During an average follow-up of 1.5 years, the incidence rate of major bleeding was 6.1% per patient/year and that of non-major, but clinically-relevant bleeding was 9.3% per patient/year. The eGFR was an independent risk factor for bleeding complications: each reduction of 1.0 ml/min of the eGFR was associated with a 2% increase in the risk of major bleeding. Furthermore, the change in staging of renal function was associated with an approximately 2-fold increase in the risk of major bleeding after age adjustment, diabetes and heart failure [49]. According to the opinion of the expert panel the advantage of DOACs compared to VKAs in the frail patient resides in the increased safety also in the subgroup with mild renal failure. The panel agrees on the need to increase the frequency of controls in frail patients [50,51].

Scenario 7. Limits to the use of DOACs (topic 16)

On the limits to the use of DOACs, participants did not reach any consensus (Table 16, statements 16.1-16.4). The main limitation to the use of DOACs can no longer be charged to i) the higher cost

in terms of single tablet compared to warfarin, ii) time spent to fill out the treatment plan, iii) the need for adequate information for GPs, and not even to iv) the issue of who and how patients treated with DOACs should be monitored in term of follow-up visits and adherence to therapy.

Regarding the statement 16 there is no consensus that the cost of the DOACs represents a limit for their use. There is consensus instead that the time required to complete the treatment plans and the insufficient information of the GPs are barriers to the use of the DOACs. On the contrary, the panel has reached no consensus on the fact that the uncertainty about who oversees the follow-up and adherence controls is a limiting factor to the use of DOACs.

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Safety of Same Day Discharge after Atrial Fibrillation Ablation

Devender N. Akula[1], Mariam Wassef[1], Pallavi Luthra[1], Edward Friedrich[1], Daniel J. Katz[1], Steven A. Levi[1] and Alfred Sacchetti[1]

[1]Our Lady of Lourdes Hospital, Camden, NJ, U.S.

Abstract

Introduction: It is routine practice to observe patients (pts) overnight in the hospital after atrial fibrillation (AF) ablation. We report single center experience comparing the rate of complications prior to and after implementing a strategy of same day discharge (SDD) following AF ablation.

Methods: We reviewed the charts of consecutive pts who underwent AF ablation between Jan 2005 to Dec 2015. Patients who were electively admitted to undergo AF ablation or left atrial flutter ablation (AFL) were included. Patients undergoing only right atrial flutter ablation and those admitted inpatient were excluded. In Sept 2012 SDD strategy was implemented. Complication rates were collected up to 3 months post ablation. Major complications were defined as death, pericardial tamponade, cerebrovascular accident (CVA), hematoma requiring intervention, pulmonary vein stenosis, diaphragmatic paralysis or atrioesophageal fistula formation. Minor complications were defined as hematoma not requiring intervention and procedure related readmissions. Comparisons were made using an intention to treat analysis.

Results: Group A (between Jan 2005 to Feb 2010) included 145 patients (87 males; 60.2 yrs mean age; 103 paroxysmal AF) who were observed overnight. Group B (between Mar 2010 to Dec 2015) included 426 patients (298 males; 62.3 yrs mean age; 247 paroxysmal AF) undergoing ablation following implementation of the SDD strategy. Patients in Group B were contacted by phone next day. In Group B, 51/426 (12%) pts were not discharged same day due to non-ablation related medical care (15/50 pts), ablation related complications (17/50 pts), pt preference (14/50 pts) and late cases (5/50 pts). Rate of total complications was more frequent in Group A (Group A 11.7% vs Group B 4.4%; p 0.026). Major complications occurred in 2 pts in Group A and 6 pts in Group B. None of the major complications in Group B occurred within 24 hrs of discharge. Only 1 pt in Group B had pericardial effusion drained 10 days post procedure. Most common minor complication in Group A was hematoma not requiring intervention and in Group B was procedure related readmissions.

Conclusions: Our data suggest that SDD after AF or AFL ablation can be safely implemented in majority of pts with similar outcomes as pts observed overnight.

Introduction

In appropriate patients ablation treatment for AF has rapidly become standard of care as recommended by various guidelines.[1-3] Several studies have shown that ablation procedure is more effective in controlling AF symptoms when compared to anti arrhythmic medications[4-6]. This has led to explosion of number of AF ablations done worldwide. Same day discharge (SDD) of patients after ablation of common arrhythmias has been shown to be safe[7-8]. It is standard of care after AF ablation to observe patients overnight in the hospital. This is mainly due to concerns regarding procedure related complications within twenty four hours of ablation. Same day discharge is an attractive option as it results in less health care utilization, which can then potentially translate to better patient satisfaction and health care cost savings. We report single center experience comparing the rate of complications prior to and after implementing a strategy of same day discharge following AF ablation.

Key Words

Atrial fibrillation, Ablation, Same day discharge, Complications.

Corresponding Author
Devender N. Akula, MD, FACC, FHRS
Lourdes Cardiology
1 Brace Rd, Ste C
Cherry Hill, NJ 08034

Methods

Patient Selection:

After obtaining IRB approval, we reviewed charts of consecutive patients who underwent AF and left atrial flutter (AFL) ablation in our institution between January 2005 and December 2015. Patients who underwent AF ablation as inpatients and standalone right sided flutter ablation were excluded from the study. In September 2012 strategy of SDD was implemented. SDD was defined as discharge home within same calendar day. All patients who had SDD were contacted next day by phone. Group A included patients who

were observed overnight. Group B included patients following implementation of the SDD strategy.

Ablation Technique:

All patients on the day of procedure were brought to the electrophysiology laboratory in a fasting non-sedated state. AF and AFL ablations were performed under either monitored anesthesia (MAC) or general anesthesia. Right and left femoral veins were accessed and typically four sheaths (one 8 French and three 7 French sheaths) were placed utilizing modified seldinger technique. A 6 French steerable decapolar catheter (Boston Scientific, Minnesota, USA) was placed in coronary sinus under fluoroscopic guidance. Double trans-septal puncture was performed under intra cardiac echo (Siemens, Johnson and Johnson, USA) and fluoroscopic guidance with continuous pressure monitoring using BRK transseptal needle (St Jude Medical, Minnesota, USA). Three dimensional mapping of the atria was performed using Carto mapping system (Biosense Webster, Johnson & Johnson, New Jersey, USA). Pulmonary vein isolation was performed in all patients mostly using Lasso (Biosense Webster, Johnson & Johnson, New Jersey, USA) guidance. Effort was made to confirm entrance block into and exit block out of pulmonary veins. Additional ablation (linear lesions, complex fractionated electrogram ablation) were done in individual patients based on their underlying arrhythmia as per physician discretion. For anticoagulation heparin was used during procedure, with activated clotting time (ACT) goals varying during the study period. Typical goal of ACT was to keep it between 300 to 350 during later part of study period. Oral anticoagulation was resumed same day post procedure. Peri-procedure anticoagulation regimen was not standardized but was done as per operator preference. In general use of peri-procedure lovenox was more common in Group A than Group B. As ablation technique evolved there was move towards doing ablation without interrupting anticoagulation in Group B.

Follow up:

Group B patients were monitored for at least 6 hours post ablation in cardiac monitoring unit. Prior to discharge patients received detailed written instructions. Group B patients were reassessed by the nursing staff prior to discharge including inspection of groin access sites. SDD was cancelled if patient had any ablation related complications, non-ablation related medical care or due to patient specific/social reasons. Group A patients who stayed overnight were discharged home next day by the cardiology service if patient was clinically stable. Predischarge echocardiogram was not routinely done in either group. Post ablation electrocardiogram was obtained in all patients. Patients were instructed to follow in 2-4 weeks in office. Hospital records and outpatient electronic records up to three months post ablation were reviewed. Data collected include patient demographics, clinical history, anticoagulation status and complications. Major complications were defined as death, pericardial tamponade, stroke, hematoma requiring intervention, pulmonary vein stenosis, diaphragmatic paralysis or atrioesophageal fistula formation. Minor complications were defined as hematoma not requiring intervention and procedure related readmissions.

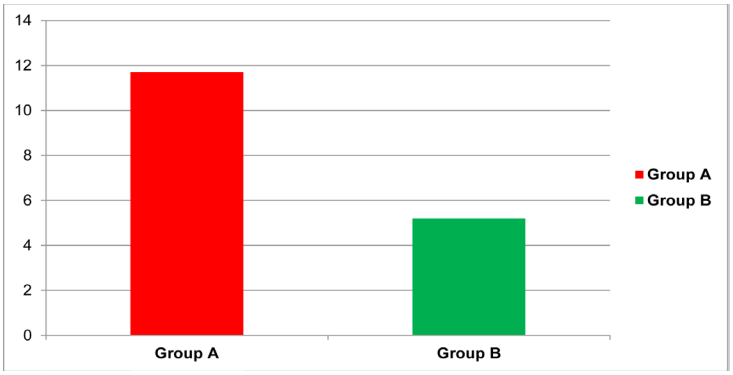

Figure 1: Total Complications in Groups A and B.

Table 1: Patient Baseline Characteristics

	Group A	Group B	P value
# patients	145 (25.4%)	426 (74.6%)	
Mean Age (yrs)	60.2	62.3	0.05
Males	86 (60%)	298 (52%)	0.06
Paroxysmal Afib	103 (72.5%)	247 (56.7%)	0.003
PVI	53 (40.5%)	162 (38.9%)	0.75

End Points:

Primary endpoint was comparison of complications rate between Group A and Group B patients.

Statistics:

Comparisons were made using intention to treat analysis.

Results

Total of 571 charts were reviewed and included in the study. Baseline characteristics of the patients in the study are shown in Table 1.

Group A included 145 patients who underwent ablation procedure between January 2005 to February 2010 and were observed overnight. Mean age was 60.2 years, with majority of patients being male (60%). Paroxysmal atrial fibrillation (PAF) was the dominant presenting arrhythmia (72.5%). Group B included 426 patients, between March 2010 to December 2015, undergoing ablation following implementation of the SDD strategy. Mean age was 62.3 years, with male (52%) and female (48%) genders almost equally represented. PAF was again the frequent presenting arrhythmia (56%). PAF was more common in Group A compared to Group B (72.5% vs 56.7% p=0.003). Pulmonary vein isolation ablation alone was performed in 40.5% in Group A and 38.9% in Group B (p=0.75).

In Group B, 50/426 (12%) patients were not discharged same day; 15 due to non-ablation related medical care, 17 for ablation related complications and 18 due to patient preference. No follow up data was available for 15 patients in Group A and 19 in Group B.

Total complications were more frequent in Group A as shown in

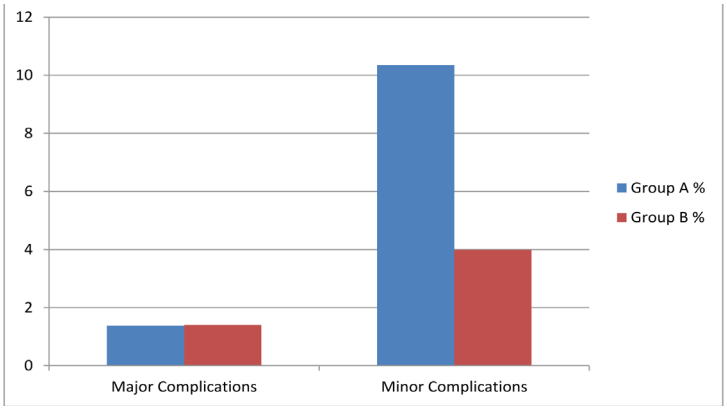

Figure 1: Total Complications in Groups A and B.

Table 2: Characteristics of patients with complications

	Group A	Group B	P value
Complications	17 (11.7%)	23 (4.4%)	p=0.026
Mean age (yrs)	65.9	64.2	p=0.66
LA size (cm)	4.3	4.5	p=0.55
Average Max ACT	331.7	325.1	p=0.69
Mean EF (%)	59.2	56.4	p=0.37
PVI only	4 (25%)	10 (47%)	p=0.15
Antiplatelet agent	7 (38.9%)	4 (18.2%)	p=0.14
DM	4 (22%)	8 (36%)	p=0.32
HTN	12 (66.6%)	11 (50%)	p=0.28
CAD	4 (22%)	1 (12.5%)	p=0.08

Figure 1 (Group A 11.7% vs Group B 4.4%; p 0.026).

Procedural characteristics of patients with complications in Group A & B are presented in Table 2.

In Group A, 17 total complications occurred while 23 total complications were seen in Group B. Major complications occurred in 2 patients (1.37%) in Group A, who had significant bleeding post procedure requiring blood transfusions (Figure 2).

In Group B major complications occurred in 6 patients (1.4%); 3 had pericardial effusion requiring drainage, 2 had transient ischemic attacks without residual sequelae and 1 required blood transfusion. None of the major complications in Group B occurred within 24 hours of discharge. Only one patient in Group B had pericardial effusion drained 10 days post procedure. Minor complications were common in Group A compared with Group B (10.3% versus 3.9%). Most common minor complication in Group A was hematoma not requiring intervention and in Group B was procedure related readmissions.

Discussion:

Our study shows that it is safe and feasible to discharge patients same day after atrial fibrillation ablation procedure. None of the patients discharged home same day had significant complications within twenty four hours of discharge. In fact total complications occurred more often in Group A patients who were observed overnight, suggesting operator inexperience and peri-procedure anticoagulation management as possible explanation.

Previous studies have shown that it is safe to discharge patients same day after common supraventricular arrhythmia ablation procedure. We believe this is the first study that has looked at the issue of same day discharge after AF ablation. Kalbfleisch et al studied 100 cases who underwent outpatient radiofrequency catheter ablation of accessory atrioventricular connections and found that only 2 patients had late femoral artery psuedoaneurysm requiring surgical repair[9]. Similarly in our study in Group B one patient had pericardial effusion that was drained 10 days post ablation, when he presented with persistent chest pain and shortness of breath. Pericardial effusion is one of the most feared early complication that can occur after AF ablation, especially as all these patients undergo trans septal procedure and require anticoagulation during ablation. Majority of these tend to happen during the procedure[10]. It was reassuring to see that none of our patients who went home same day had pericardial effusion within 24 hours after their discharge. Our study suggests that if patients have no pericardial effusion at end of procedure as visualized on intra-cardiac echocardiogram and are hemodynamically stable for 6 hours post ablation, their risk of developing pericardial effusion within 24 hours of discharge is very low. We did not require routine echocardiogram prior to discharge in the same day patients, as all our ablations are done utilizing intracardiac echocardiogram.

Since arterial cannulation is not routinely required during atrial fibrillation ablation, late vascular complications tend to be rare. Hematoma formation requiring no intervention was more common in Group A suggesting either anticoagulation regimen (frequent peri-procedure use of lower molecular weight heparin) or less experience as possible contributing factor. None of the patients, in either groups, required blood transfusion or intervention for vascular complication after discharge.

Other serious complications unique to AF ablation, like pulmonary vein stenosis and atrioesophageal fistula formation, tend to present days or weeks later[11-12], hence early discharge will not determine outcomes due to these issues.

Early discharge can lead to improved patient satisfaction at same time reducing health care utilization. Delivering safe and cost effective health care has become the corner stone of all health care policies. Same day discharge after AF has potential for cost savings. Though we have not yet analyzed the cost saving data in our study, prior studies utilizing same day discharge strategy after electrophysiology procedures have shown cost benefits[13]. Since AF ablation is fast becoming the most common ablation procedure done by electrophysiologist around the world, potential cost savings associated with same day discharge after this procedure can have significant impact on our health care delivery system.

Our study is not without limitations. It was a single center, retrospective study. Retrospective nature of the study clearly is the main limitation of the study even though main characteristics of the patients in both the groups were similar as shown in Table 2. Confounding cannot be excluded despite intention to treat analysis.

Over period of time, the ablation technique, technology and operator experience also changed. These factors can obviously influence outcomes. Clearly, as operators become more experienced the risk of complications tend to get lower, which can explain lower complication rate in Group B. Historically, use of Enoxaparin has been associated with significant peri procedural bleeding complications. Higher incidence of minor bleeding complications is probably related to that. One has to realize AF ablation is a complex procedure and should not be trivialized in terms of post procedural care. Overnight observation still provides a very high level of post-operative care, patient education and comfort that is of paramount important in taking care of these highly complex patients. The complexity of AF ablation has evolved over the years. Operators are ablating more extensively utilizing general anesthesia more often than otherwise. This imposes a higher level of morbidity mandating a closer and intense post-operative care. The decision to discharge a patient on the same day after AF ablation should be adjudicated on a case by case basis. This process should not be generalized and create a false sense of confidence for less experience operators.

In addition, ablations were performed in a high volume center by experienced electrophysiologist. These data may not be applicable to low volume centers or less experienced electrophysiologist. There was no pre-specified ablation strategy and peri-procedure anticoagulation regimen was not uniform through-out the study period. Some studies have used preset criteria to determine same day discharge after electrophysiology procedures. It would be reasonable to follow these criteria by individual electrophysiologist in their practices. None of these patients underwent ablation using cryoballoon technology. Hence these data cannot be extrapolated to patients undergoing AF ablation using cryoballoon technology.

Conclusions:

Our study suggests that same day discharge after AF ablation may be feasible in highly selected cases. Further multicenter or randomized studies are needed before routine implementation of this strategy.

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Utility of Head up Tilt Table Testing to Demonstrate Selective Denervation of the Sinus Node after Cardioneuroablation

Tolga Aksu[1], Tumer Erdem Guler[1] , Serdar Bozyel[1], Dhanunjaya Lakkireddy[2], Kivanc Yalin[2], Rakesh Gopinathannair[3]

[1]University of Health Sciences, Kocaeli Derince Training and Research Hospital, Department of Cardiology, Kocaeli, Turkey.
[2]Kansas City Heart Rhythm Institute and Research Foundation, Overland Park, KS.
[3]Istanbul University-Cerrahpasa, Faculty of Medicine, Department of Cardiology, Istanbul, Turkey.

Abstract

A 65-year-old female who underwent cardioneuroablation for recurrent vasovagal syncope presented for 6 month follow-up visit. She had no further syncope after the procedure. A follow up tilt table testing (TT) demonstrated sinus tachycardia and variable degrees of atrioventricular block (AVB) after sublingual glyceryl trinitrate. She had no syncope during the test. As per existing knowledge, the occurrence of AVB during vasovagal reaction induced by TT should be preceded by sinus rhythm slowing. In this patient, sinus tachycardia during TT demonstrates highly specific denervation of ganglion cells which send postganglionic fibers directly to the sinus node without obvious influence on the atrioventricular node

Introduction

Cardioneuroablation (CNA) was proposed to modify the behavior of the cardiac autonomic nervous system to prevent the autonomic processes occurring in vasovagal syncope (VVS).[1] In a recently published study, we demonstrated that fractionated electrogram based CNA may decrease the procedure and fluoroscopy times without affecting efficacy when compared with previously defined high frequency stimulation and spectral analysis in patients with refractory VVS.[2] Experimental studies indicated that parasympathetic innervations of the sinus and the atrioventricular (AV) nodes are provided by different ganglionated plexi (GPs).[3] We tried to demonstrate selective denervation of sinus node with CNA by using tilt testing (TT) for the first time.

Case Report

A 65-year-old female with recurrent cardioinhibitory VVS, confirmed by reproducible syncope with a 10-s asystole during non-provoked TT (Figure 1A, 2A), underwent CNA 6 months ago after the patient refused pacemaker implantation. Baseline pre-procedure heart rate was 59 bpm.

Key Words

Syncope; Ablation; Neurocardiogenic syncope; Pacemaker; Vasovagal syncope; Bradycardia.

Corresponding Author
Dr. Tolga Aksu,
Mailing address: University of Health Sciences, Kocaeli Derince Education and Research Hospital, Department of Cardiology, Kocaeli, Turkey

Procedure Details:

The procedure was performed under conscious sedation with intravenous administration of midazolam and fentanyl. The patient underwent fractionated electrogram guided CNA. The sites demonstrating high or low amplitude fragmentation pattern in the regions that are consistent with probable GP locations were targeted. Ablation was started from fragmented electrograms on the left superior GP. Radiofrequency application caused a significant vagal response (VR) with sinus bradycardia. AA intervals increased from 1050 ms to 2160 ms during the left superior GP ablation. Ablation was continued until all targeted EGMs were eliminated. We then continued the ablation on the left inferior GP but no vagal response was seen during ablation at that site. The right superior GP was next. During ablation on the right superior GP, AA interval decreased from 1420 msec to 1100 msec. The ablation catheter was retracted along the interatrial septum and all fragmented areas were ablated on the right inferior GP. Next, we targeted right atrial part of GPs according to our ablation order. In the right atrium, the aorta– superior vena cava GP and right part of the right superior GP was targeted and ablated. AA interval decreased from 1098 msec baseline value to 659 msec (Movie 1). The inferior vena cava-left atrial GP which provides vagal innervations of AV node was not ablated because desired heart rate response was achieved with ablation of other GPs (Figure 2).

Link For Movie 1

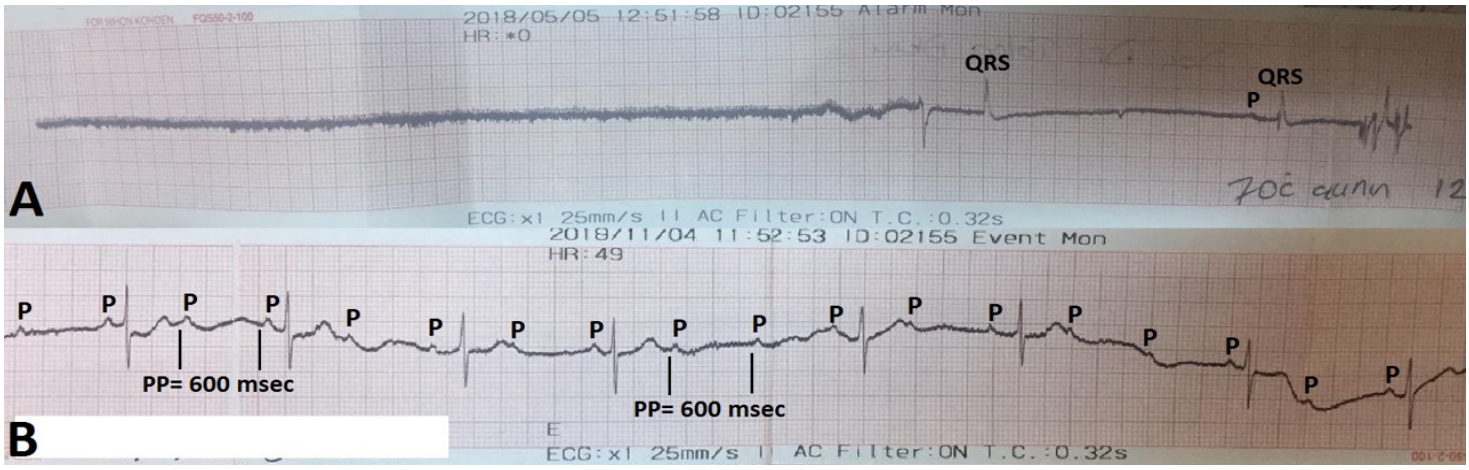

Figure 1A,1B : **Electrocardiogram recording during tilt testing before the procedure (A) and at 6 months of follow-up after cardioneuroablation (B)**

A. Electrocardiogram recording demonstrates 10-s asystole during non-provoked tilt testing. B. Electrocardiogram recording demonstrates variable degree atrioventricular block with sinus tachycardia without syncope after sublingual glyceryl trinitrate administration. Please see that PP interval is 600 msec during atrioventricular block.

Follow-up:

The frequency of syncopal episodes was twice a month before CNA and at 6 months following the procedure, she did not have any further recurrence of syncope. Follow-up resting ECG confirmed durable effect on sinus rate which was now 95 bpm. On routine follow-up TT, variable degree atrioventricular (AV) block with sinus tachycardia was detected without syncope after sublingual glyceryl trinitrate administration (Figure 1B, 2). Because the patient was totally asymptomatic, we decided to continue to observe the patient without any treatment. No new syncope or bradyarrhythmia related symptoms were noted during an additional 12-month follow-up.

Discussion

The main findings of the present case report are as follows: (1) different GP sites provide vagal innervation of the sinus and AV nodal regions, respectively; (2) although ablation of the right superior GP or the aorta– superior vena cava GP causes a significant increase in sinus rate, AV block may still be seen due to selective innervation principles of the sinus and AV nodal regions; (3) bi-atrial approach may be needed to get desired increase of the sinus rate (4) fractionated EGMs might be used to define anatomical location of GPs without using any additional equipment during electrophysiological study; and (5) fractionated electrogram based CNA can effectively prevent recurrent spontaneous syncopal episodes in a patient with refractory VVS.

Although the AV block induced by TT is a rare phenomenon, it was reported both in patients with VVS and in healthy volunteers.[4,5] The main feature of AV block related to the neurocardiogenic reflex provoked by TT was the substantial slowing of sinus rhythm and the presence of significant variability in PP intervals. A similar pattern of sinus bradycardia and AV block was also present during spontaneous syncopal episodes documented by implantable loop recorder.[6] The patients with non-neurocardiogenic reflex etiology of AV block do not appear to have this feature. In the present case, existence of such a response demonstrates highly specific denervation of ganglion cells which send postganglionic fibers directly to the sinus nodal region without obvious influence upon the AV nodal region.

In a recently published study, Hu et al 7 studied heart rate response characteristics of different GPs by using left-sided approach. During ablation of the right superior GP, heart rate increased from 61.3 ± 12.2 bpm to 82.4 ± 14.7 bpm, whereas during ablation of other GPs only vagal responses were observed. Based on this unique phenomenon, potential role of the right superior GP as the primary target of CNA was hypothesized by the authors. In the present case, targeted heart rate increase was achieved only after right-sided ablation.

The difference between heart rate response of left-sided approach of Hu et al[7] and the present case may have several explanations. Because great majority of GPs demonstrate subepicardial clustering, bi-atrial ablation might be needed to eliminate a significant number of post-ganglionic neurons in some cases. Because GPs usually regulate the sinus and AV nodes via interconnecting nerve fibers, theoretically, ablation of the right superior GP which was proposed to be the "head station" between the extrinsic and intrinsic cardiac autonomic nervous system may seem as valuable target in CNA.[8,9] However, selective vagal innervation of sinus and AV node was previously studied in animal studies.[3, 10,11] In an animal study, Randall et al3 demonstrated that the great majority of GPs supplying sinus node reside in aorta– superior vena cava GP and right superior GP. In contrast, GPs supplying AV node are found within a smaller fat pad overlying epicardium at the junction of the inferior vana cava-left atrial GP. The authors concluded that these vagal pathways to either sinus or AV nodes may be selectively ablated without interfering with vagal regulation of the remaining intact system. A similar experience was recently showed in humans by Pachon et al[12] by using extracardiac vagal stimulation. By this way, status of vagal denervation may be evaluated as many times as necessary.

In the current case, although the patient developed AV block with heart rate slowing down to less than 40 bpm during follow up TT, implantation of a pacemaker was not recommended because the patient was completely asymptomatic. In our previous works, no procedure related complication was seen. [13-15] Inappropriate sinus

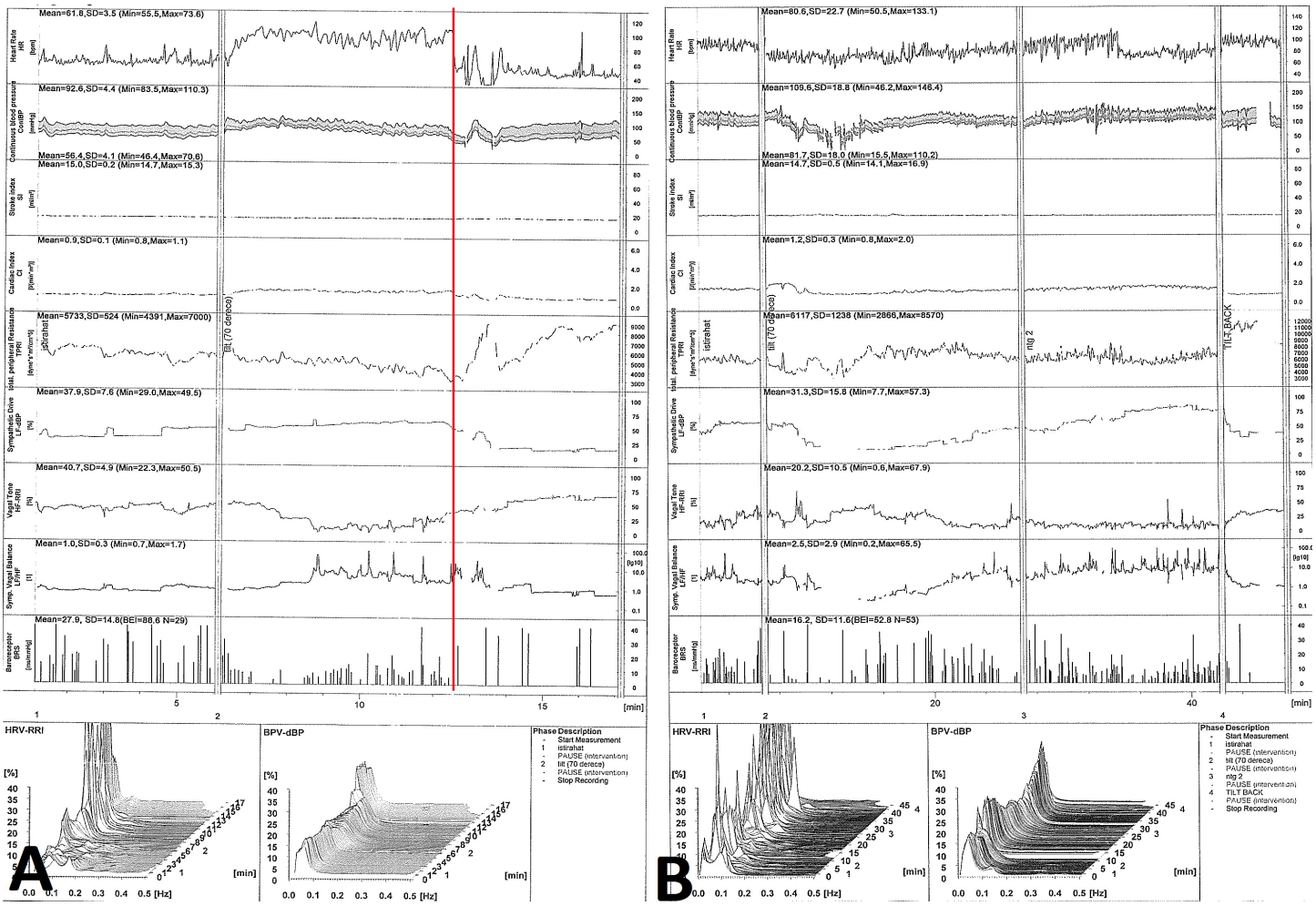

Figure 2A, 2B: **Electroanatomical mapping views before (A) and after (B) cardioneuroablation**

Most efferent vagal fibers to the atria travel through the aorta (Ao)-superior vena cava (SVC) ganglionated plexus or fat pad (Ao-SVC GP) located between the medial SVC and aortic root. Vagal fibers to the sinus and atrioventricular nodes converge at this fat pad before projecting to following selective innervation sites. The right superior ganglionated plexus (RSGP) is located between SVC and the right superior pulmonary vein. It is also called as the right anterior ganglionated plexus. Theoretically, RSGP mainly provides vagal innervations of sinus node. The right inferior ganglionated plexus (RIGP) is located between the right pulmonary veins and the right atrium. It is also called as the posterior right ganglionated plexus. The posteromedial left ganglionated plexus (PMLGP) is located in the posterior aspect of the interatrial septum, between the posterior wall of the left atrium (LA), the inferior vena cava (IVC), and coronary sinus (CS) ostium. It is also called as IVC-LA GP. Some part of neuronal bodies related to this GP is in the left atrial side. Vagal innervation of atrioventricular node is provided by PMLGP. The left superior ganglionated plexus (LSGP) is located between the left atrial appendage and the left superior pulmonary vein. The left inferior ganglionated plexus (LIGP) is located within the fat pad anterior to the left inferior pulmonary vein. It is also called as the Marshall tract GP by different groups.
Spheres demonstrate ablation points in GP sites based on fractionated electrograms.
Intracardiac electrograms are seen at the bottom of figure. Please see that cycle length increases from 1307 msec to 638 msec after cardioneuroablation.

tachycardia was observed in 2 of all included patients during follow-up.[15] In one, there was no symptom associated with sinus tachycardia and the heart rates gradually decreased during follow-up. Although the other case was asymptomatic during the first 12 months, she had EHRA class 2 symptoms thereafter which completely resolved with ivabradine treatment.

Pre-ablation TT of the present case demonstrated an increase in total peripheral resistance while the vagal tone went up and sympathetic drive reduced (Figure 3A). However, after CNA, vagal tone remained stable, heart rate dropped down due to AV block and sympathetic tone went up, but total peripheral resistance remains the same (Figure 3B). In patients with VVS, the total peripheral resistance during the positive response period is significantly higher than the total peripheral resistance before this period.[16] Benditt et al.[17] showed that catecholamine levels significantly increased at both 2–3 and 4–6 minutes before syncope in children with VVS. The authors suggested that a change in the total peripheral resistance from the supine position to the positive response period positively correlated with syncope frequency, which suggested that abnormal total peripheral resistance might be responsible for the occurrence of VVS.

Conclusions:

Existence of sinus tachycardia with AV block during TT may demonstrate selective denervation of ganglion cells which send postganglionic fibers directly to the sinus node without obvious influence on the AV node. Understanding of different inputs to both the sinus node and AV node will help in planning ablation and a better outcome.

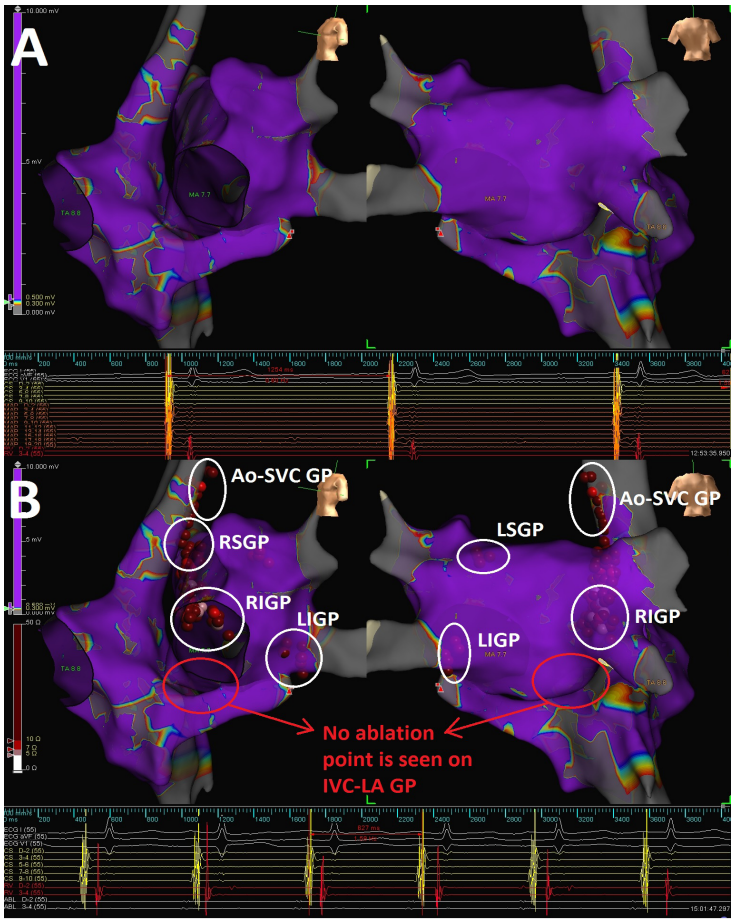

Figure 3A, 3B: **Hemodynamical results of the case during tilt testing before the procedure (A) and at 6th months of follow-up after cardioneuroablation (B)**

Top trace shows the heart rate curve; bottom trace shows continuous blood pressure curves. Blood pressure stabilizes shortly after the assumption of the upright position with no changes for the duration of the preparatory phase; the heart rate immediately rises, then stabilizes. The vertical red line indicates the time of onset of the vasovagal reaction, which is characterized, at first, by a mild decrease in blood pressure with a steep fall in heart rate and syncope occurs. The total duration of the vasovagal reaction is about 4 min. HR=heart rate; BP=blood pressure

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Medical Treatment of A Symptomatic Acute Pulmonary Vein Stenosis Following Antral Pulmonary Vein İsolation

Taner Ulus[1]; Muhammet Dural[1]; Emre Şener[1]; Pelin Meşe[1]; Emel Kurt[2]; Nevin Aydın[3]

[1]Department of Cardiology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey.
[2]Department of Chest Diseases, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey.
[3]Department of Radiology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

Abstract

Pulmonary vein (PV) stenosis is a rare but serious complication of PV isolation. It usually develops 3-6 months after the procedure, but may rarely develop in the acute phase. We present a case of symptomatic PV stenosis within 48 hours after antral PV isolation. Following the initiation of medical treatment including a glucocorticoid, acute changes in the PV wall regressed and the patient's complaint of dyspnea at rest improved rapidly. In addition, long-term renin-angiotensin-aldosterone system (RAAS) blockers were given. The symptoms did not recur during follow-up and PV stenosis was mild at 6 months.

Introduction

Pulmonary vein (PV) stenosis is a rare but serious complication that can be seen following radiofrequency catheter ablation for atrial fibrillation (AF). Clinical presentation may be asymptomatic or symptomatic with severe dyspnea, cough, chest pain, and hemoptysis[1]. Although PV stenosis usually develops 3-6 months after the procedure, it may rarely develop in the acute phase[2]. We present a case of symptomatic moderate PV stenosis within 48 hours after antral PV isolation. Following the initiation of medical treatment including a glucocorticoid, acute changes in PV regressed and the patient's complaint of dyspnea at rest improved rapidly. In addition, long-term renin-angiotensin-aldosterone system (RAAS) blockers were given. The symptoms did not recur during follow-up and PV stenosis was mild at 6 months.

Case

51 year-old woman was admitted to our center for palpitation attacks resistant to antiarrhythmic therapy. She had undergone electrical cardioversion due to persistent AF in our center one year ago. However, AF recurred 6 months after the cardioversion. She had a history of systemic hypertension. Medications were metoprolol 50 mg once a day, dabigatran 150 mg twice a day and ramipril/hydrochlorothiazide 5/25 mg once a day. The patient was taken to the electrophysiology laboratory for persistent AF ablation after consent was obtained. A contrast-enhanced thorax computed tomography (CT) was performed before the procedure (Figure 1A). The procedure was performed under general anesthesia. Double transseptal punctures were performed and a three-dimensional electroanatomic left atrium map (EnSite Precision™ Cardiac Mapping System, St Jude Medical, St. Paul, Minnesota, MN, USA) was obtained. Point-to-point linear lesions were created with an irrigated tip catheter (The TactiCath™ Quartz ablation catheter, St Jude Medical) in the antrum regions of the right and left PVs (Figure 2). Radiofrequency energy was delivered with a maximum power of 30 W at the anterior wall and 25 W at the posterior wall. Maximum temperature was 42 °C and irrigation flow rate was 17 ml/min.

Sudden onset dyspnea at rest developed 36 hours after the procedure. Physical examination revealed crepitant rales in the basal region of the lungs. Transthoracic echocardiography did not demonstrate pericardial effusion or any left ventricular or valvular dysfunction. Chest X-ray revealed pulmonary edema. The patient was given intravenous (IV) furosemide and IV glyceryl trinitrate for 48 hours. The second CT taken 48 hours after the procedure showed 51.9% stenosis in the left upper PV and swelling of the PV wall (Figure 1B). There was no bronchial wall thickening and near parenchymal ground glass opacities which could be thought as bronchial damage near

Key Words
Atrial fibrillation, Ablation, Same day discharge, Complications.

Corresponding Author
TanerUlus
Eskişehir Osmangazi Üniversitesi Tıp Fakültesi,
Kardiyoloji Anabilim Dalı, Meşelik Kampüsü, 26480,
Odunpazarı, Eskişehir, Türkiye.

to ablation area. 100 mg IV methylprednisolone was administered immediately after the CT and 60 mg daily was continued for additional 4 days. Four days after the procedure, the patient's blood pressure (BP) increased (160/100 mmHg) and serum potassium level decreased (3.4 meq/L). Spironolactone 25 mg once a day was added and furosemide was discontinued. The patient's complaint of dyspnea disappeared 5 days after the procedure and BP returned to normal. The control CT at 7 days after the procedure showed decreasements in the thickness of the PV wall and in the degree of PV stenosis (41.7%) (Figure 1C). The patient was discharged 8 days after the ablation and received 20 mg fluocortolone daily for 5 days at home.

At 6 months after the procedure, the patient had no clinical complaints. The patient was taking ramipril/hydrochlorothiazide and spironolactone at 6 months after the procedure. Follow- up CT showed that the PV wall, the PV wall thickness was normal and there was less stenosis in the PV (38.5%) than the baseline (Figure 1D).

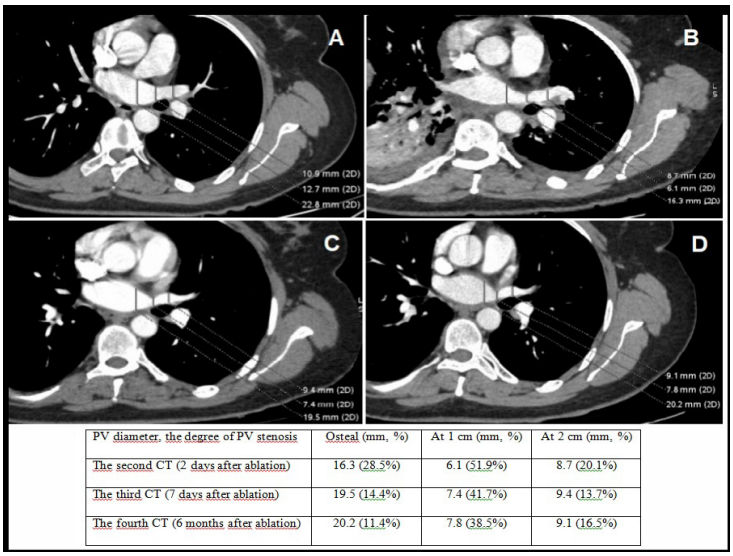
Discussion:

Here, we describe a patient who developed symptomatic moderate PV stenosis in the acute phase after the procedure despite ablation away from the PVs. After the initiation of corticosteroid therapy in the early period, acute changes in the PV wall regressed, and pulmonary congestion recovered rapidly. At 6 months after the procedure, PV stenosis was mild and the patient had no clinical findings.

The PV stenosis is classified as mild (30% to 50%), moderate (50% to 70%), and severe (>70% diameter reduction)[1]. While it was reported up to 42% in early procedures, the incidence of severe PV stenosis after AF ablation has decreased below 1% in the current era[1,3]. However, the actual incidence is unknown because some patients are asymptomatic or symptoms are nonspecific. Symptoms may vary depending on the number of PVs affected, the severity of PV stenosis, the response of the pulmonary vascularity to the lesion, the presence of collaterals, clinical setting, and rate of development of PV stenosis[4]. Promising strategies to reduce PV stenosis include ablation away from PVs, use of an open irrigated-tip ablation catheter, and the use of three-dimensional mapping systems[3,5].

Immediately after ablation, vessel narrowing and PV wall edema were proposed as mechanisms of PV stenosis[5]. Shrinkage due to heat-induced contraction, especially the contraction of the internal elastic lamina, has been proposed as the mechanism of PV diameter reduction[5,6]. Chronic inflammation, intimal proliferation and myocardial fibrosis cause late onset PV stenosis after ablation[3,6].

Corticosteroids have antiinflammatory effects by increasing the transcription of anti-inflammatory cytokines and by reducing the transcription of inflammatory cytokines[7]. The RAAS system is responsible for structural and electrical remodeling in the heart, including the development of fibrosis. The RAAS blockers have been shown to reduce cardiac fibrosis and decrease the expression of inflammatory markers in human and animal models[8]. In a piglet model with PV stenosis, Zhu et al showed that losartan reduced intimal hyperplasia by maintaining vascular endothelial cadherin levels[9].



PV diameter, the degree of PV stenosis	Osteal (mm, %)	At 1 cm (mm, %)	At 2 cm (mm, %)
The second CT (2 days after ablation)	16.3 (28.5%)	6.1 (51.9%)	8.7 (20.1%)
The third CT (7 days after ablation)	19.5 (14.4%)	7.4 (41.7%)	9.4 (13.7%)
The fourth CT (6 months after ablation)	20.2 (11.4%)	7.8 (38.5%)	9.1 (16.5%)

Figure 1: **The CT image of the left superior PV in the axial plane A) Before B) 48 hours after C) 7 days after D) 6 months after the procedure. The PV diameter were measured at the ostial level, at 1 and 2 cm more distally. At each level, PV diameter was measured with a manual caliper as the distance between 2 points perpendicular to the PV axis. Post-ablation PV diameter was compared with the pre-ablation and the degree of PV stenosis was calculated at each level. The table below shows PV diameter, the degree of PV stenosis at the measured levels, and the date the CT was taken. CT: Computed tomography, PV: Pulmonary vein.**

In our case, although the ablation site was far from the PV ostia, PV diameter decreased in the acute period after the procedure. The possible mechanism in our case was acute tissue edema due to ablation. Edema may extend well beyond the ablation site[6]. Although PV stenosis was moderate, pulmonary edema symptoms developed. This may be due to the rapid development of changes in the PV wall. An acute reduction in atrial natriuretic peptide level may have contributed to the pulmonary congestion in our case. There are other methods other than CT to diagnose PV stenosis such as perfusion scans or pulmonary venography[3]. In our case, we only performed CT, and in this way, we diagnosed PV stenosis and were able to eliminate other possible causes. She was in pulmonary edema and we did not perform a more invasive imaging method in view of clinical benefit/ risk ratio.

Glucocorticoid treatment was initiated within the first 48 hours after the procedure. After steroid treatment, acute changes in the PV wall decreased dramatically and the pulmonary congestion resolved. Glucocorticoids may have caused regression of the acute changes in the PV wall with anti-inflammatory effects[7]. In addition, we started spironolactone due to hypertension and hypokalemia. The RAAS blockers may have contributed to the prevention of the development of PV stenosis in the long term with their antifibrotic effects.

Some of the patients undergoing PV isolation may have some degree of PV stenosis immediately after the procedure. Jin et al demonstrated that some degree of PV stenosis was seen immediately after PV isolation in 14 (16%) of 87 veins in 12 (46%) of 26 patients[10]. Berkowitsch et al. showed that a 25% reduction in PV diameter was observed immediately after ablation in 36 of 357 PVs[11]. In our case, the degree of stenosis at the 6th month was

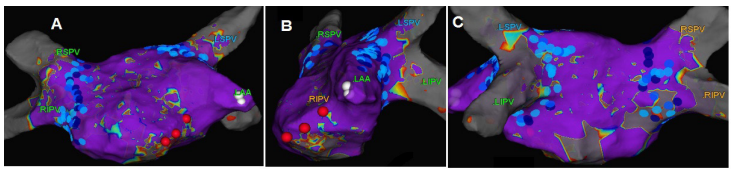


Figure 2: **Three-dimensional electroanatomic mapping views of the patient from A) Anteroposterior projection B) Left anterior oblique projection C) Posteroanterior projection. LAA: Left atrial appendage, LIPV: Left inferior pulmonary vein, LSPV: Left superior pulmonary vein, RIPV: Right inferior pulmonary vein, RSPV: Right superior pulmonary vein.**

mild (38.5%). Acute changes in the PV diameter may lead to the development of PV stenosis in the chronic period[5]. For this reason, it may be important to monitor patients with mild / moderate PV stenosis after the procedure for the development of more severe PV stenosis. We planned to follow our patient with an annual CT to monitor the degree of PV stenosis.

We left the circular mapping catheter in the PV ostium during ablation to demonstrate the PV ostium. However, it should be kept in mind that the three-dimensional mapping system may not show the PV ostium completely during ablation and there may be a shift in the map. Stenting is an important treatment option in individuals with symptomatic significant PV stenosis after AF ablation. Stenting is superior to balloon angioplasty in terms of reducing restenosis[1]. However, restenosis may occur in 24% of cases after stenting in such cases[12].

In summary, acute PV stenosis may rarely develop after antral PV isolation. It is very important to keep in mind the possibility of PV stenosis in patients who develop consistent clinical findings after such a procedure. Acute changes in the PV wall can be reversed by intensive corticosteroid therapy in the early period. Again, the RAAS blockers may contribute to the prevention of the development of higher grade PV stenosis in the future in such patients. However, further studies are needed to clarify this issue.

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A Way to Find of The Hard to-Reach and Risky Locations Arrhythmia Focus: Double Coronary Guidewire Mapping Technique

Mustafa Yildiz[1]

[1]Department of Cardiology, Istanbul University-Cerrahpasa Cardiology Institute, Istanbul, Turkey.

During electrophysiological study and ablation, intracardiac recordings using catheters are important for the diagnosis and treatment of complex arrhythmia. Accessing some locations of the heart such as left ventricle summit and epicardial coronary arteries using routine catheters are difficult and risky. In this report, it was presented a case of successful left ventricle summit ventricular tachycardia (VT) ablation with an irrigated catheter using the new mapping technique namely "Double Coronary Guidewire Mapping Tchnique" described by Yildiz M [(1)].

A young male patient was admitted antiarrhythmic drugs resistant ventricular tachycardia. He had previous failed ablation using three-dimensional system with the NavX™ (St Jude Medical) in the another arrhythmia center for several years ago. The surface electrocardiogram revealed premature ventricular contraction (PVC) with positive precordial concordance (Figure 1A). The transthoracic echocardiogram showed mild decreased left ventricle ejection fraction (45%). The endocardial radiofrequency ablation (RFA) was planned and the epicardial RFA was offered to patients as a second choice but the patient refused to undergo epicardial RFA. During electrophysiological study, the same PVCs were seen and the earliest recordings were taken in the distal coronary sinus (CS). The transseptal puncture was performed and the left ventricular propagation mapping was done using HD GridR (AbbottR) catheter (Figure 1B,C). Although the RFA was delivered by irrigated catheter in the area between aortomitral continuity and left ventricle summit, PVC/Nonsustained ventricular tachycardia was reappeared. Then the diagnostic catheters (4F- 6F, respevtively) were tried to map the distal segment of the CS and great cardiac vein but they failed to be advanced through the CS. The two coronary floppy wire were advanced through the CS and they were placed into the great cardiac vein (Figure 1D). The "Double Coronary Guidewire Mapping Technique" was used to get uni- and bipolar noise-free intracardiac signals from great cardiac vein (Figure 1E,F). The inputs in the connection box are connected to the distal tip of coronary guidewires using the recording device (Figure 1G,H.J). The pace-mapping was done in the area of the earliest signals (-39 msn) taken and there was 97% matching with PVCs. The irrigated catheter was advanced through aortic valves retrogradely and it was placed corresponding to the place of the opposite site of the earliest signal point taken by double wires (Figure 1K). The selective coronary angiogram was performed and RFA was applied to the area >5 mm from the coronary artery (Figure 1L). The firing was seen and then PVCs were gone after RFA. After 30 minutes of the waiting period, the intravenous metaproterenol and dobutamine infusion were given and neither PVC nor nonsustained ventricular tachycardia was induced. There were no complications. The medical treatments were stopped and the patient was discharged. Two months after the procedure, the patient does not have any symptoms. The rest surface electrocardiogram and 24 hours electrocardiogram monitoring did not reveal PVC or nonsustained ventricular tachycardia.

The routine electrophysiological catheters as like 4-6 French (1 French is exactly 0.33 mm) used in daily electrophysiological practice that can't reach some difficult and risky locations including left ventricular summit. The coronary guidewires, which are an essential element in interventional cardiology practice; can be useful in the mapping of the hard-to-reach and risky locations because of their small diameters, high torgue response and flexibility, ability to be guided. In this technique, two coronary floppy guidewire (Boston Scientific) (0.014 inches in diameter, combines a hydrophilic-coated polymer sleeve with a soft J tip and flexible body, good torgue response and radiopacity for especially tortuous coronary artery and venous anatomy) were used to obtain uni- and/or bipolar noise-free recordings from difficult and risky locations including left ventricular summit. In conclusion, this technique namely "Double Coronary Guidewire Mapping Technique" can help us on mapping and ablation of difficult locations of the heart.

Corresponding Author
Mustafa Yildiz, MD, PhD, Prof.
Cardiologist, Internal Medicine Specialist and Physiologist
Department of Cardiology, Istanbul University-Cerrahpasa Cardiology Institute, Istanbul, Turkey

References

1. Yildiz M. Technical report: Obtaining noise-free bipolar recordings from different locations of the heart using coronary guidewires. Koşuyolu Heart J 2019;22(2):143-144.

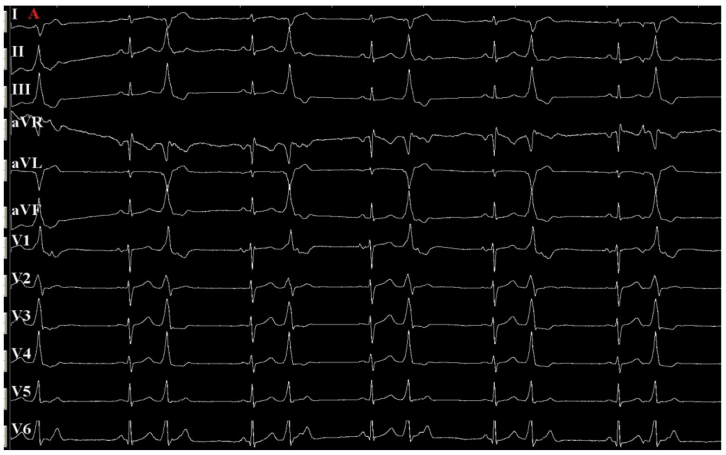

Figure 1A: Premature ventricular contractions were seen on the 12-lead electrocardiography

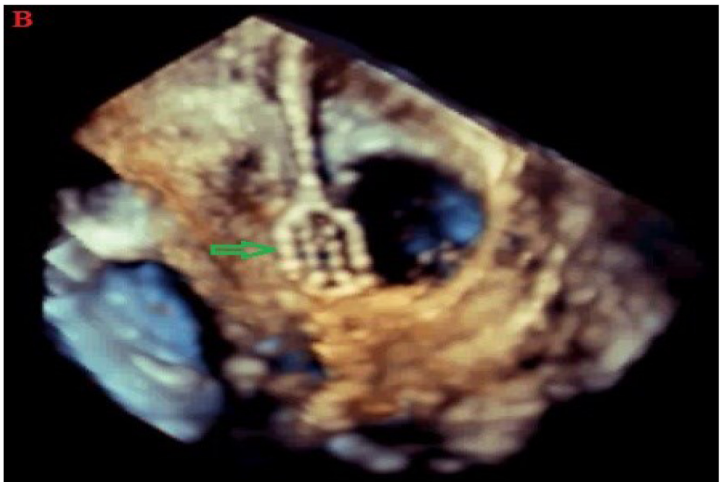

Figure 1B: HD Grid catheter was seen on the real time 3-dimensional transeosaphageal echocardiography (gren arrow)

Figure 1C: HD Grid catheter was seen on the Ensite 3-dimensional mapping system (gren arrow)

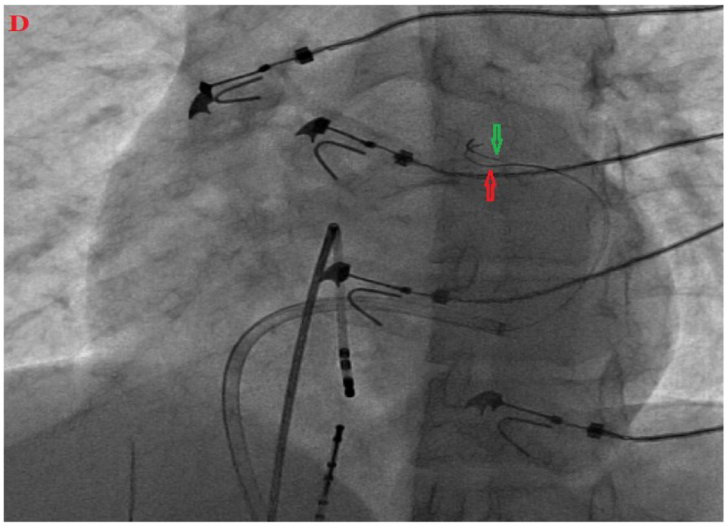

Figure 1D: Two floppy wire (gren and red arrow) were used as a bipolar catheter for mapping the distal of the coronary sinus on the flouroscopic view

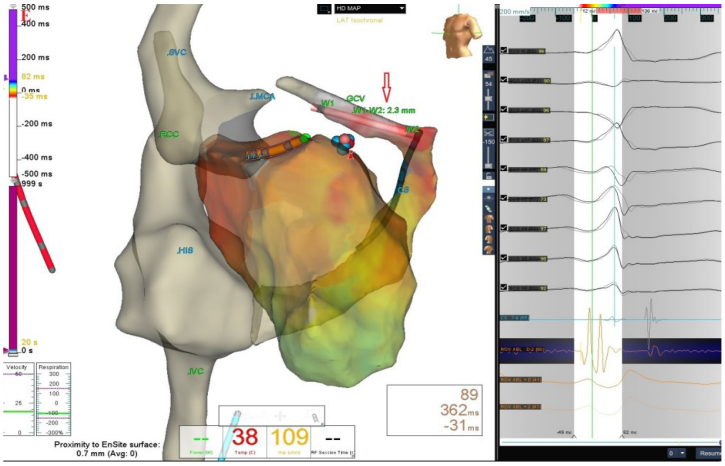

Figure 1E: The Ensite 3-dimensional mapping system shows the anatomy of the left ventricle summit area, double floppy wire (red arrow), intracardiac signals and the ablation point

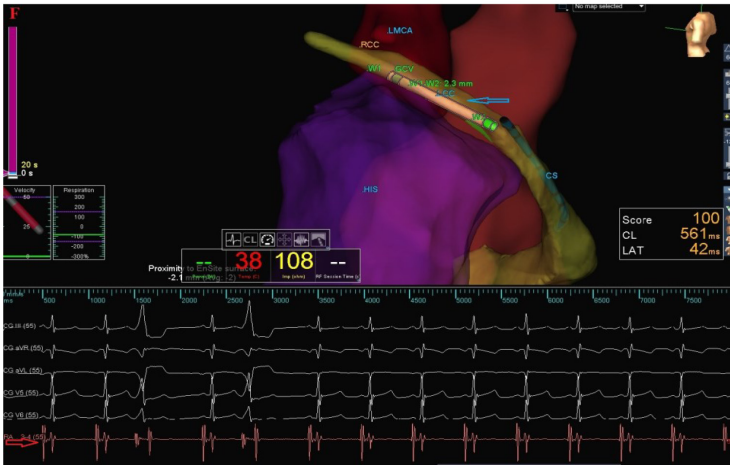

Figure 1F: Bipolar mapping were seen on Ensite (blue arrow) and intracardiac recording (red arrow)

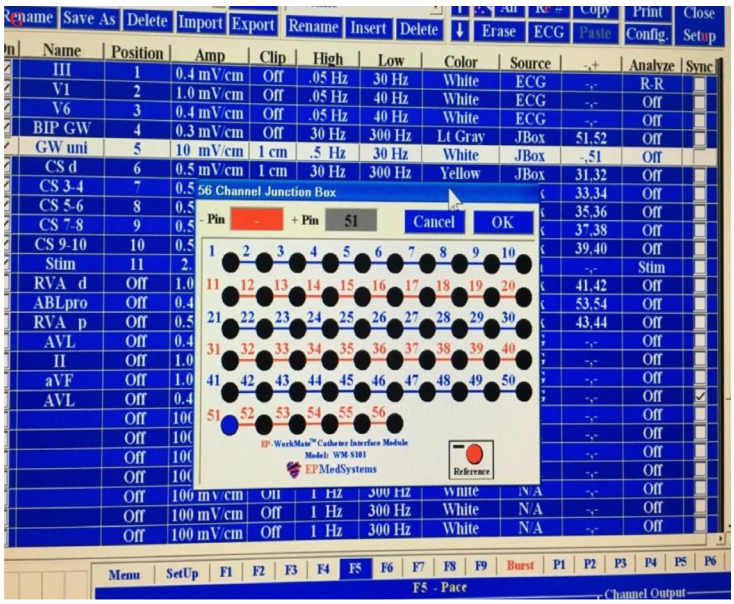

Figure 1G: The monitor of the electrophysiological system

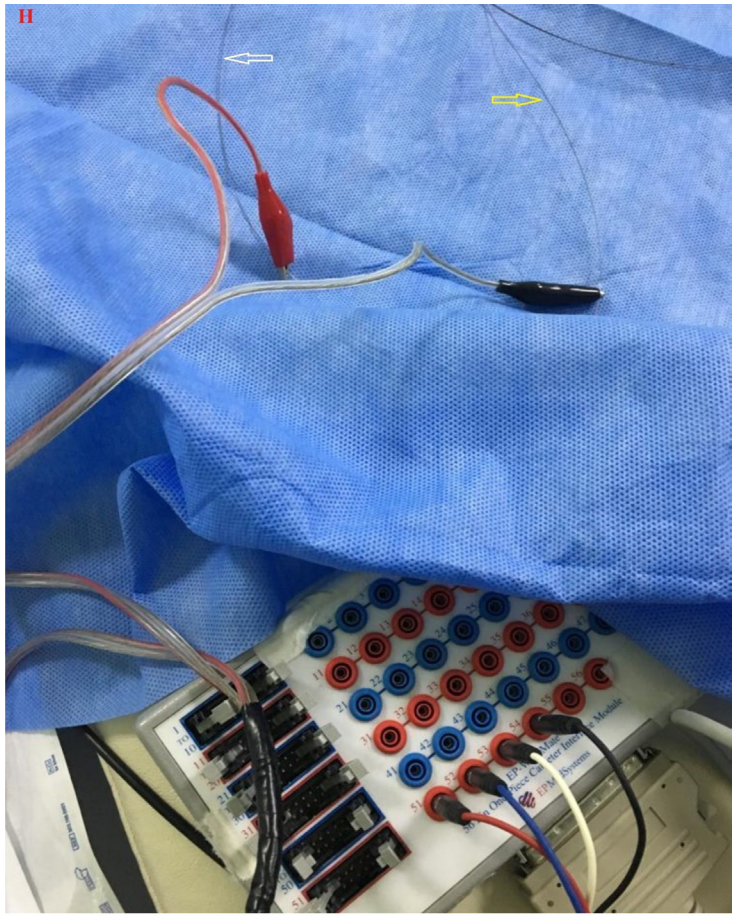

Figure 1H: The inputs of the connection box are connected to the distal tip of coronary guidewires (yellow and white arrow) using the recording device

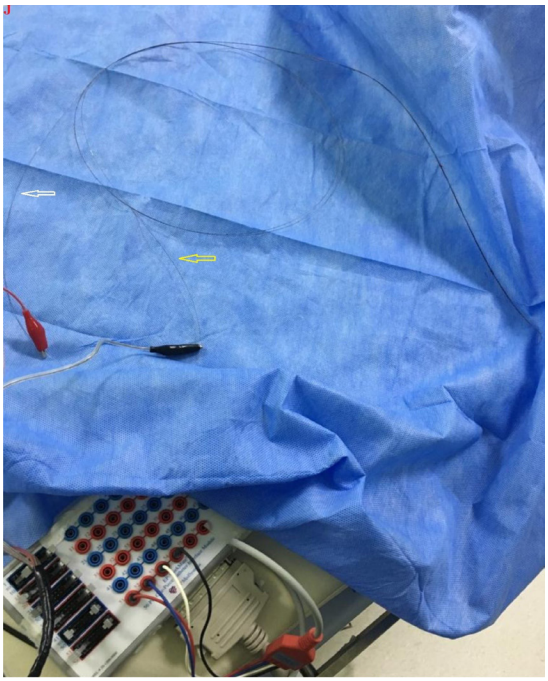

Figure 1J: The inputs of the connection box are connected to the distal tip of whole coronary guidewires (yellow and white arrow) using the recording device

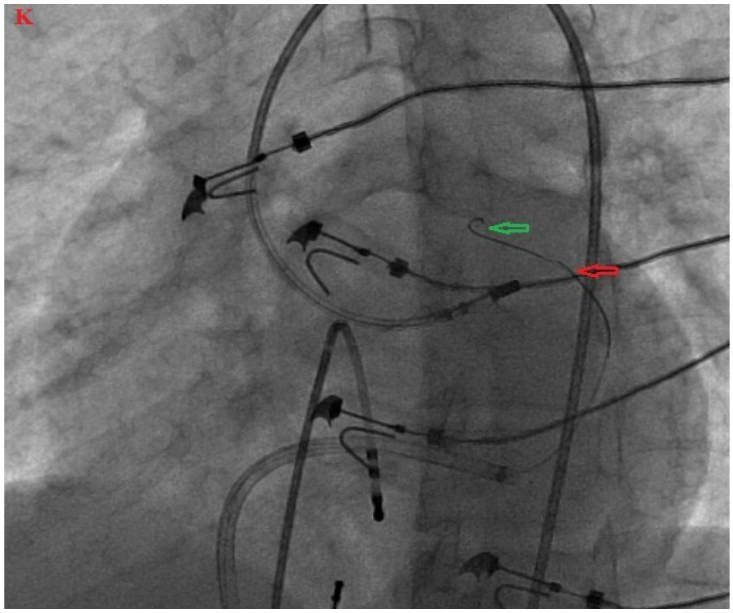

Figure 1K: Two floppy wire were seen close to retrograde ablation catheter on flouroscopy (gren and red arrow)

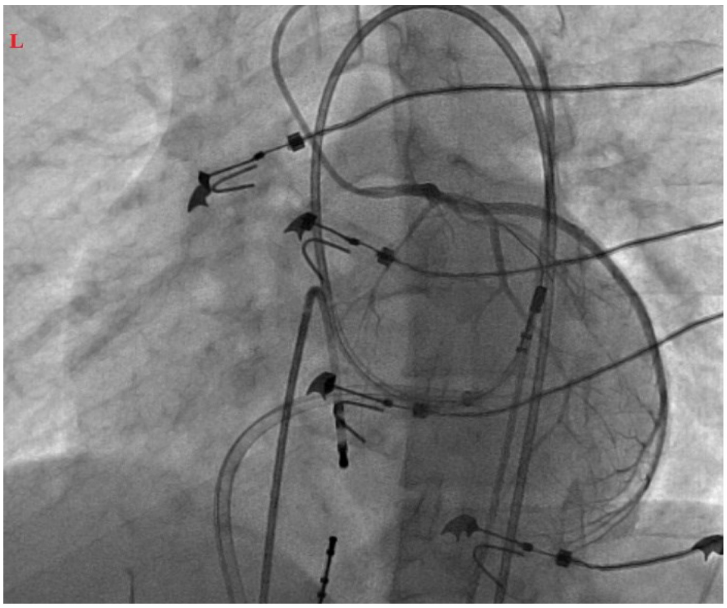

Figure 1L: The selective coronary angiogram was performed and RFA was applied to the area >5 mm from the coronary artery

Dr. Jeff Healey MD, MSc, FRCP(C), FHRS

Jeff Healey is the director of arrhythmia services at Hamilton Health Sciences, Professor of medicine at McMaster University and the Population Health Research Institute Chair in Cardiology Research. He is also the principal investigator and chair of the Canadian Stroke Prevention Intervention Network (CSPIN), which is conducting a series of clinical trials related to atrial fibrillation and stroke prevention and will also support the development of new Canadian researchers in this field. He is the past co-chair of the Canadian Cardiovascular Society's Atrial Fibrillation Guidelines Committee and past chair of the Cardiac Care Network of Ontario's Heart Rhythm Working group.

Dr. Amr Salah Omar, MBBch, Msc, PhD, MD, MBA

Dr Amr Salah Omar MBBch, Msc, PhD, MD, MBA; has completed his Ph.D. and a doctorate degree in Critical care medicine from Cairo University, Egypt. He received an academic position as a professor in Beni Suef University Egypt last year; he also received assistant professor position in Weill Cornell Medical College Qatar in 2016. He is holding a position as a consultant in intensive care cardiothoracic surgery department, Hamad medical corporation, Qatar..

Dr. Denis Terekhov

I work as chief of emergency at the Cardiovascular Institute of Buenos Aires, Argentina. My area of interest in research is chest pain, biomarkers and acute coronary syndromes.

Dr. Damian Redfearn , MD

Dr Damian Redfearn was recruited to Queen's University in Kingston, Ontario in 2006 and was appointed Director of the Heart Rhythm Service in 2007. He has overseen the growth of the electrophysiology program at Kingston General Hospital with the addition of complex ablation and the delivery of a full spectrum of electrophysiology services and procedures to the south eastern Ontario region. Dr Redfearn is a clinician scientist with a special interest in applied computer science holds several peer reviewed research grants to investigate the mechanisms of atrial fibrillation and ventricular arrhythmia through advanced signal processing.

Dr. Avishag Laish-Farkash, MD, PhD

Dr. Laish-Farkash is an electrophysiologist at Rambam Medical Campus in Haifa and a lecturer at Ben-Gurion University of the Negev in Israel. A graduate of Tel Aviv University, she completed a residency in internal medicine and Cardiology at Sheba Medical Center in Israel and fellowship in Electrophysiology at Sunnybrook Health Science Center, University of Toronto, ON, Canada. She has a PhD degree in basic electrophysiology from the Sackler Faculty of Medicine, Tel-Aviv University in Israel.

Dr. Ayman Morttada Abd ElMoteleb Mohamed

Dr. Ayman Morttada Abd ElMoteleb Mohamed,Assisstant professor of Cardioloy,,Intervention cardiologist and electrophsiologist, Ain Shams University

Dr. Enriquez received his medical degree from the Universidad de Concepcion, in Chile. He specialized in Internal Medicine, Cardiology and Cardiac Electrophysiology at Pontificia Universidad Catolica de Chile in Santiago.

Between 2013 and 2015 he moved to Canada to continue his electrophysiology training at Queen's University, Kingston, Ontario.

He currently resides in Philadelphia with her wife Karen and is a second-year fellow in the Advanced Clinical Electrophysiology program at the Hospital of the University of Pennsylvania, under the mentorship of Dr. Francis Marchlinski.

Dr. Enriquez interests include electrocardiology, clinical electorphysiology catheter ablation and cardiac devices.

Dr. Ryan Dean White. MD

Dr. Ryan Dean White, MD, medical degree from the University of Missouri and currently training in internal medicine at Indiana University School of Medicine in Indianapolis, Indiana.

Dr. Johannes Siebermair , MD

Cardiologist at the Department of Medicine I, University Hospital Munich, Ludwig-Maximilians University, Munich, Germany. Scientific focus is the interventional treatment of atrial

fibrillation and functional imaging in collaboration with the Department of Nuclear Medicine for risk stratification in inherited arrhythmia syndromes. Clinical focus is catheter based treatment of arrhythmias.