FOCUS ISSUE: ATRIAL FIBRILLATION

Ablation Therapy of Atrial Fibrillation

Clinical Outcomes of Catheter Substrate Ablation for High-Risk Patients With Atrial Fibrillation

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Objectives   The purpose of this study was to determine the long-term clinical outcomes of catheter ablation of atrial fibrillation (AF) substrate for high-risk patients with AF.

Background   The benefits of catheter ablation for high-risk AF patients with respect to mortality and stroke reductions remain unclear.

Methods   We performed AF substrate ablation guided by complex fractionated atrial electrogram (CFAE) mapping in 674 high-risk AF patients. The clinical end points were sinus rhythm (SR), death, stroke, or bleeding. Of these 674 patients, 635 were available for follow-up and made up the study cohort. The patients were relatively old (mean age 67 ± 12 years) and 129 had an ejection fraction (EF) <40%.

Results   After the mean follow-up period of 836 ± 605 days, 517 were in SR (81.4%). There were 15 deaths among the patients who stayed in SR compared with 14 deaths among those who remained in AF (5-year survival rate, 92% vs. 64%, respectively; p < 0.0001). SR was the most important independent favorable parameter for survival (hazard ratio 0.14, 95% confidence interval 0.06 to 0.36, p < 0.0001), whereas old age was unfavorable. Warfarin therapy was discontinued in 434 of the 517 patients in SR post-ablation (84%) whose annual stroke rate was only 0.4% compared with 2% in those with continuing warfarin treatment (p = 0.004).

Conclusions   CFAE-targeted ablation of AF is effective in maintaining SR in selected high-risk AF patients and might allow patients to stop warfarin therapy. SR after AF ablation is a marker of relatively low mortality and stroke risk. Our findings support conducting further randomized studies to determine whether AF ablation is associated with mortality and/or stroke reduction.   (J Am Coll Cardiol 2008;51:843–9) © 2008 by the American College of Cardiology Foundation

Despite advances in cardiovascular therapeutics in recent years, management of AF remains a frustrating dilemma for physicians. Since the publication of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study and several other randomized trials, which compared 2 strategies of AF treatment (rate vs. rhythm control), most arrhythmia scholars have acknowledged that in addition to anticoagulation the use of antiarrhythmic drugs to maintain sinus rhythm (SR) adds no benefit to reduction in mortality or stroke in AF patients when compared with the use of drugs for rate control (1–4). However, although recognizing that rate-control treatment

is an acceptable pharmacologic approach, many physicians are unsatisfied with having their high-risk patients remain in AF. Subsequent analysis of the AFFIRM data suggests that the unwanted effects of antiarrhythmic drugs might offset the benefits of being in SR (5). Naturally, this discontentment with the pharmacologic approach is the major step leading to the development of nonpharmacologic treatment approaches to AF.

Over the past decade, catheter ablation has emerged as a promising approach for treating AF (6–12). However, most AF ablation studies had a short-term follow-up period and encompassed a relatively young patient population, unlike the patient population reported in the AFFIRM trial. As a result, most physicians often ask the key question: will patients who are maintained in SR by catheter ablation have a better outcome than those treated conventionally, especially with respect to the end points of death and/or stroke?

We recently described a new approach to AF ablation, which identifies the target "substrate" sites with electroanatomic mapping of complex fractionated atrial electrogram (CFAE) (12). Our technique achieved a high rate of success in maintaining SR in both paroxysmal and chronic (persistent or permanent) AF patients. We report our findings in this observational study designed to determine the long-term outcomes of high-risk AF patients, including stroke and mortality rates after catheter ablation of AF.

Methods

Study population. Our study cohort consisted of patients who were at least 65 years old or had at least 1 or more risk factors for stroke, including hypertension, diabetes, structural heart diseases, a prior history of stroke, transient ischemic attack (TIA), congestive heart failure (CHF), or an ejection fraction (EF) of ≤40%. We excluded patients with chronic alcoholism, myocardial infarction within 1 month of the study, terminal disease, and patients with documented left atrial thrombus. All patients signed an informed consent that was approved by the Institutional Review Board.

Mapping and ablation of AF. Our AF ablation technique has been previously described (12). In brief, our patients underwent nonfluoroscopic electroanatomical mapping with the CARTO mapping system (Biosense Webster, Inc., Diamond Bar, California), after stopping antiarrhythmic drugs for 5 half-lives or 3 months with amiodarone. The reasons for stopping antiarrhythmic drugs were to avoid the possibility that the drugs might have interfered with AF induction if the patient presented in SR on the procedural date and to avoid the possibility that antiarrhythmic effects might have masked any tachycardia that was the initiator of AF in these patients. Heparin (5,000 IU bolus and subsequent 1,000 to 1,500 IU bolus to keep the activated clotting time >250 s) was used for anticoagulation.

All electroanatomical maps were created for patients who were in AF, either spontaneously or by induction. CARTO provided a voltage map and enabled the operator to associate areas of CFAE with both atria and coronary sinus. We used bipolar recordings filtered at 30 to 500 Hz and defined the CFAE as follows: 1) fractionated electrograms composed of 2 or more deflections and/or a perturbation of the baseline with continuous deflection of a prolonged activation complex; and 2) atrial electrograms with a very short cycle length (≤120 ms). The CFAE was tagged and associated with the atrial anatomy created by CARTO, thereby identifying target sites for ablation.

Radiofrequency (RF) applications were delivered with a maximal temperature of 55°C to 60°C at the catheter tip (4- and 8-mm NaviStar catheters [Biosense Webster, Diamond Bar, California]). The 4-mm NaviStar catheter was used initially until the 8-mm NaviStar became available in January 2003. We used the 8-mm NaviStar almost exclusively for AF ablation from January 2003 to February 2006. We stopped using the 8-mm NaviStar and switched to the irrigated-tip NaviStar catheter, which became available after February 2006. This report does not include patients whose AF ablations were performed with the irrigated-tip NaviStar, because the follow-up period was relatively short.

The primary end points during RF ablation were either complete elimination of areas with CFAE or conversion of AF to SR. When areas with CFAE were completely eliminated but the atrial arrhythmias persisted (organized atrial flutter or atrial tachycardia), they were subsequently mapped and ablated (occasionally in conjunction with ibutilide 1 to 2 mg intravenously over 10 to 20 min). If the arrhythmias were not successfully terminated, external cardioversion was performed.

Clinical end points and assessment of AF recurrences. The primary end points were restoration and maintenance of SR, stroke or TIA, major and minor bleeds, systemic emboli, and all-cause mortality. All patients were followed in our arrhythmia clinic every 3 months. In this study, we based our clinical success of ablation solely on patient clinical symptoms in conjunction with follow-up electrocardiogram or event monitor recording and annual Holter monitoring. Our "blanking period" for arrhythmia recurrent assessment was 3 months from the date of the last ablation procedure.

Echocardiography assessment. A transesophageal echocardiogram was performed to rule out left atrial clot in all patients who had persistent or permanent AF as well as in patients with paroxysmal AF who were in AF >48 h before the procedure. Although left ventricular EF was not a clinical end point, it was available as part of our routine echocardiographic evaluation both before and after ablation (6 months to 1 year after the ablation) in the majority of our patients. Independent echocardiographers who were not involved in the study performed the EF assessment.

Anticoagulation management. Patients were treated with warfarin to maintain an international normalized ratio (INR) between 2 and 3 for at least 3 weeks before the ablation as well as after the ablation. Warfarin was discontinued 4 days before the ablation. Patients with persistent or permanent AF were given enoxaparin sodium 1 mg/kg subcutaneously every 12 h before the ablation. Both warfarin and enoxaparin were restarted immediately after the procedure, but enoxaparin was discontinued 3 days afterwards.

If the patient remained in SR 3 months after the ablation, warfarin was then discontinued and aspirin or clopidogrel or both were arbitrarily and immediately prescribed for antithrombotic treatment. We also stopped warfarin treatment

3 months after established SR in patients who developed early recurrent AF/atrial tachyarrhythmia episodes during the "blanking period" but reverted to SR afterwards.

Patients who developed recurrent AF were restarted on warfarin if their clinical recurrent AF episodes lasted longer than 12 h. The rationale for using a 12-h duration of AF as a cut-off to resume warfarin treatment was based on our preliminary studies involving AF patients who had catheter ablation and implantable devices (implantable cardioverter-defibrillator or pacemaker) (13).

Statistical and data analysis. Baseline characteristics of patients were compared with *t* tests and chi-square tests. The primary analysis was comparison of mortality and stroke rates from the last ablation procedure; patient mortality, stroke probabilities, and standard error were estimated with the Kaplan-Meier method and tested by log-rank test. Secondary analyses were conducted to compare the results among different specific subgroups and adjusting cofactors, including SR, congestive heart failure (CHF), hypertension, EF ≤40%, and female gender. A Cox proportional hazards survival model with stepwise procedure was used to evaluate the effect of these covariates (14). Fisher exact tests were used to analyze the associations of the AF ablation in maintaining SR with various categorical factors (type of AF, left atrial size >50 mm, EF <40%, AF duration >2 years, and age >75 years). Their multivariate relationships were evaluated with multinomial logistic regression.

Results

The enrollment period was from March 2000 to February 2006; the last cut-off date for the follow-up period was May

Table 1	Baseline Clinical Characteristics of Study Patients
Total number of patients	635
Age (yrs)	67 ± 12 (median = 69)
≥75 yrs (n)	169 (26.6%)
Female (n)	212 (33.4%)
Type of AF (n)	
Paroxysmal	254 (40%)
Persistent	146 (23%)
Permanent	235 (37%)
Risk factors (n)	
Hypertension	308 (48.5%)
Previous stroke	61 (10%)
Heart failure	73 (12%)
Coronary disease	131 (21%)
Cardiomyopathy	70 (11%)
Valvular disease	106 (17%)
Diabetes	75 (12%)
AF duration (months)	40 ± 62
Average EF % (n = 565)	50 ± 13
EF <40% (n)	129 (22.8%)
LA size (mm)	45 ± 6
Previous antiarrhythmics	2.6 ± 0.8

AF = atrial fibrillation; EF = ejection fraction; LA = left atrial.

Table 2	Comparison of Baseline Clinical Characteristics of Patients Maintaining SR Versus Patients Remaining in AF After Ablation		
	SR (n = 517)	AF (n = 118)	p Value
Age (yrs)	67 ± 12	67 ± 12	0.9
AF duration (months)	36 ± 57	57 ± 79	0.008
Ejection fraction (%)	51 ± 14	51 ± 12	0.97
LA size (mm)	45 ± 6	48 ± 7	<0.0001
Type of AF			
Paroxysmal (n = 254)	226	28	
Persistent (n = 146)	124	22	<0.0001
Permanent (n = 235)	167	68	

AF = atrial fibrillation; LA = left atrial; SR = sinus rhythm.

31, 2007. During this period, we evaluated 2,356 patients with symptomatic refractory AF; 771 patients met our inclusion criteria, all having a high risk of stroke and similar to those patients studied in the AFFIRM trial. Of these 771 patients, 674 underwent a catheter ablation for AF. Of the 97 patients who were not treated, 27 were excluded because of a left atrial thrombus, and the other 70 patients declined the procedure.

Table 1 summarizes the clinical characteristics of our study cohort, which consisted of 635 of the 674 patients who underwent AF ablation and were followed in our arrhythmia clinic. The other 39 patients who had only 1 ablation and did not have a follow-up period beyond 3 months after the ablation were not included in statistical analysis, because they fell in the "blanking period" (3 months after the ablation) of the recurrent arrhythmia assessment and could not be categorized as to whether the ablations in these patients were effective and in the SR group or ineffective and in the AF group.

A total of 1,065 ablations were performed on the 635 patients: 329 patients (52%) underwent 1 procedure, 204 (32%) required 2 procedures, 80 (12.6%) required the procedure 3 times, and only 22 patients (3.5%) required 4 procedures.

Maintaining SR after ablation. After a mean follow-up period of 836 ± 605 days from the last ablation procedure, 517 of the 635 remained in SR (81.4%); the remaining 118 patients (18.6%) continued to have atrial tachyarrhythmias (paroxysmal AF in 25 patients, persistent AF in 24, permanent AF in 53, and atypical atrial flutter in 16 patients). Of the 517 patients who remained in SR, only 68 patients (13%) required antiarrhythmic agents to maintain SR (48 amiodarone, 19 sotalol, and 1 dofetilide).

As shown in Table 2, AF ablations are significantly more effective in maintaining SR in patients with paroxysmal AF (89%; 226 of 254 patients) and persistent AF (85%; 124 of 146 patients) compared with those with permanent AF (71%; 167 of 235 patients). Longer AF duration and larger left atrial size lowered the success rate of maintaining SR. Univariate and multivariate analysis of discrete variables clearly demonstrated that AF duration ≥2 years and left

Table 3	Underlying Diseases and Causes of Death of Individual Patients Who Died				
Patient #	Age (Gender)	Underlying Disease(s)	Final Rhythm	Cause of Death	Follow-Up (Days)
1	55 (F)	Mitral valvular disease (valve replacement)	AF	SD	1,140
2	83 (M)	HTN	AF	SD	791
3	73 (M)	CAD & HTN	AF	Renal failure	291
4	82 (M)	HTN	AF	Prostate cancer	1,744
5	77 (M)	CAD	AF	Intracranial hemorrhage	1,565
6	64 (M)	HTN	AF	Stroke	194
7	73 (M)	CAD & DM	AF	CHF	855
8	86 (M)	CAD	AF	CHF	724
9	78 (M)	CAD & CHF	AF	CHF	582
10	89 (M)	CAD & CHF	AF	CHF	408
11	70 (M)	CAD & valve replacement	AF	CHF	409
12	77 (F)	HTN & stroke	AF	CHF	582
13	83 (F)	CAD & CHF	AF	CHF	596
14	68 (M)	CAD & CHF	AF	CHF	518
15	88 (M)	CAD & HTN	SR	SD	567
16	85 (F)	HTN & CHF	SR	Pneumonia	1,201
17	80 (M)	HTN & CHF	SR	Cancer	2,041
18	62 (F)	Cardiomyopathy & CHF	SR	Ruptured bowels	898
19	84 (F)	HTN	SR	Pancreatic cancer	1,274
20	72 (M)	CAD & COPD	SR	Respiratory failure	729
21	75 (F)	CHF & COPD	SR	Respiratory failure	865
22	78 (F)	HTN & DM	SR	Pneumonia	1,070
23	86 (F)	HTN	SR	Sepsis	1,103
24	79 (F)	CAD & CHF	SR	Pulmonary emboli?	1,805
25	88 (M)	HTN	SR	Prostate cancer	567
26	75 (M)	CAD & CHF	SR	CHF	489
27	52 (M)	Cardiomyopathy	SR	CHF	566
28	79 (M)	HTN & CHF	SR	CHF	512
29	75 (M)	CHF & COPD	SR	CHF	408

CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HTN = hypertension; SD = sudden death; other abbreviations as in Table 2.

Figure 1	Effects of Maintaining NSR After AF Ablation on Survival

Kaplan-Meier curve demonstrating improved survival in patients who remained in normal sinus rhythm (NSR) (red circles) from all-cause mortality compared with patients who remained in atrial fibrillation (AF) (green circles).

atrial size ≥50 mm were negative predictors of maintaining SR (p < 0.01), whereas EF <40% had no impact on the long-term success of maintaining SR in our patient population (p = 0.69).

Effects of sinus rhythm on mortality. Over the follow-up period, there were 29 deaths (Table 3); 15 of the 517 patients who remained in SR died (3%; 4 from CHF, 1 sudden death, and 10 noncardiac deaths), compared with 14 of 118 patients with recurrent AF who died (12%; 8 from CHF, 2 sudden deaths, 2 noncardiac deaths, and 2 from stroke including 1 patient with a spontaneous intracranial hemorrhage while taking warfarin). Clearly, the cardiac death rate was much lower in patients who stayed in SR (0.96% vs. 8%; p < 0.0001).
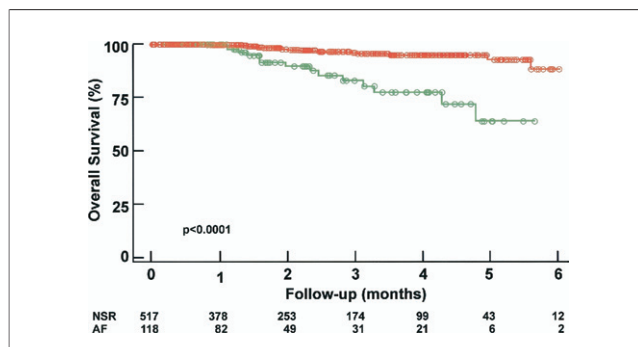
Patients whose AF ablation was effective in maintaining SR had a much lower 5-year mortality rate (8%) when compared with a 36% 5-year mortality rate in those with recurrent AF after the ablation (Fig. 1) (p < 0.0001). The hazard ratios (HRs) for death for SR, history of CHF, EF ≤40%, hypertension, and female gender are shown in Table 4. The SR was the strongest independent factor associated with a lower mortality (HR 0.14, 95% confidence interval [CI] 0.06 to 0.36, p < 0.0001). Age is an independent predictor of mortality (HR 1.06, 95% CI 1.02 to 1.11, p = 0.004), whereas other factors such as EF, CHF, and hypertension were not independently associated with an increase in mortality in this patient population.

Figure 2 clearly shows that patients in AF who had an EF <40% had the worst prognosis. More importantly, patients whose EF was >40% but remained in AF had a higher mortality rate compared with patients in SR regardless of their EF.

Effects of maintaining SR on EF. Of the 129 patients with an EF ≤40%, 102 maintained SR (79%). After 6 months of SR, the EF was significantly improved (Fig. 3); the EF increased from 31 ± 7% to 41 ± 13% (p < 0.001). In contrast, there were no changes in EF in the 27 patients who failed to respond to AF ablations and remained in AF (before ablation EF was 24 ± 8% and after ablation EF was 23.5 ± 9%).

Table 4	Multivariate Cox Regression Analysis of Hazard Ratio of Key Risk Variables		
	Hazard Ratio	95% Confidence Interval	p Value
Sinus rhythm	0.14	0.058–0.36	<0.0001
CHF	2.5	0.93–6.69	0.068
Age	1.06	1.02–1.11	0.004
EF ≤40%	0.982	0.949–1.016	0.298
LA size (≥50 mm)	1.068	0.99–1.15	0.08
Hypertension	1.77	0.78–4.03	0.17
Female	1.079	0.45–2.58	0.86

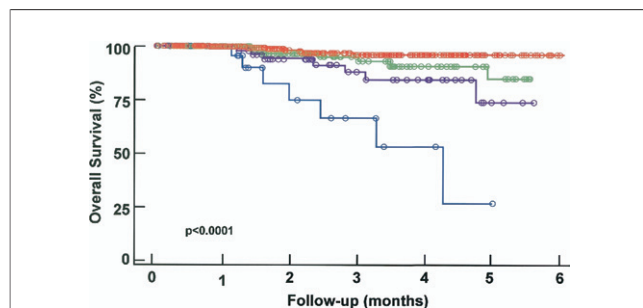CHF = congestive heart failure; EF = ejection fraction; LA = left atrial.

Figure 2　　**Effects of NSR After AF Ablation and EF on Survival**

Multiple overlay Kaplan-Meier survival curves among 4 strata of patients: 1) patients with ejection fraction (EF) >40% and NSR **(red circles)**; 2) patients with EF ≤40% and SR **(green circles)**; 3) patients with EF >40% and AF **(purple circles)**; and 4) patients with EF ≤40% and AF **(blue circles)**. Abbreviations as in Figure 1.

Figure 4　　**Comparison of Stroke-Free Survival: Warfarin vs. No Warfarin**

Red circles = no warfarin sodium; **green circles** = warfarin sodium.

Relation between discontinuation of anticoagulation therapy, bleeding, stroke, and embolic incidence. Warfarin therapy was discontinued in 434 of the 517 patients who remained in SR (84%). Eleven patients experienced a major stroke or TIA. In the patients who discontinued warfarin, 5 patients had a cerebrovascular accident (CVA) (3 ischemic strokes and 2 TIAs); 4 patients had no recurrent symptomatic AF. One patient who had TIA reported symptoms of palpitations before the central nervous system event, but he was in SR at the time of the hospital visit.

In comparison, 6 patients in the AF group who required warfarin (4 had adequate INR within 3 months before the event, but in 2 patients, no INR was available within 3 months of the event) had CVAs (5 ischemic strokes and 1 fatal intracranial hemorrhage). Figure 4 shows the 5-year stroke rate was 3% in the patients who had stopped taking warfarin compared with 23% in the patients who remained in AF and continued taking warfarin (p = 0.004).

Procedure complications. Five patients suffered a CVA (0.8%); 2 of the CVAs occurred 24 to 48 h after the procedure. Hemopericardium occurred in 9 patients (1.4%); 1 required a surgical repair, owing to perforation of the left
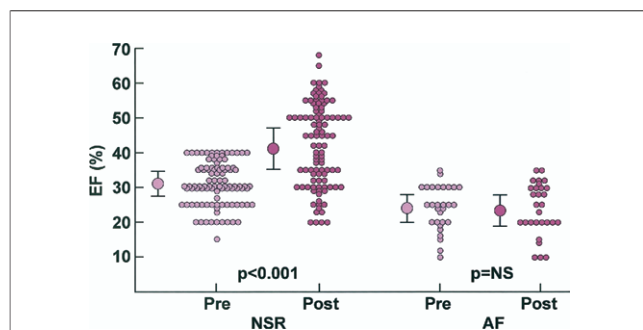

Figure 3　　**Beneficial Effect of NSR After AF Ablation on Left Ventricular Function**

Comparison of individual changes of EF before and after ablation. Pre = before ablation; Post = 6 to 12 months after ablation. Abbreviations as in Figure 1.
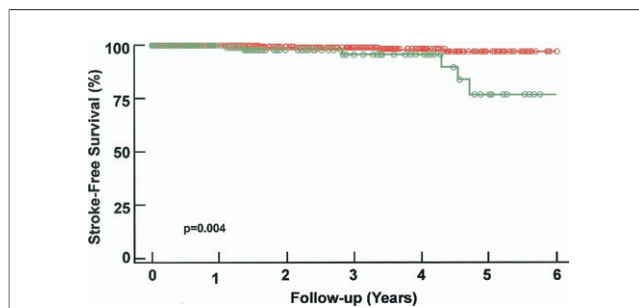
atrium. The remaining 6 patients were treated uneventfully with pericardiocentesis. Thirteen patients developed vascular complications at the femoral puncture site (7 pseudoaneurysms, 2 arteriovenous fistulas, and 4 with severe bleeding [including 1 patient with retroperitoneal bleeding] at the groin site, which required a blood transfusion). Two patients developed high-grade atrioventricular nodal block requiring permanent pacemaker implantation. Three patients developed transient pulmonary edema after the procedure, which resolved with diuretic therapy. We observed no serious procedure-related late complications, such as esophageal-left atrial fistula or clinical pulmonary vein stenosis.

No procedurally related deaths occurred; however, 2 patients died within 30 days after the procedure. One of the patients had a CVA within 48 h of the procedure and eventually died weeks later. The other patient died from respiratory failure due to complications of chronic obstructive pulmonary disease and pneumonia.

Discussion

Our study is the first to systematically evaluate the safety and effectiveness of catheter-based substrate ablation in a high-risk AF patient population with an extended long-term follow-up period. Our patients were much older (median age, 69 years) than those reported in other studies involving catheter ablation treatment of AF.

Despite this high-risk profile, our data support the fact that AF substrate ablation guided by CFAE mapping is effective in maintaining SR. At 2.3-year mean follow-up, patients who had the highest success rates (89% and 85%, respectively) were those whose presenting rhythm was paroxysmal or persistent AF compared with 71% of those with permanent AF (p < 0.0001).

A key question regarding maintenance of SR after catheter ablation in our study is inevitably raised: how does one rule out occurrences of asymptomatic AF episodes? And if there are asymptomatic AF episodes, what are the risks of stroke and embolic complications if the patients are not protected by anticoagulation?

However, our stroke and embolic complication rates are low, despite the majority of our patients who remained in SR stopping their anticoagulation. The annual stroke rate in our successfully treated patients who discontinued anticoagulation was only 0.4% compared with 2% (both ischemic and nonischemic) in the patients with recurrent AF who required warfarin. The Kaplan-Meier–derived 5-year stroke incidence was only 3% compared with 23% for patients who required ongoing warfarin therapy (p = 0.04).

Although the reasons for the lower stroke rate in our patient population are unclear, several possible explanations could have contributed to this observation in our study: 1) our patients who have had successful AF ablation continue to maintain SR at a much better rate than that seen in the pharmacologic treatment and possibly have a much less frequent and/or shorter duration of asymptomatic AF episodes; and 2) continuance of SR promotes atrial remodeling that is less conducive to thrombus formation (15). Although this reasoning is merely speculative, our observation shows that once SR is restored and maintained by catheter substrate ablation, the risk of stroke decreases.

Undoubtedly, the preceding data will generate future debate over the requirements for continued anticoagulation in patients after successful AF ablation. Oral et al. (16) recently reported data from their laboratory demonstrating that the stroke rate in their patients was quite low after successful RF ablation. Our data not only support their findings but also extend these benefits to a higher-risk patient population, particularly the very elderly. Randomized trials are warranted to substantiate and confirm the preceding findings.

Meanwhile, our data suggest that AF substrate ablation might represent a viable treatment modality for high-risk AF patients who either have a contraindication to anticoagulation or cannot reliably adhere to the rigorous monitoring protocol. Whether physicians will embrace the therapeutic goal of stopping anticoagulation as a benefit of AF, ablative treatment is likely to remain controversial. However, there are more benefits from being in SR after AF ablation than just a reduction in stroke rate.

Our data also showed a better 5-year survival rate in patients who maintained SR (Fig. 3) than in those who remained in AF (92% vs. 64%; p < 0.0001). It is possible that patients whose AF ablation failed to restore SR had more advanced heart disease or unrecognized risk factors that could have prevented them from maintaining SR and unfavorably influenced their overall survival as well. However, with the exception of the left atrial size and duration of AF, which are greater in patients who did not respond to AF ablation (Table 2), there were no differences in terms of baseline patient characteristics including EF. Multivariate analysis and Cox regression analysis convincingly show SR as an independent predictor of a favorable prognosis, whereas EF, hypertension, and female gender had little effect (Table 3).

Patients who maintained SR regardless of the baseline EF had a lower mortality rate than their counterparts on the same corresponding EF stratum (Fig. 2). One reason that patients who had a lower EF (≤40%) but maintained SR fared better is the significant recovery of their ventricular function after restoring SR. The average EF increased from a mean of 31% before ablation to 41% after successful ablation (p < 0.001). In contrast, patients who had recurrent AF after ablation had no change in their EF.

Our data dovetail nicely with the findings of Hsu et al. (17) and Gentlesk et al. (18), that many AF patients with a depressed baseline EF show improvement in their EF after SR has been restored with a successful AF ablation. It is also plausible that the improved LV function after maintaining SR in our patients with prior depressed EF resulted in improved survival. Indeed, our data suggest that this might be the case, because the significant reduction in cardiac death, especially from CHF, is quite evident in our study; 4 of 517 patients (0.8%) who stayed in SR died from CHF compared with 8 of 118 (6.7%) patients who remained in AF (p < 0.0001).

Study limitations. Our study is not a randomized trial and does not have a control group receiving conventional treatment for AF. One could criticize the possibility of selection bias in our study patients. For example, one might question whether our patient population is less ill than those observed in the AFFIRM study. We believe that this is not the case, because our patient selection criteria are the same as in the AFFIRM study. Furthermore, the median age of our patient population is comparable to that observed in the AFFIRM trial.

More importantly, the benefit of our patients being in SR was apparent with respect to mortality, stroke reduction, and improved LV function. In addition, there are no statistically significant differences in baseline population characteristics between patients who maintained SR after ablation and those who remained in AF, with the exception of larger left atrial size and longer AF duration in the latter group. Also, patients with permanent AF had a higher failure rate compared with patients with paroxysmal AF. Still, multivariate analysis clearly shows SR as an independent factor for favorable prognosis, emphasizing that the consequences of AF are unfavorable to long-term survival and cardiac function.

One might also question stopping warfarin treatment without rigorous monitoring of asymptomatic AF episodes. Glotzer et al. (19) reported data from the MOST (MOde Selection Trial), which showed that patients with sick sinus syndrome and permanent pacemaker implantation, who had high atrial event rates (>5 min), had higher mortality and nonfatal stroke rates. However, Capucci et al. (20) reported different findings in a cohort of patients with bradycardia and AF who received DDDR pacemakers (AT500, Medtronic Inc., Minneapolis, Minnesota). They found that the incidence of stroke and arterial embolism is quite low in patients whose AF duration is <24 h. The reason for conflicting findings between these 2 studies remains unclear (both have similar patient populations and median age of

the study patients). However, their patient populations are clearly different than our patient population, because all our patients had undergone AF ablation.

It is possible that the asymptomatic atrial tachyarrhythmias, which occurred after AF ablation in our study, were different than those observed in the MOST study. It is plausible that patients with a high rate of atrial events in the MOST study eventually developed persistent or longer episodes of AF (>1 day)—as suggested in their data—and in turn further increased risk of stroke substantially, whereas our asymptomatic atrial tachyarrhythmia episodes did not further degenerate to persistent AF because of the effect of the AF ablations.

One might speculate that the majority of our patients who developed recurrent atrial tachyarrhythmia episodes after ablation became symptomatic and therefore were identified and treated with warfarin. In any event, the stroke rate in our patients who maintained SR is very low, with a 5-year stroke rate of only 3%, suggesting that, if any asymptomatic AF episodes occurred in these patients, they were inconsequential.

Clinical implications. Our data demonstrate that catheter substrate ablation of AF guided by CFAE mapping is effective in maintaining SR in high-risk AF patients and that this effect is long-lasting. The benefits of being in SR in our patient population are remarkable with respect to stroke and mortality reduction. These findings might have an impact on our management of high-risk AF patients, especially in elderly patients, who are not always ideal candidates for anticoagulation (21).

The benefits of AF substrate ablation have to be balanced against the potential complications of the procedure. Although the procedure-related stroke rate of 0.8% is relatively low, it remains concerning. The recent introduction of an irrigated-tip ablation catheter might represent a major advance in reducing the risk of peri-procedural embolic complications. If successful in reducing peri-procedural CVA, it will likely replace the 4- and 8-mm nonirrigated tip ablation catheters that were used in our study. A significant number of our patients had multiple ablative sessions, and this unavoidably poses incremental risk to such patients. Likewise, cardiac tamponade is a small but serious risk that requires continuous attention and preparation to promptly recognize and treat these patients.

Our report from a single center clearly suggests that maintaining SR by catheter substrate ablation is a marker of relatively low mortality and stroke risk. Our findings support that further randomized controlled studies are merited to determine whether AF ablation is associated with a mortality and stroke reduction in a high-risk AF patient population.

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