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Diabetes Mellitus and Atrial Remodeling in patients with Atrial Fibrillation: role of electro-anatomical mapping and catheter ablation.

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12. Aim of the study

DM has become a pandemic disease in the western world as well as in developing countries. AF is the most common form of arrhythmia in the world. DM is one of the most important risk factors for AF and is a predictor of stroke and thromboembolism. DM may increase the incidence of AF, and when it is combined with other risk factors, the incidence of stroke and thromboembolism may also be higher; furthermore, hospitalization due to heart failure appears to increase. The mechanisms of AF associated with DM are autonomic remodeling, electrical remodeling, structural remodeling, and insulin resistance[1].

AF ablation has become an established therapy for maintaining sinus rhythm in patients with symptomatic paroxysmal AF and, when performed in experienced centres by adequately trained teams, is more effective than antiarrhythmic drug therapy with similar complication rate[2]. This is primarily achieved through isolation of the pulmonary veins, probably requiring complete isolation for full effectiveness[3], and additional ablation in the posterior left atrial wall. In non-paroxysmal forms, more extensive ablations (i.e. substrate modification with CFAEs ablation) may be required. Overall, such alternative ablation procedures seem to be more effective than PVI, even if their success rates appear extremely variable and in many cases the procedure is complex and time-consuming. In particular, the studies analyzing CFAE ablation alone and as an adjunct to left atrial linear lesions and/or PV isolation have demonstrated contrasting results[4-6].

The aim of this randomized study was to compare in terms of clinical outcome two strategies of catheter ablation (PVI vs PVI+CFAEs) for paroxysmal AF in DM patients.

Domenico Grieco

Methods

Study population and design

The population of this study consisted of 64 patients with DM undergoing catheter ablation for AF: 32 of the them were randomized to PVI and 32 to PVI+CFAEs ablation.

Inclusion criteria were: type 1 DM and symptomatic paroxysmal AF refractory to at least 1 antiarrhythmic drug; age >18 or < 75 years; left ventricular ejection fraction (LVEF) > 30%; LA size < 55 mm; more than 1 year life expectancie; no prior AF ablation; no prior cardiac surgery.

Primary endpoint has been defined as a ECG confirmed AF/AT recurrence lasting at least 30 seconds and occurred after 5 weeks and within 12 months from the ablation procedure. As secondary endpoints, bleeding (> 2g Hb loss), hospitalization rate and thromboembolic events (transient ichemic attack, stroke, pulmonary thrombo-embolism, deep venous thrombosis) have been analyzed.

The study population was also compared to a historical population of non-DM patients undergone catheter ablation (PVI) for paroxysmal, symptomatic drug-refractory AF.

Electronic medical records were searched for demographic characteristics (age, gender, aetiology and stage of underlying heart disease and DM, clinical history, and medical therapy). Transthoracic echocardiography was performed within one month period preceding the implant using a Vivid 7 (GE) system and 2.5 MHz transducer. M-mode and bi-dimensional measurements were made according to the recommendations of the American Society of Echocardiography[7].

LVEF was used as a parameter of the left ventricular systolic function. Blood samples were obtained, while the patients were at rest in a supine position, the morning of the procedure, at 6 hours and at 18-24 hours after the procedure and were collected in plastic vials containing ethylenediamine tetracetic acid (EDTA).

The study protocol was approved by the ethics committee of the institution and all patients provided informed, written consent before the study.

EP study

All antiarrhythmic drugs were stopped at least 5 half-lives before ablation. Amiodarone was discontinued at least 3 months before the procedure. All patients underwent transesophageal echocardiography before the procedure to exclude the presence of thrombus. Electrophysiologic study was performed with the patient in the fasting state using mild sedation.

Venous vascular access was obtained with Seldinger technique. A duodecapolar or decapolar catheter was placed in the coronary sinus (CS). After transseptal catheterization, heparin was

titrated to maintain an activated clotting time of 250 to 300 seconds. A special deflectable 3.5 mm open irrigated-tip catheter (THERMOCOOL or SMARTTOUCH, Biosense-Webster) was used for mapping and ablation. Real-time 3D left atrial and right atrial maps were reconstructed using a nonfluoroscopic mapping system (CARTO, Biosense-Webster). The mapping procedure was performed during sinus rhytthm or AF. RF energy was delivered with a range of power of 20-30 W (reduced to 20-25 W when ablating on the posterior wall) and temperature was limited to 43° C. The pulmonary vein (PV) ostium was identified based on the local electrical signal and on the morphology in the acquired electroanatomical map. PVs electrical isolation was confirmed, in both groups, by using a circular mapping catheter positioned at the ostium of each vein. PVs isolation was considered successful when abolition or dissociation of all PVs potentials (entry block). If the patient was in sinus rhythm the absence of left atrial capture when sequentially pacing from the dipoles of the circular catheter (exit block) was documented.

In patients in which CFAEs ablation was performed, rapid activity was defined as atrial electrograms with a very short cycle length (≤120 ms) averaged over a 10-s recording period[8]. Areas of fractionated atrial electrograms or rapid atrial activity were tagged using the CARTO System, provided with a new software for CFAEs analysis. The software associates to each acquired point the corresponding electrogram that lasts 2.5 seconds. On this electrogram, a measurement of the distance between two consecutive deflections of the isoelectric is taken, according to a specific set of parameters. Parameters regard the voltage amplitude of the signal and the distance between consecutive peaks. The software annotates only spikes that have amplitude included in a predefined window, and then it measures all intervals between two consecutive spikes (positive or negative). All intervals with value included between a minimum duration and the maximum duration threshold (expressed in ms) are assigned to each point of the map. The total amount of assigned intervals leads the level of fragmentation of the potential. The CARTO System with CFAE Software associates to each point all intervals that satisfy this set of parameters. The software for CFAE's analysis, can display, in addition to the local activation time, unipolar and bipolar voltage, propagation and isochronal map, three additional kinds of maps, according to the analysis of the intracardiac signal of each acquired point. These three new maps are: (1) shortest complex interval (SCI) that displays the value of the shortest interval between two consecutive deflections, according to an arbitrary predefined setting of the voltage and the distance between consecutive peaks; (2) average complex interval (ACI) that displays the average value for all intervals considered for each point; (3) interval confidence level (ICL) that displays the total amount of intervals counted for each point, with the possibility to show two different color tags for points with high (red) or medium (blue) level of fragmentation. The threshold of ICL that

distinguishes points with high ICL (high fragmentation = HF) and medium ICL (medium fragmentation = MF) can be determined for each patient. For this study, we have considered as high ICL the points with ≥ 20 intervals and medium ICL the points with 10 to 20 intervals. These cut-offs are arbitrary and have been determined on the basis of a preliminary visual analysis of a biatrial mapping in 10 patients, in order to avoid the inclusion of points with few or transient CFAEs. The CARTO map used to determine the presence of CFAEs was the ICL map. Both the points with HF and those with MF were considered together for our analysis as fragmented electrograms.

The prevalence of CFAE was determined by using the ICL map. The setting used for this analysis was the best obtained in terms of sensitivity and specificity in the identification of CFAE. Each point was automatically classified by the software into three categories: (1) HF; (2) MF; (3) not fragmented. The FF interval was measured by using the ACI map. The setting used was: low voltage threshold 0.05 mV; high voltage threshold 1 mV; minute duration 110 ms; max duration 250 ms. Only points with ICL>10 were considered in order to avoid the inclusion of points with few intervals measured. The mean value of the FF intervals obtained from the points taken from each region of both atria was used for the analysis. This setting for the FF interval analysis was decided to better identify "real" sites of rapid atrial activity (rotors), considering that FF intervals shorter than 110 ms could be in most cases expression of sites of block or collision, particularly using a bipolar mapping, and not the real atrial activity in the mapped points.

In patients who remained in AF after the procedure, sinus rhythm was restored by elective transthoracic cardioversion 4 weeks after the procedure.

Glucose monitoring

In every patient Hb1Ac level was measured each 2 month for the previous 12 months before ablation. In addition, instant glucose levels were obtained by conventional glucometer and/or continuous glucose monitoring (CGM) devices at least 8 times/day in the week before and after the ablation and every 30 minutes during the procedure. Transcutaneous CGM systems consist of a wired sensor containing glucose-sensing enzymes, a transmitter, and a display device. The wired sensor is placed just below the skin in the subcutaneous fat and is continuous with the transmitter base. The transmitter is placed in the transmitter base and sends data wirelessly to a display device such as a dedicated receiver or a smartphone. Evaluation of of glucose control and any changes in insuline therapy was performed by a dedicated endocrinologist. Episodes of hypoglycemia have been defined as a glucose level < 70 mg/dl or as the occurrence of symptoms related to low blood glucose, low blood glucose at the time of symptoms, and improvement after normalization blood glucose values.

Follow-up

After the ablation, patients were placed on anticoagulant therapy and on antiarrhythmic therapy. After 6 months, in the absence of AF recurrences, anticoagulant treatments were discontinued, unless other major risk factors were present. Follow-up consisted of outpatient visits and Holter monitoring performed after 1 month and each 3 months after the ablation procedure. Fasting glycemic values of the previous 30 days (measured either with CGM or conventional glucometer) were also analyzed together with insuline therapy changes occurred. Patients were also evaluated in case of occurrence of any clinical symptom. All patients were instructed to daily assess their pulse and to confirm on ECG any suspected recurrence of arrhythmia. The antiarrhythmic therapy was continued for at least 3 months. After this period, the decision to continue antiarrhythmic medications was based on AF occurrence or the presence of frequent and/or repetitive atrial ectopic beats. Because early recurrences of AF may be a transient phenomenon after PVI, a 5-week blanking period was used.

Statistical analysis

The data were analized using SPSS version 20.0 statistical software. The variables are expressed as mean values ± SD or percentage. Comparisons between groups were performed by Student's *t* test for normally distributed variables, by Mann–Whitney U test for those not normally distributed, and by Fisher test for categorical variables. Cox's proportional hazards model was used to assess the association of variables with the considered endpoint (AF free survival). Hazard ratios (HRs) are given with their 95% confidence intervals (CIs). The HR refers to a unit increase in the variable. The overall AF free survival, estimated with the Kaplan–Meier method, was defined as the time from ablation until the date of first recurrency of AF or the end of the observation. The comparisons were made by log-rank test.

Results

Baseline demographic, clinical and procedural characteristics are shown in Table 1. The two groups of patients were similar in terms age, sex, underling heart disease, number of anti-arrhythmic drug tested and time from DM diagnosis. Percentage of PV isolated was similar in the two groups.

No major complication occurred. In 2 patients in the PVI group and in 3 patients in the PVI+CFAEs group a femoral hematoma was noticed ant treated conservatively. As expected the PVI+CFAEs ablation procedure, compared to PVI alone, were more time-consuming and required more RF applications.

In the study population (DM patients), with respect to a historical population of non-DM patients undergone paroxysmal AF ablation (Table 2), a significant higher percentage of patients showed more than 25% of atrial area interested by CFAEs (Study Population 58% vs 15% Historical Group; $P< 0.05$) (Figure 1 A and B). A wider CFAEs area was reported in DM patients with Hb1Ac constantly above 7.5% during the 12 months preceding ablation (Hb1Ac > 7.5% 41% vs. Hb1Ac ≤ 7.5% 24%; $P<0.05$) (Figure 2)

Success rate of catheter ablation in study population was similar to that of historical population (Study Population 83% vs 85% Historical Group; P=NS) (Figure 3).

During follow-up the recurrences rate was similar in the two group (PVI 27% vs. PVI+CFAEs 21%; P=NS) (Figure 4 A and B). In patients with recurrences the AF burden, expressed as number of AF episodes/patients, was similar in the two groups (PVI 4±2 vs. PVI+CFAEs 3±2; P=NS) (Figure 5).

In the PVI group, recurrences occurred with similar rate in patients with Hb1Ac ≤ 7.5% compare to those with Hb1Ac > 7.5% (Hb1Ac > 7.5% 30% vs. Hb1Ac ≤ 7.5% 22%; P=NS), but a greater AF burden was observed in those with Hb1Ac > 7.5% (6±2 Hb1Ac > 7.5% vs. 1±2 Hb1Ac ≤ 7.5%; $P<0.05$) (Figure 6 A and B). This was not the case for PVI+CFAEs group (Figure 7 A and B).

Hazard ratios for primary endpoint are shown in Figure 8. A significant benefit with PVI+CFAEs was identified in patients with Hb1Ac > 7.5% (HR 1.28, CI 1.11-1.45, $P<0.05$), more than 25 years from DM diagnose (HR 1.25, CI 1.09-1.50, $P<0.05$) and more than 5 AF episodes/year (HR 1.2, CI 1.03-1.55, $P<0.05$). No significant interaction was identified for other subgroup of patient.

15. Conclusions and discussion

This is the first randomized study that investigated atrial remodeling in type 1 DM humans using electroanatomical mapping system. The main findings of this study are: a) DM patients had a more complex atrial "substrate" than non-DM patients; b) in study population at 1-year follow-up the recurrences rate was similar in the groups of patients; c) specific subgroup of patients may benefit from more complex ablations.

CFAEs areas as well as sites showing rapid, regular signal discharge (so called dominant frequency (DF) sites or "rotors") have been proposed as markers of "substrate" and clinical results have shown some promise to ablating these targets[9,10]. Yet, we still understand remarkably little about what these targets mechanistically represent, especially in the human situation. Rotor sites have been demonstrated in animal isolated preparation models of AF using optical mapping techniques[11], but existence of rotors in the human model has never been definitively proven due to the limited resolution of our mapping techniques. CFAEs, on the other hand, have been shown to exist immediately adjacent to rotor sites, a result of collision of wavefronts emanating from the driver sites[12]. Seminal work by Konings et al. showed in human induced AF that CFAEs occurred in regions of slow conduction or at pivot points of wavefront perpetuation[13]. This is supported by further evidence that CFAEs may be associated with sites of structural remodeling and microscopic fibrosis[14]. However, none of these observations directly answers whether CFAEs sites are direct contributors or passive bystanders in the AF process. Furthermore, the work of Sherlag Po, and colleagues has shown that CFAEs occur at sites of autonomic ganglionated plexi and that elimination of CFE is associated with autonomic denervation and resulting noninducibility of AF in the animal model[15]. Yet, this has to be definitively proven in the human condition. Finally, both DF and CFAEs might represent sites of ectopic triggering foci that initiate AF. Human AF mapping, for example, has shown that DF sites occur predominantly in the PV antra in paroxysmal AF, while non-PV locations are much more common in persistent AF, mirroring our knowledge of the location of AF triggering foci[16]. However, which of these CFAEs and DF sites needs to be targeted and to what extent remains to be defined. The initial positive experience of Nademanee in successfully eliminating AF with CFAEs ablation resulted in much subsequent clinical investigation before mechanistic questions have been answered[5,17]. Studies by other investigators, however, have shown that CFAEs ablation alone is not effective for AF[18]. Yet CFAEs ablation may be a very effective adjuvant strategy when combined with PV isolation, particularly in patients with more persistent AF[9]. Certain subtypes of CFAEs may also be more important than others. Chen and

colleagues have shown that while CFAEs associated with rapid cycle lengths are associated with triggering foci for AF, sites of continuous fractionation may be passive sites of wavefront collision[18]. Takahashi and colleagues, in contrast, found that continuous fractionated sites were most likely to be associated with sites of AF termination[19].

The results of this study are in line with the ones reported by other groups who perform regularly CFAEs ablation[5,9,17]. However It is important to underline that in most of the studies published so far on CFAEs ablation included patient with persistent AF and type 2 DM in which the more complex substrate could be explained by the longer duration of arrhythmia itself ("AF begets AF") and the presence of co-morbidities together with a delay in the type 2 DM diagnosis. It is not surprising that CFAEs ablation in addition to PVI did not provide a higher benefit in terms of AF recurrences. This reflects the recent observation of the STAR-AF II trial that in persistent AF patients treated with PVI the additional ablation of CFAEs did not reduce the recurrence rate[20].

Even if CFAEs ablation is not contemplated in current AF ablation guidelines, according to the results of this study, patients with long-lasting DM, with more than 5 AF episodes/year and with Hb1Ac > 7.5% may benefit from longer and more complex procedure, with the same risk of complications.

A lot of uncertainty there is also regarding the role of glucose control in determing AF recurrences. Elevated Hb1Ac values have been associated with endothelial disfunction and a reduction of its values has been associated with improved vascular properties such as aortic compliance and flow-mediated dilation.[21] Alterations of endothelial function predispose to AF by increasing atrial stretch, activation of inflammatory markers and favouring atrial fibrosis[22]. In the present study, patients with Hb1Ac > 7.5% had a wider CFAEs area and, when treated with PVI, a higher recurrences burden compared to patients with Hb1Ac < 7.5%. Three patients showed a marked variation of glycemia during procedure time: in all of three patients early recurrence (during window period) and electrolyte imbalance was also observed. Two previous studies linked glycemic indexes to incident AF in patients with DM[23,24]. In a population-based case-control study, Dublin et al[23] found a 14% increased risk for incident AF in treated patients for every 1% increase in Hb1Ac of treatment intensity. In the Atherosclerosis Risk in Communities (ARIC) cohort, Huxley et al[24] found Hb1Ac levels to be positively and independently correlated with incident AF in patients with and without DM. These results suggest that catheter ablation combined with hypoglycemic agents may further increase the rate of maintenance of sinus rhythm and reduce the need for reablation. Maintenance of well-controlled blood glucose and low levels of HbA1c in accordance with guidelines may decrease the incidence of AF[1]. In the current study, patients with hypoglycemic events had a similar recurrences rate compared to others. Nevertheless hypoglycemic episodes and

glycemic fluctuations have also been associated with an increased frequency of AF in patients with DM[25,26]. Detrimental effects of glycemic fluctuations may have offset theoretical advantages of intensive glycemic control for AF incidence, a known association with AF[25,27,28]. Hypoglycemia induces sympathetic activation, leads to a catecholamine surge, increases cardiac workload, and induces electrocardiographic changes; numerous case reports demonstrate hypoglycemia-associated AF[27]. Furthermore, markers of inflammation such as high-sensitivity C-reactive protein and interleukin-6 are increased in acute hypoglycemia and are linked to the initiation and perpetuation of AF[28,29]. Fluid retention, which occur in case of hypoglycemia, is a known predisposing risk factor for AF via the mechanism of renin-angiotensin-aldosterone system activation and increased atrial stretch[30].

These observations put the emphasis on the pathogenesis of AF in DM patients in which the "disglycemic state" together with reactive oxygen species, interleukins and intracellular transducing signal proteins[31] play an important role, and open new perspectives in the field of the "upstream therapies" (i.e. probucol or resveratrol[32,33]) able to prevent atrial remodeling and suppress AF development.

Limitations

The small sample size is definitely a limitation for the study.

For safety reasons (i.e. to avoid atrio-esophageal fistula of phrenic nerve palsy) not the 100% of PV were isolated and this may have contributed to recurrences occurrence.

For recurrences documentation patients were instructed to daily assess their pulse and to access to the clinic for ECG confirmation: no continuous rhythm monitoring devices (i.e. implantable loop recorder) were used.

It should be underlined that the study has not been powered for subgroup or multivariate analysis.

Figures

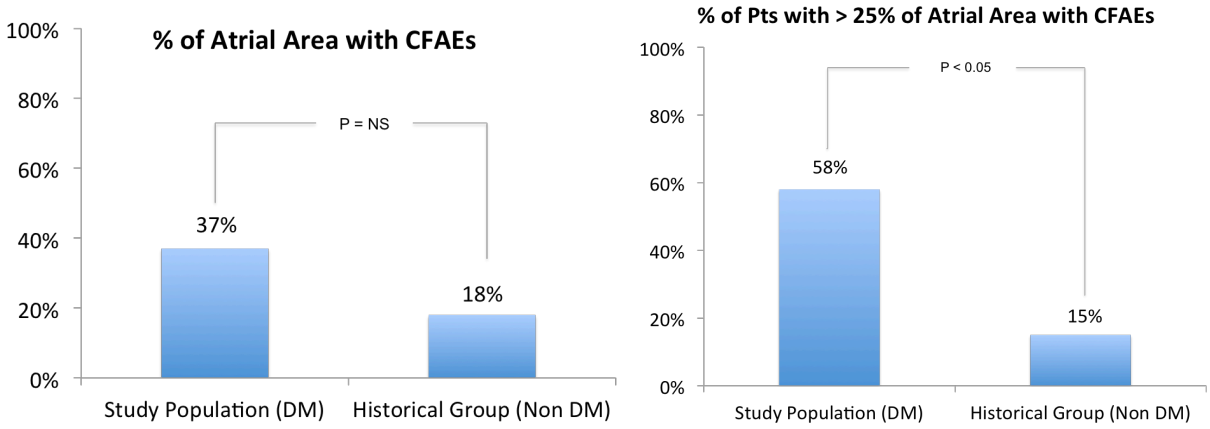

Figure 1 A (left) and B (right): atrial area interested by CFAEs in the study population and in the historical group.

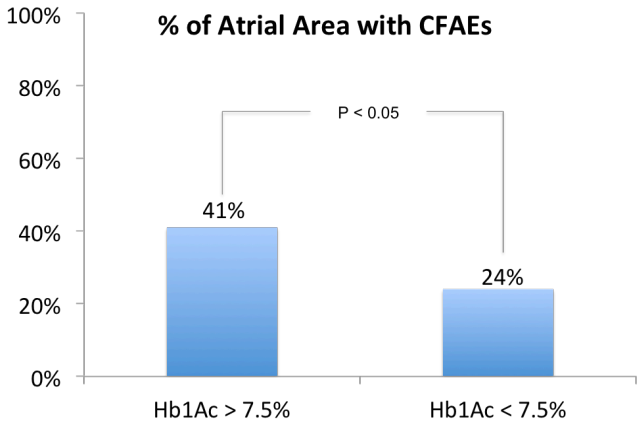

Figure 2: atrial area interested by CFAEs in study population in patient with Hb1Ac in the 12 months before ablation constantly > 7.5% compared to those with Hb1Ac < 7.5%.

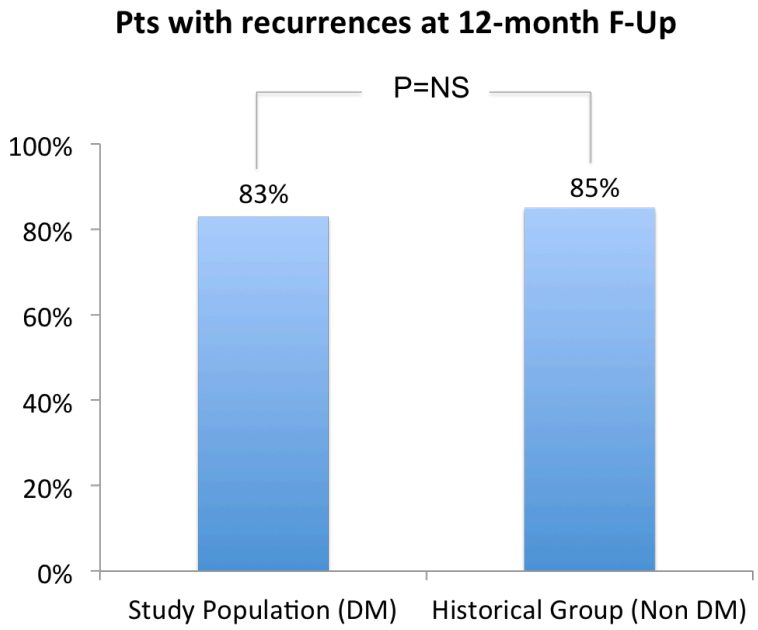

Figure 3: AF recurrences during 12 months follow-up in study population and in historical group.

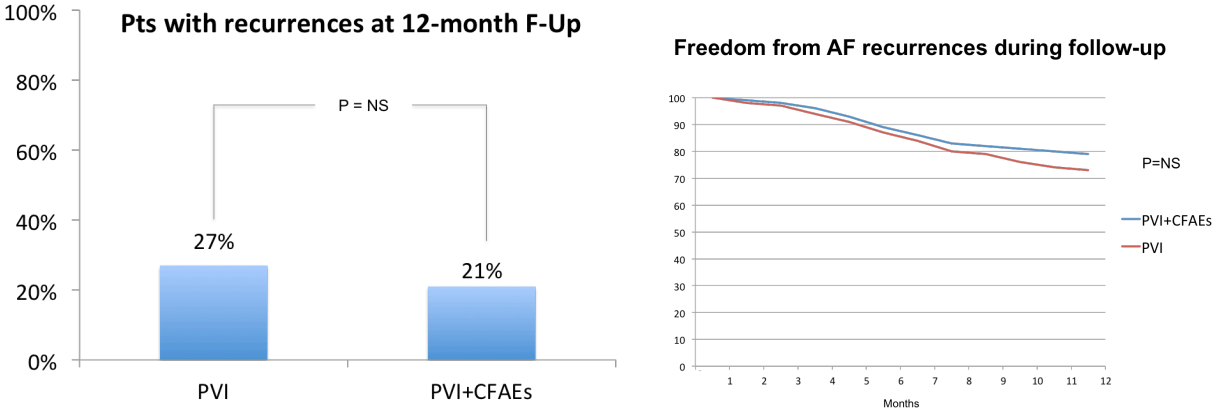

Figure 4 A (left) and B (right): AF recurrences during 12 months follow-up.

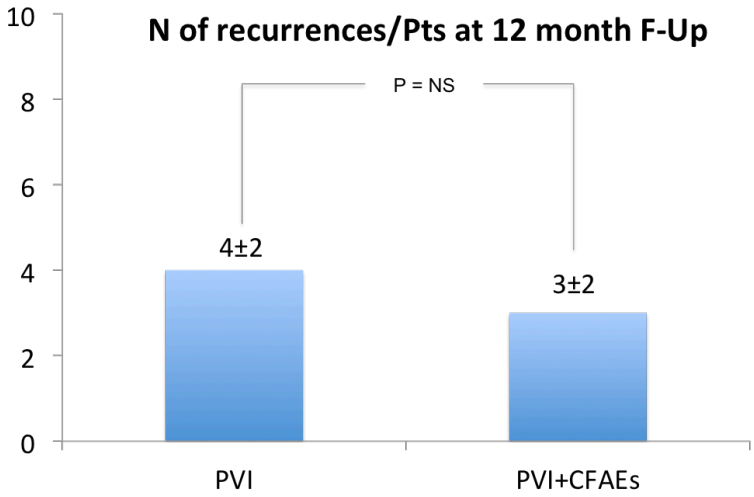

Figure 5: AF burden in patients with recurrences.

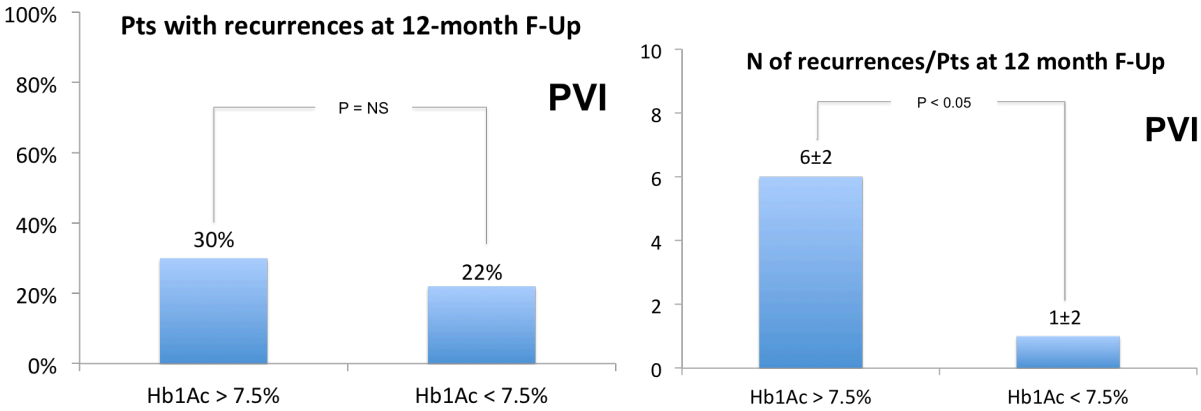

Figure 6 A (left) and B (right): AF recurrences during 12 months follow-up in PVI group according to Hb1Ac values.

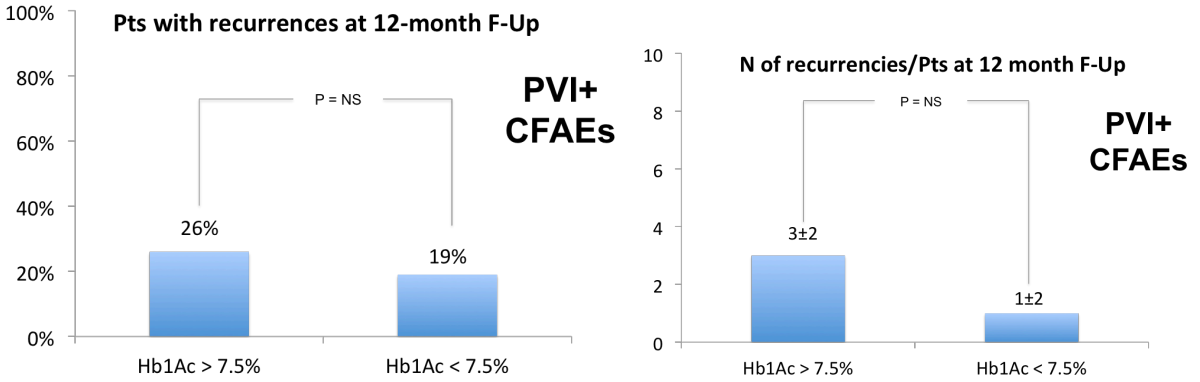

Figure 7 A (left) and B (right): AF recurrences during 12 months follow-up in PVI+CFAEs group according to Hb1Ac values.

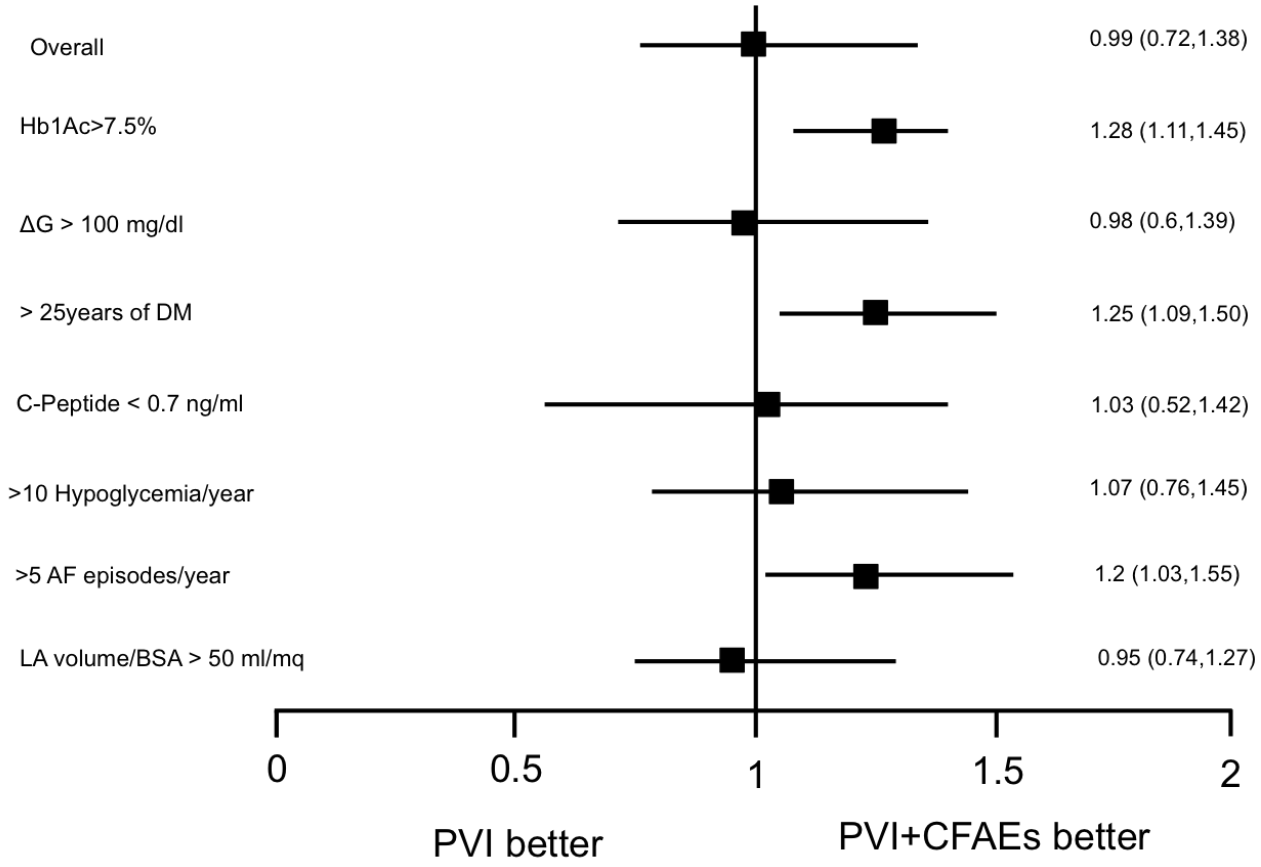

Figure 8: Hazard ratios for primary endpoint.

Tables

Clinical Characteristics of study population (N 64)	PVI (N 32)	PVI+CFAEs (N 32)	P
Age (years)	45.1 ± 9.8	48.6 ± 9.6	0.12
Male (%)	82 %	83%	0.87
Structural heart disease (%)	23	25	0.69
Number if AAD tested	2 ± 1	2 ± 1	0.71
Month from DM diagnose	238 ± 25	256 ± 32	0.09
Left atrial size (mm)	25.1 ± 3.5	23 ± 4.3	0.067
LVEF (%)	57.1 ± 3.5	57.6 ± 3.1	0.63
Clinical Manifest Complications	**PVI**	**PVI+CFAEs**	**P**
Stroke (%)	0	0	
Atrio-esophageal fistula (%)	0	0	
Phrenic Nerve Palsy (%)	0	0	
Cardiac Tamponade (%)	0	0	
Vascular Access Complications (%)	2	3	0.92
Procedural Outcomes	**PVI**	**PVI+CFAEs**	**P**
Number of PV per patient	4.0±0.3	4.1±0.2	0.71
Common Ostium	3	4	0.09
Number of Isolated PV	230	229	0.71
% isolated PV	96	93	0.62
RF time (min)	13.6±5.6	30.9±14.5	<0.01
Fluoroscopy Time (min)	19.0±10.1	19.5±8.3	0.86
Procedural Time (min)	112.2±37.5	149.6±50.5	<0.01
Average Power (W)	23.9±3,0	25,0±1,3	0.65

Table 1: demographic, clinical and procedural characteristics of study population

Clinical Characteristics	Study Population	Control Group	P
Age (Years)	45.1±9.8	48.6±9.6	0.12
Male (%)	82%	83%	0.87
Structural heart disease (%)	23	25	0.69
Number of AAD tested	2±1	2±1	0.71
Month from DM diagnose	238±25	256±32	0.09
Left atrial size (mm)	25.1±3.5	23±4.3	0.067
LVEF (%)	57.1±3.5	57.6±3.1	0.63
DM	100%	0	< 0.05
Clinical Manifest Complications	**Study Population**	**Control Group**	**P**
Stroke (%)	0	0	
Atrio-esophageal fistula (%)	0	0	
Phrenic Nerve Palsy (%)	0	0	
Cardiac Tamponade (%)	0	0	
Vascular Access Complications (%)	2	3	0.92
Procedural Outcomes	**Study Population**	**Control Group**	**P**
Number of PV per patient	4.0±0.3	4.1±0.2	0.71
Common Ostium	3	4	0.09
Number of isolated PV	130	129	0.71
%isolated PV	96	93	0.62
RF time (min)	23.6±5.6	30.9±14.5	0.06
Fluoroscopy Time (min)	19.0±10.1	19.5±8.3	0.86
Procedural Time (min)	132.2±37.5	149.6±50.5	0.07
Average Power (W)	23.9±3,0	25,0±1,3	0.65

Table 2: demographic, clinical and procedural characteristics of historical group compared to study population

18. References

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