Catheter Ablation of Atrial Fibrillation in Patients with Diabetes Mellitus Type 2: Results from a Randomized Study Comparing Pulmonary Vein Isolation Versus Antiarrhythmic Drug Therapy

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PVI Versus Drug Therapy in Diabetics. ***Introduction:*** **Atrial fibrillation (AF) and diabetes mellitus type 2 (DM2) often coexist; however, a small number of patients with DM2 undergoing catheter ablation (CA) of AF have been included in previous studies. The aim of this study was to evaluate safety and efficacy of ablation therapy in DM2 patients with drug refractory AF.**

Methods and Results: **From January 2005 to September 2006, 70 patients with a diagnosis of DM2 and paroxysmal (n = 29) or persistent (n = 41) AF were randomized to receive either pulmonary vein isolation or a new antiarrhythmic drug treatment (ADT) with a 1-year follow-up. The primary endpoint was the time to first AF recurrence. By Kaplan-Meier analysis, at the end of follow-up, 42.9% of patients in the ADT group and 80% of patients who received a single ablation procedure and were without medications were free of AF (P = 0.001). In the ablation group, a significant improvement in quality-of-life (QoL) scores as compared with ADT group was observed. Six patients in the ADT group (17.1%) developed significant adverse drug effects. Hospitalization rate during follow-up was higher in the ADT group (P = 0.01). The only complication attributable to ablation was one significant access-site hematoma.**

Conclusion: **In patients with DM2, CA of AF provides significant clinical benefits over the ADT and appears to be a reasonable approach regarding feasibility, effectiveness, and low procedural risk.** *(J Cardiovasc Electrophysiol, Vol. 20, pp. 22-28, January 2009)*

antiarrhythmic drugs, atrial fibrillation, catheter ablation, diabetes mellitus

Introduction

Diabetes mellitus type 2 (DM2) is one of the most prominent conditions associated with atrial fibrillation (AF).[1-3] In patients with preexisting DM2, AF might be expected to increase morbidity and cardiovascular mortality; therefore, the presence of both requires aggressive management strategies.[4-6] It is obvious that rhythm control, that is, restoration and maintenance of sinus rhythm, may be essential in these patients. However, the increased prevalence of coronary artery disease in patients with DM2 restricts the use of class IA and IC (Singh-Vaughan Williams classification) antiarrhythmic agents. In addition, DM2 is a risk factor for anticoagulation-related bleeding complications.[7] Therefore, maintaining sinus rhythm in this subset of patients is challenging, and treatment should be individualized under closer monitoring.

Curative catheter ablation (CA) for AF has been established as an effective therapeutic option for AF that is resistant to pharmacological treatment.[8,9] Published articles of AF ablation have included few patients with DM2, and relatively little is known for this patient population. Recently presented data from a small study with diabetic subjects undergoing CA for AF reported a high incidence of procedural complications, mostly thrombotic or hemorrhagic.[10]

Therefore, uncertainties exist as to the procedural safety and whether CA of AF leads to significant beneficial effects compared with conventional medical therapy remains to be investigated. Accordingly, the aim of this study was to assess in a prospective randomized investigation the safety and the efficacy of CA for AF in patients with DM2.

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Methods

Study Design

This was a multicentric, open, and randomized pilot study with parallel groups. DM2 patients with symptomatic paroxysmal or persistent AF for ≥6 months refractory to ≥1 class 1–3 antiarrhythmic drugs (AADs) were eligible for the study. Exclusion criteria were as follows: age <18 or >75 years, ejection fraction <30%, left atrial size >55 mm, absence of informed patient consent, and any condition that would make survival for 1 year unlikely. Furthermore, patients with prior cardiac surgery as well patients with history of previous ablation for AF were excluded. Eligible patients were randomized to receive either pulmonary vein isolation (PVI) or a new antiarrhythmic drug treatment (ADT) according to a computer-generated study list (Fig. 1). Follow-up ended at 12 months. All patients were informed of the nature of the study and provided written consent before the randomization.

DM2 was defined according to the World Health Organization Report.[11] AF was defined according to the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with AF.[8] Paroxysmal AF was defined as recurrent AF with episodes that lasted 7 days or less and terminated spontaneously. Persistent AF was not self-terminating within 7 days and permanent AF if cardioversion had failed or had not been attempted.

Endpoints

The primary endpoint of the study was the time to the first AF recurrence after 5 weeks and within 12 months after randomization. AF recurrence was defined as any electrocardiographically confirmed episode of AF or atypical atrial flutter lasting >30 seconds. With the first episode of AF, formal study participation ended and the patient was withdrawn from any further analysis. Secondary endpoints included thromboembolic events, bleedings, hospitalization rate, and changes in quality of life (QoL) as assessed using the Medical Outcomes Study 36-item short-form health survey (SF-36). Thromboembolic events were defined as transient ischemic events, stroke, pulmonary embolism, or deep vein thrombosis. Bleedings were recorded as an endpoint if the hemoglobin value decreased by more than 2 g per liter or if blood transfusion or hospitalization was necessary.

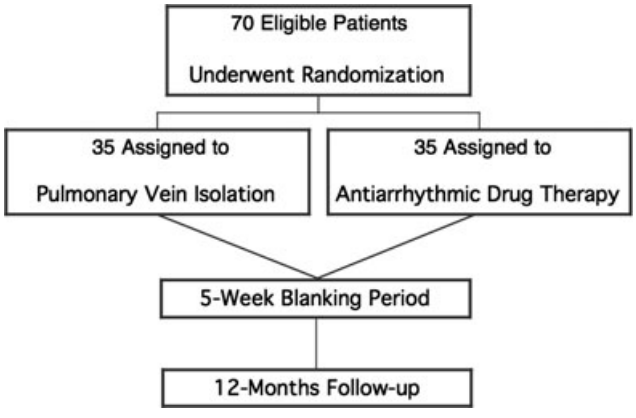

Figure 1. *Flow diagram of the study.*

Ablation Group

All patients had effective anticoagulation for ≥1 month, followed by subcutaneous fractionated heparin 3–5 days before the procedure. AADs were not suspended before the ablation. Transesophageal echocardiography was performed within 48 hours before the procedure in all study patients to rule out the presence of atrial thrombi. Catheter electrodes were inserted with the use of one or both femoral veins or through the right internal jugular vein. A multipolar mapping catheter was placed into the coronary sinus to record right atrial and coronary sinus electrograms. Using a single or double transseptal access, the ablation catheter and the circular mapping catheter were placed in the left atrium.[12] After transseptal access, intravenous heparin was infused to maintain an activated clotting time of at least 300 seconds. Nonfluoroscopic-guided mapping and isolation of PV vestibula were applied in all patients with the NavX mapping system (Endocardial Solution Inc., St. Paul, MN, USA) or with the CARTO system (Biosense Webster, Diamond Bar, CA, USA). Radiofrequency energy was delivered using a 3.5 mm cooled-tip catheter at a target temperature set up to 45°C and a maximal power output of 35 W. The goal of the procedure was the creation of a circumferential line around each PV vestibule or adjacent vestibules of two ipsilateral PV associated with complete elimination of PV potentials as measured by the loop-shaped multipolar mapping catheter at the PV ostium and subsequent demonstration of bidirectional block. Cavotricuspid isthmus ablation was performed at the end of the left atrium ablation. In patients with prior cavotricuspid isthmus ablation, bidirectional block was reassessed during the procedure. Moreover, at the discretion of the operator, a block at roofline joining the superior PV and a block at the isthmus between the mitral annulus and the left inferior PV was performed. Left isthmus line was created with the target of bidirectional block, assessed by pacing from the two opposite sites of the line (i.e., left atrial appendage and the posterior mitral annulus). The block in the roofline was confirmed during left atrial appendage pacing, mapping a corridor of double potentials along the line, and by measuring the delay posterior along the line.

Patients were discharged on AADs. Discontinuation of any antiarrhythmic treatment was considered in each patient according to the clinical preoperative presentation and the clinical course during follow-up. Discontinuation was complete within 1 month in patients without structural heart disease and up to 3 months in the remaining patients. Subcutaneous heparin was continued until the international normalized ratio was 2 to 3. After 6 months, in the absence of AF recurrences, anticoagulant treatments were discontinued, unless other major risk factors were present.

ADT Group

Patients were randomized to ADT at maximum tolerable dose either as single drug or combination. In patients with persistent AF, cardioversion was performed under a new ADT to maintain the sinus rhythm. The recommended medical regimen consisted of oral flecainide 100 mg every 12 hours, oral propafenone (150–300 mg) three times daily, oral sotalol at an initial dose of 80 mg three times daily, and oral amiodarone 600 mg/day for 2 weeks, 400 mg/day for the next 2 weeks, and 200 mg daily thereafter.

In case of early recurrences within 1 month, patients were offered an additional trial of ADT. Warfarin was maintained throughout the 1-year follow-up in all ADT patients with a target international normalized ratio of 2 to 3.

Follow-Up

All patients were instructed to regularly assess their pulse and to confirm on electrocardiogram any suspected recurrence of arrhythmia. Follow-up was scheduled at 1, 3, and every 3 months thereafter or in case of occurrence of any clinical symptom. At each visit, patients were asked whether medical events or symptoms suggestive of cardiac arrhythmias occurred and an ECG Holter monitoring was performed to detect the presence of asymptomatic arrhythmias. Furthermore, using the Medical Outcomes Study SF-36, we assessed patients at baseline and 6 months after the procedure with respect to several indexes of QoL.[13]

Because early recurrences of AF may be a transient phenomenon after PVI, a 5-week blanking period was used and recurrence of AF was defined as AF or atypical atrial flutter occurring beyond 5 weeks post-PV isolation. In order to avoid a potential bias in favor of the ablation group, early recurrences were excluded in the two groups from the analysis.

Statistical Analysis

Continuous variables were analyzed for a normal distribution with the Kolmogorov-Smirnov test. Continuous variables following a normal distribution are expressed as mean value ± standard deviation (SD). Categorical variables are expressed as frequencies and percentages. Differences in baseline characteristics among groups were analyzed using analysis of variance for continuous variables and Pearson's chi-square test for categorical variables. Baseline QoL and change in QoL over time between the groups were compared with the Wilcoxon test. Paired nonparametric exact methods were used to compare the change in QoL over time for each patient. Survival curves were constructed by the Kaplan-Meier method, and differences between the curves were evaluated with the log-rank statistic.

We assessed the relationship between baseline variables and recurrences using a Cox proportional hazards survival model. Hazard ratios (relative risk [RR]) with 95% confidence intervals (CI) demonstrate the risk of AF recurrence when a variable is present. The multivariate Cox model included variables seen to be predictors of recurrences on univariate analysis as well as the type of procedure (PVI or ADT) and other known predictors for AF recurrences or factors not uniformly distributed among groups.

All P-values were two-sided, and a P-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Population

A total of 187 patients with DM2 and AF were initially screened for eligibility. One hundred twenty-two of them fulfilled the inclusion criteria, and 70 agreed to participate. Patients were enrolled from January 2005 to September 2006. Before the randomization, all patients failed to respond to at least one antiarrhythmic drug aimed at rhythm control. Thirty-five patients were assigned to the ablation group and 35 to the ADT group. All patients received the assigned treatment and no patient was lost to follow-up. Baseline demographics and clinical characteristics of the patients in the two groups did no differ significantly (Table 1).

TABLE 1
Baseline Characteristics

Characteristics	Ablation Group (N = 35)	ADT Group (N = 35)	P-Value
Age (years)	63.2 ± 8.6	64.8 ± 6.5	NS
Male sex, n (%)	20 (57.1)	23 (65.7)	NS
Paroxysmal AF, n (%)	16 (45.7)	13 (37.1)	NS
AF duration, months, median (IQR)	41 (18–66)	36 (17–55)	NS
Previously ineffective AAD	1.5 ± 0.4	1.8 ± 0.5	NS
Comorbidities			
Fasting glucose level (mg/dL)	119 ± 23	115 ± 21	0.17
HbA1c (%)	7.2 ± 0.5	7.1 ± 0.5	NS
Hypertension, n (%)	22 (62.9)	24 (68.6)	NS
Structural heart disease, n (%)	16 (45.7)	19 (54.3)	NS
Coronary artery disease, n (%)	7 (20.0)	7 (20.0)	NS
Dilated cardiomyopathy, n (%)	3 (8.6)	2 (5.7)	NS
Valve disease, n (%)	2 (5.7)	4 (11.4)	NS
Previous embolic episodes, n (%)	5 (14.3)	3 (8.6)	NS
Lung disease (asthma/COPD), n (%)	1 (2.9)	1 (2.9)	NS
Echocardiographic measurements			
LA diameter, long axis (mm)	44.3 ± 5.6	45.2 ± 5.2	NS
Left ventricular EF (%)	54.6 ± 7.0	52.6 ± 8.6	0.31

Values are mean ± SD unless otherwise indicated. AAD = antiarrhythmic drugs; ADT = antiarrhythmic drug therapy; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; n = number of patients; HbA1c = glycated hemoglobin; IQR = interquartile range; LA = left atrial.

Ablation Results

PVI was achieved in all patients. The mean procedure time was 207 ± 54 minutes. Bidirectional cavotricuspid isthmus block was successfully achieved in all patients. Mitral isthmus ablation was performed in 8 patients (23%), most of whom requiring additional pulses from within the coronary sinus. In addition, roofline ablation was performed in three patients (9%). No serious procedure-related complications were observed except for an access-site hematoma severe enough to require a prolongation of hospitalization, which did not require blood transfusion and resolved without any sequelae.

Outcomes

A schematic representation of the outcomes is depicted in Table 2. Before discharge, two patients in the ablation group developed spontaneous atrial arrhythmia episodes. All patients were discharged in sinus rhythm. Three patients in the ablation group experienced early recurrences within the blanking period, requiring in one case electrical cardioversion. In the ADT group, early recurrences occurred in five patients and an additional cardioversion after a trial of new ADT was ineffective for two patients because of early recurrent

TABLE 2
Outcomes

	Ablation Group (N = 35)	ADT Group (N = 35)	P-Value
AF recurrences, n (%)	7 (20.0)	20 (57.1)	0.001
Bleedings, n (%)	2 (5.7%)	2 (5.7)	NS
Thromboembolic events, n (%)	0	0	–
Hospitalizations, n (%)	3 (8.6%)	12 (34.3%)	0.01
AADs adverse events, n (%)	1 (2.9%)	6 (17.1%)	0.02

AAD = antiarrhythmic drugs; ADT = antiarrhythmic drug therapy; AF = atrial fibrillation; n = number of patients.

relapses. There were no thromboembolic events in either treatment groups.

Primary endpoint

At the end of follow-up, 28 patients (80.0%) in the ablation group and 15 patients (42.9%) in the ADT group remained free from AF recurrences. By Kaplan-Meier analysis (Fig. 2), cumulative event-free survival from AF recurrences was significantly higher in ablated patients compared with the control group (P = 0.001). On multivariate analysis, ADT without PVI was the only significant independent predictor of AF recurrence (hazard ratio = 2.57, 95% CI: 1.09–6.05; P = 0.031).

Pharmacological therapy and adverse effects

Among ablated patients, AADs were discontinued in all patients within 3 months after the procedure. Oral anticoagulants were stopped in all but 6 patients (82.9%), including 1 having mechanical valve, 1 with dilated cardiomyopathy, and 4 having a history of stroke. Bleeding rates were similar between groups (Table 2).

In the ADT group, the AAD used was a class 1C in 27 patients, sotalol in 3 patients, and amiodarone in 22 patients. A calcium channel antagonist was given to six patients. Continuation of beta-blocker therapy was left to the physician providing care and was continued in 22.9% of the ablated patients and in 42.8% of patients in the ADT group.

In one female, AADs were suspended 2 days after the ablation because of symptomatic bradycardia. She remained free of AF recurrence at the 12-month follow-up. Six patients in the ADT group (17.1%) developed significant drug adverse effects. Symptomatic bradycardia requiring a dosage reduction or a change to an alternative drug occurred in five patients, all known to have hypertension. One of the patients underwent implantation of a dual-chamber pacemaker for symptomatic sinus nodal dysfunction. Another patient developed 1:1 atrial flutter while on flecainide.

Hospitalization

Hospitalization during follow-up occurred in 34.3% of patients randomized to ADT compared with 8.6% of patients randomized to PVI (log-rank P = 0.01). One patient in ADT group with known dilated cardiomyopathy was admitted with a transient pulmonary edema 6 months after the randomization. At admission, he was on sinus rhythm while taking amiodarone.

Changes in QoL

In the ablation group, the evolution scores obtained with an SF-36 instrument were clearly positive (P < 0.05 vs before ablation). Comparing the differences between the two groups, patients in PVI group reported significantly greater improvement in QoL scores as compared with patients in the ADT group for 5 of 8 SF-36 subscales. The significant

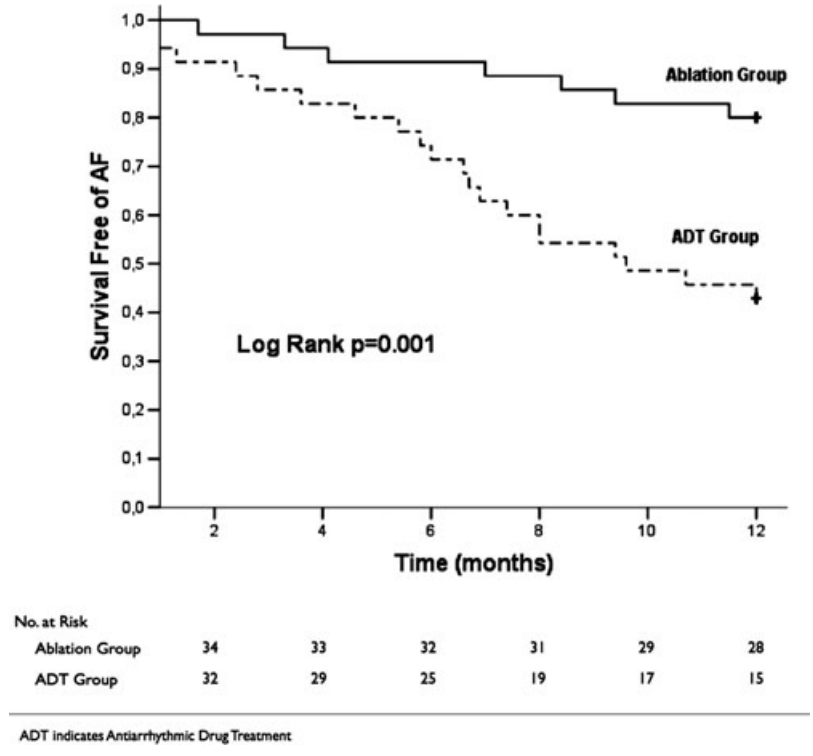

Figure 2. *Kaplan-Meier estimates of AF recurrence-free survival. AF episodes within 5 weeks after randomization were excluded from the analysis. After a single ablation procedure, freedom from AF was significantly higher in ablated patients.*

differences in mean change of QoL scores between groups ($P < 0.05$, PVI vs ADT group) were: 8.9 for general health, 7.7 for social functioning, 8.4 for physical functioning, 5.9 for bodily pain, and 6.8 for role emotional. There were trends toward additional improvement for the other 3 SF-36 subscales (mental health, vitality, and role physical).

Discussion

Main Findings

This randomized study showed that in DM2 subjects, a single session of CA for AF resulted in long-term maintenance of sinus rhythm without the need for AADs in 80% of patients. In addition, AF ablation was associated with an improved QoL, a lower hospitalization rate, and no significant complication attributable to ablation occurred during follow-up.

Prothrombothic Risk and AADs Efficacy in DM2 Subjects with AF

AF is the most common sustained cardiac arrhythmia in the population and DM is one of the most rapidly growing chronic illnesses in the western country. The rising epidemic of diabetes and AF leads to a substantial increase of thrombosis-related complications such as stroke and thromboembolism. Endothelial damage/dysfunction and platelet abnormalities, which are manifest in AF and DM2, may underlie the etiology of a prothrombotic state in these conditions, individually and in combination.[14-17] Diabetes may negatively influence the natural history of AF, enhancing the progression from paroxysmal AF to the chronic type, and masking the cardiac symptoms of AF possibly because of DM neuropathy.[18] Of note, the lack of early clinical signs could lead to delayed referrals for care that increase the risk of thromboembolic events. On the other hand, anticoagulation in DM2 subjects is associated with an increased risk of bleeding[7] that in some patients may outweigh the benefits in reducing the risk of stroke. Importantly, patients with DM2 have an increased prevalence of structural heart disease and therefore are more prone to AADs adverse effects. Indeed, as compared with other reports, a high prevalence of patients with structural heart disease (50.0%) was found in our study subjects and AADs adverse effects occurred in 17.1% of patients in the ADT group. This issue can emphasize the disappointing results of the RACE/AFFIRM trials[19,20] in terms of efficacy of the rate control strategy in patients with DM2, supporting that attempted maintenance of sinus rhythm with AADs might be potentially harmful in these patients. In addition, it was previously reported that diabetes increases the risk for AF recurrence after cardioversion by AADs.[21]

As a result, diabetes predicts arrhythmia onset and adverse events in AF patients; therefore, there is currently great interest in nonpharmacological therapies such as CA of AF because the presence of sinus rhythm is associated with favorable prognosis in DM patients. Although attractive, this issue had never been tested in a randomized study, and the results of this study for the first time strongly support that PVI provides significant clinical benefits beyond those seen with conventional ADT.

Which Strategy for DM2 Patients with Symptomatic AF

According to other reports, in our study ADT seems to be insufficient in treating patients with DM and AF. Maintenance of sinus rhythm (NSR) has been achieved in 80% of ablated patients compared with 43% of nonablated patients. In addition, patients randomized to PVI experienced less hospital admission for cardiovascular causes than those randomized to ADT. The low success rate in the ADT arm as well as the baseline low QoL scores in the study reflects the highly symptomatic study subjects.

Prospective studies like rate control versus electrical cardioversion for persistent atrial fibrillation (RACE) and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) showed that patients who could tolerate rate-controlled AF had outcomes similar to those randomized to rhythm control using AADs.[19,20] We did not include a rate-control group for several reasons. First, in one study (RACE), only 39% of patients in the rhythm-control group had sinus rhythm at the end of follow-up; therefore, a significant limitation of these studies is that the rhythm-control strategy with AADs was not efficacious. In addition, our study population was underrepresented in these trials; in fact, RACE/AFFIRM patients were older and less symptomatic, and AADs administration for the rhythm-control strategy in our DM2 patients with an increased prevalence of coronary artery disease has the potential for serious adverse effects. Importantly, as stated above, AF and DM2 when associated produce further additive deleterious effect; therefore, the benefits of restoring rhythm is supposed to be greater in our patients. Consequently, the results of RACE and AFFIRM should not be applied to our study population.

Safety and Efficacy of CA for AF in Patients with DM2

To our knowledge, this is the first randomized study to compare CA versus medical therapy in diabetic patients with symptomatic AF. In one study, 31 consecutive patients with DM2 were compared with nondiabetic patients undergoing CA of AF.[10] Despite favorable outcomes, DM2 was an independent risk factor for the occurrence of complications mostly thrombotic or hemorrhagic. By contrast in our study, despite the complex preoperative presentation, complication rates attributable to ablation were low including only one access-site hematoma. This observation is not surprising because in the above-mentioned study, patients with DM2 were significantly older with greater prevalence of structural heart disease compared with patients without DM; therefore, the greater percentage of complication in DM2 subjects may reflect the higher risk preoperative presentation. In addition, we suspect that different results between studies may reflect the small sample size of patients and a somewhat dissimilar patient population. In this study, the low complication rate of the ablated patients compare favorably with published studies on CA of AF[22-24] suggesting that ablation is as safe in DM2 as in non-DM2 patients. Although this study cannot be easily compared with others because the study population is inevitably dissimilar, the issue that our study subjects had several comorbidities known to increase procedural complications[25] highlights this finding. Interestingly, hypertension was present in a substantial proportion of patients; this is in line with studies showing that DM is commonly associated with hypertension.[26] However, to best answer the question of whether DM patients undergoing CA of AF have an increased

risk of procedural complication, it is evident that studies with a larger number of centers and patients are required.

Interestingly, despite a significant proportion of our patients having coexisting comorbidities and previous embolic episodes, no thromboembolic events were observed in either group during the 1-year follow-up. This remarkable issue can be partially explained by the anticoagulant treatment policy of the study: warfarin was kept in the ADT group for the 12-month follow-up and also in asymptomatics, whereas in the ablation group it was mainly discontinued after 6 months. Importantly, even with warfarin discontinuation after the ablation, bleeding rates were similar between groups. We suppose that the study was underpowered to detect such a difference, and a greater benefit for the ablation arm could become evident after a longer follow-up duration.

QoL is an important endpoint for assessing any therapy. This randomized study comparing the efficacy of CA with that of medical therapy in patients with AF and DM2 suggests the superiority of CA with respect to QoL measures. Indeed, ablated patients showed a better improvement in QoL scores when compared with nonablated patients.

Study Limitations

This is a pilot study and, therefore, inherently limited by the small number of patients enrolled. However, the study was sufficient to observe significant differences between groups. We believe that the small number was responsible for the lack of detection of significant differences between groups in all the QoL scores.

We are aware that the control group did not comprise the rate control arm that might have added some information. We may also have underestimated the recurrence rate because of asymptomatic undocumented arrhythmia episodes. Since in consequence of AF ablation asymptomatic recurrences may be underestimated, it is not known whether these are equally distributed in both groups, as theoretically a bias in favor of PVI group would be present. However, this issue cannot understate the great extent of benefit observed in ablated patients.

Finally, a computed tomography scan to evaluate PV stenosis was not routinely performed in all patients. It is likely that asymptomatic PV stenosis was present in some patients.

Conclusions

In patients with DM2, CA of AF is safe and provides significant clinical benefits beyond those seen with conventional AADs. In addition, there are potential advantages such as the low risk of adverse drug effects. However, AF ablation should be reserved for patients who fail an initial trial of a rhythm control medication until additional clinical trial information is available to justify the use of AF ablation as first-line therapy.

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