Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 60, No. 19, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.04.060

Catheter Ablation of Long-Standing Persistent Atrial Fibrillation

5-Year Outcomes of the Hamburg Sequential Ablation Strategy

Roland Richard Tilz, MD, Andreas Rillig, MD, Anna-Maria Thum, Anita Arya, MD, Peter Wohlmuth, Andreas Metzner, MD, Shibu Mathew, MD, Yasuhiro Yoshiga, MD, Erik Wissner, MD, Karl-Heinz Kuck, MD, Feifan Ouyang, MD

Hamburg, Germany

Objectives This study describes the 5-year efficacy of catheter ablation for long-standing persistent atrial fibrillation (LS-AF).

Background Long-term outcome data after catheter ablation for LS-AF are limited.

Methods Long-term follow-up of 56 months (range 49 to 67 months) was performed in 202 patients (age 61 ± 9 years) who underwent the sequential ablation strategy for symptomatic LS-AF. Initial ablation strategy was circumferential pulmonary vein isolation (PVI). Additional ablation was performed only in acute PVI nonresponder, if direct current cardioversion failed after PVI.

Results After the first ablation procedure, sinus rhythm was documented in 41 of 202 (20.3%) patients. After multiple procedures, sinus rhythm was maintained in 91 of 202 (45.0%) patients, including 24 patients receiving antiarrhythmic drugs. In 105 patients, PVI was the sole ablative therapy, 49 (46.7%) of those patients remained in sinus rhythm during follow-up. Patients with a total AF duration of <2 years had a significantly higher ablation success rate than patients whose AF duration was >2 years (76.5% vs. 42.2%, respectively; $p = 0.033$). Persistent AF duration (hazard ratio: 1.09 [95% confidence interval: 1.04 to 1.13]; $p < 0.001$) independently predicted arrhythmia recurrences, and acute PVI responders had a reduced risk of relapse (hazard ratio: 0.57 [95% confidence interval: 0.41 to 0.78]; $p < 0.001$) after the first ablation.

Conclusions During 5-year follow-up, single- and multiple ablation procedure success was 20% and 45%, respectively, for patients with LS-AF. For patients with a total AF duration of <2 years, the outcomes were favorable. (J Am Coll Cardiol 2012;60:1921–9) © 2012 by the American College of Cardiology Foundation

Pulmonary vein isolation (PVI) is a well-established treatment option in patients with atrial fibrillation (AF). In long-term follow-up of as long as 5 years, the multiple procedure success rate is approximately 80% in patients with paroxysmal AF (PAF) (1–3). However, recurrences are frequent, and repeat ablation is often required to maintain freedom from AF (1–3).

Current guidelines from HRS/EHRA/ECAS state that: 1) ablation strategies that target the PVs and/or PV antrum should form the cornerstone for most AF ablation procedures; and 2) if the PVs are targeted, complete electrical isolation should be the goal (1). However, in patients with long-standing persistent AF (LS-AF), PVI alone may not be sufficient as outcomes after PVI alone are disappointing, with success rates ranging from 36% to 56% at medium term follow-up (2–5). To improve outcomes in patients with LS-AF, various ablation strategies in addition to PVI have been described. The most widely used additional ablation strategy is the ablation of complex fractionated atrial electrograms (CFAE) (6,7). However, numerous gaps in our knowledge remain such as the adjunctive benefit of these techniques and the long-term efficacy of LS-AF ablation in general. Until recently, long-term outcome data of >2 years' follow-up after catheter ablation for LS-AF have been sparse (8).

See page 1930

We previously evaluated the short-term outcomes of catheter ablation for LS-AF (5). In this study, we present long-term follow-up data from the same cohort. The objectives of this study were to determine: 1) the long-term efficacy of the sequential

From the Department of Cardiology, Asklepios Klinik St. Georg, Hamburg, Germany. Dr. Tilz has received travel grants, research grants, and speakers' honoraria from Biosense Webster and St. Jude Medical. Dr. Rillig has received travel grants from St. Jude Medical and Biosense Webster. Prof. Kuck has received research grants from Biosense Webster, Stereotaxis, Prorhythm, Medtronic, Edwards, and Cryocath; and is a consultant to St. Jude Medical, Biosense Webster, Prorhythm, and Stereotaxis. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 17, 2012; revised manuscript received April 23, 2012, accepted April 24, 2012.

Downloaded From: http://content.onlinejacc.org/ on 01/20/2014

Abbreviations and Acronyms

AAD = antiarrhythmic drug
AF = atrial fibrillation
AT = atrial tachycardia
CFAE = complex fractionated atrial electrograms
CI = confidence interval
HR = hazard ratio
LA = left atrium
LS-AF = long-standing persistent atrial fibrillation
OAC = oral anticoagulation
PAF = paroxysmal atrial fibrillation
PV = pulmonary vein
PVI = pulmonary vein isolation
SR = sinus rhythm

ablation strategy for treatment of LS-AF; 2) the regression of LS-AF toward PAF after ablation; and 3) predictors of recurrence.

Methods

Study population. Two hundred and five patients were consecutively enrolled in the initial study. The study population and methods have been published previously (5). Three patients were lost to follow-up. Long-term follow-up and data analysis were performed for the remaining 202 patients (age 61 ± 9 years). All patients had symptomatic LS-AF refractory to antiarrhythmic drugs (AAD) and underwent radiofrequency current catheter ablation at our institution between November 2003 and July 2007. The LS-AF was defined as continuous AF of >1 year duration (9). Baseline characteristics of the patient population are presented in Table 1. Total AF duration was 99 ± 64 months (median 84 months [range 60 to 120 months]), duration of continuous AF (persistent AF) was 49 ± 44 (median 36 months [range 20 to 60 months]). Clinical follow-up was completed in March 2011.

Electrophysiological study. After written informed consent, all patients underwent a transesophageal echocardiogram before the procedure. Oral anticoagulation (OAC) therapy was stopped at least 3 days before ablation and replaced with low-molecular-weight heparin. The procedure was performed under deep sedation utilizing midazolam, fentanyl, and a continuous infusion of propofol. Two standard catheters were positioned at the His bundle region and inside the coronary sinus. Two or 3 SL1 sheaths (St. Jude Medical, Minneapolis, Minnesota) were advanced to the left atrium (LA) using a modified Brockenbrough technique. After transseptal catheterization, intravenous heparin was administered, targeting an activated clotting time of 250 s to 300 s. Transseptal sheaths were continuously flushed with heparinized saline. Three-dimensional electroanatomical LA reconstruction using the CARTO system (Biosense Webster, Diamond Bar, California) and ablation were performed using a 3.5-mm tip catheter (ThermoCool Navi-Star, Biosense Webster) (10).

Table 1 Baseline Patient Characteristics (N = 202)

Age, yrs	61 ± 9
Male	160 (79)
Total AF duration, months	99 ± 64
Persistent AF duration, months	49 ± 44
Patients treated with amiodarone	115 (57)
Structural heart disease	32 (16)
LA diameter, mm	49 ± 6
Hypertension	155 (77)
LVEF, %	60 ± 7

Values are mean ± SD or n (%).
AF = atrial fibrillation; LA = left atrial; LVEF = left ventricular ejection fraction.

Ablation protocol during the initial procedure. All patients underwent circumferential PVI using irrigated radiofrequency current, as previously published (Fig. 1) (11). During PVI, 1 or 2 spiral mapping catheters (Lasso, Biosense Webster) were positioned inside the ipsilateral PVs. The endpoint of PVI was defined as the absence of any PV spike potential recorded on either Lasso catheter for at least 30 min after PVI. If after PVI, AF did not convert to sinus rhythm (SR) or atrial tachycardia (AT), up to 3 biphasic direct current shocks (200 J, 360 J, and 360 J) were administered aiming at restoration of SR. Defibrillator patches were positioned in an anterior-posterior position. If AF was reinduced by a non-PV trigger during the 30-min waiting period, the AF trigger was targeted for ablation but no CFAE ablation was performed. The CFAE ablation was only performed if SR could not be achieved at all. No medications or pacing maneuvers were used at that point. If DC cardioversion was successful, patients were defined as acute PVI responder (Fig. 1). The CFAE ablation was performed, as described before, in an attempt to convert AF to SR or AT (5). Termination was defined as transition directly from AF to SR or by 1 or multiple ATs (8). The CFAEs were analyzed visually and were defined as published by Nademanee et al. (6): 1) fractionated electrograms composed of >1 deflections and/or continuous deflection of a prolonged activation complex; and 2) atrial electrograms with <120 ms CL recorded over a 5-s recording period.

During ablation of CFAEs or LA linear lesions, the Lasso catheter was positioned in the left atrial appendage (LAA) to continuously record LAA activity. Only in the presence of a (macro) AT were linear lesions applied. Electrophysiological evidence of bidirectional block was validated in SR (12). Superior vena cava isolation was attempted only if spontaneous focal-discharge was demonstrated from this location. Patients requiring ablation strategies in addition to PVI were defined as acute PVI nonresponder.

Ablation protocol during repeat procedure. Repeated electrophysiology procedures were undertaken for recurrent atrial tachyarrhythmias (ATa). The initial strategy was an assessment of PV reconduction, followed by closure of all PV conduction gaps and electrical reisolation. Ablation of CFAEs was only performed in a PVI nonresponder if: 1) DC cardioversion failed after repeat PVI; or 2) patients demonstrated no PV reconduction (5). In patients with no PV reconduction presenting in SR, AF was induced by burst stimulation from the LAA before CFAE ablation.

Post-ablation treatment and follow-up. The OAC therapy was started immediately post-procedure, targeting an

Downloaded From: http://content.onlinejacc.org/ on 01/20/2014

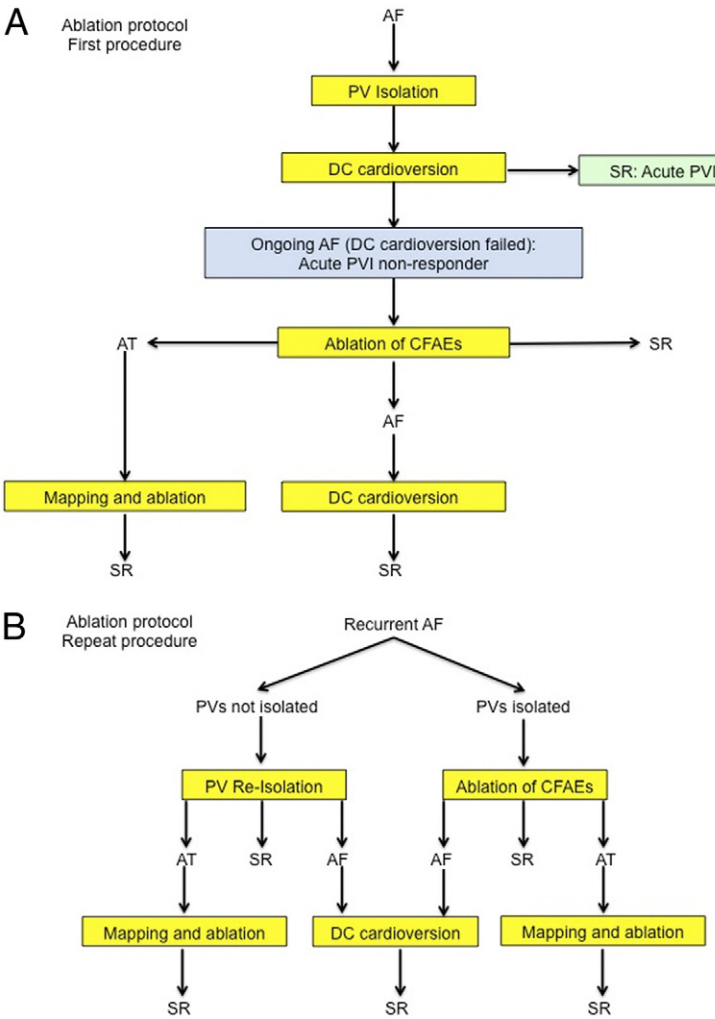

Figure 1 **Ablation Study Protocol**

Ablation study protocol at **(A)** the first ablation procedure and **(B)** the repeat ablation procedure. AF = atrial fibrillation; AT = atrial tachycardia; CFAE = complex fractionated atrial electrogram; DC = direct current; PV = pulmonary vein; PVI = pulmonary vein isolation; SR = sinus rhythm.

international normalized ratio of 2 to 3. Where the LAA was isolated, lifelong OAC therapy was recommended. In all other patients, OAC therapy was continued for at least 3 months. Thereafter, indication for anticoagulation therapy was solely based on the patient's $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score (9). Before discharge, a 24-h Holter recording and echocardiographic evaluation was performed. Discontinuation of AADs was recommended 3 months after ablation. A transthoracic echocardiogram, 12-lead electrocardiogram, and 24-h Holter recording were obtained at our outpatient clinic or by the referring physician 1, 3, and 6 months after ablation and thereafter at 6-month intervals.

Recurrence was defined as episodes of AF or AT lasting >30 s as documented by 12-lead electrocardiogram or Holter monitoring. This study did not adhere to a predefined blanking period. Clinical success was defined as freedom from recurrence during the entire follow-up period. Regression of persistent AF was defined as change from LS-AF to PAF or maintenance of SR on AAD after arrhythmia recurrence.

Statistical analysis. Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as mean ± SD or median and interquartile range as appropriate. Group mean differences were examined by the Student's *t* test for independent samples. Differences in categorical variables between groups were compared by the chi-square test of significance. Event-free survival were estimated by the method of Kaplan-Meier and compared by the log-rank test. Predictors of arrhythmia recurrence were performed using Cox proportional hazards regression models.

Downloaded From: http://content.onlinejacc.org/ on 01/20/2014

JACC Vol. 60, No. 19, 2012
November 6, 2012:1921–9

The following variables were used as exploratory variables in univariate and multiple survival prediction models: age, sex, total AF duration, persistent AF duration, amiodarone, structural heart disease, coronary artery disease, LA diameter, hypertension, left ventricular ejection fraction, $CHADS_2$ score, procedure duration, fluoroscopy duration, termination, complications, and PVI as the sole ablation strategy. Variables that were univariately associated with survival ($p < 0.2$) were considered for a multiple survival prediction model.

The multivariate prediction models for time to recurrence after the index procedure and after the final ablation procedure were performed by stepwise regression based on likelihood ratios. For each variable, hazard ratio (HR), 95% confidence interval (CI), and Wald test p values of the final model are displayed. A HR of <1 indicates a reduced likelihood of relapse for increasing values of the variable. A 2-tailed probability value of < 0.05 was deemed significant. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

Clinical outcomes after a single procedure. During a median follow-up of 56 months (range 49 to 67 months), SR was maintained in 41 of 202 (20.3%) patients (Figs. 2 and 3). Recurrent arrhythmia after the index procedure was persistent AF in 103 of 202 (51.0%) patients, PAF in 27 of 202 (13.4%) patients, and AT in 31 of 202 (15.3%) patients (Fig. 2). Regression of AF occurred in 36 of 202 (17.8%) patients (16 patients maintained SR after the reinitiation of AADs, and 20 patients regressed to PAF). Arrhythmia recurred within the first year after ablation in 13 of 202 (64.4%) patients. Thirty-one (15.3%) patients had recurrences after 12 months including 10 (5.0%) patients with recurrences >3 years after ablation.

Clinical outcomes after the last procedure. During a median follow-up of 50 months (range 36 to 61 months), 91 of 202 (45.0%) patients remained in SR, including 24 patients taking AADs (amiodarone in 2 patients). Regression of AF was noted in 47 (23.3%) patients (36 patients maintained SR after reinitiation of AADs, and 11 patients changed to PAF). Recurrent arrhythmia was persistent AF in 65 (58.6%) patients, AT in 19 (17.1%), and PAF in 27 (24.3%).

Summary of ablation procedures. Procedural details are summarized in Table 2. A total of 383 procedures were performed in 202 patients (median 2, range 1 to 5). PVI was performed in all 202 patients and was the sole ablative strategy in 105 (52.0%) patients by the final procedure.

Recovered PV conduction was found in 97 of 126 (77.0%) patients at the first, 12 of 42 (28.6%) at the second, and no (0%) patient at the third or fourth redo procedures. Three patients at the first redo procedure and 1 patient at the second redo procedure presented in SR without PV reconduction, therefore requiring AF induction before CFAE ablation.

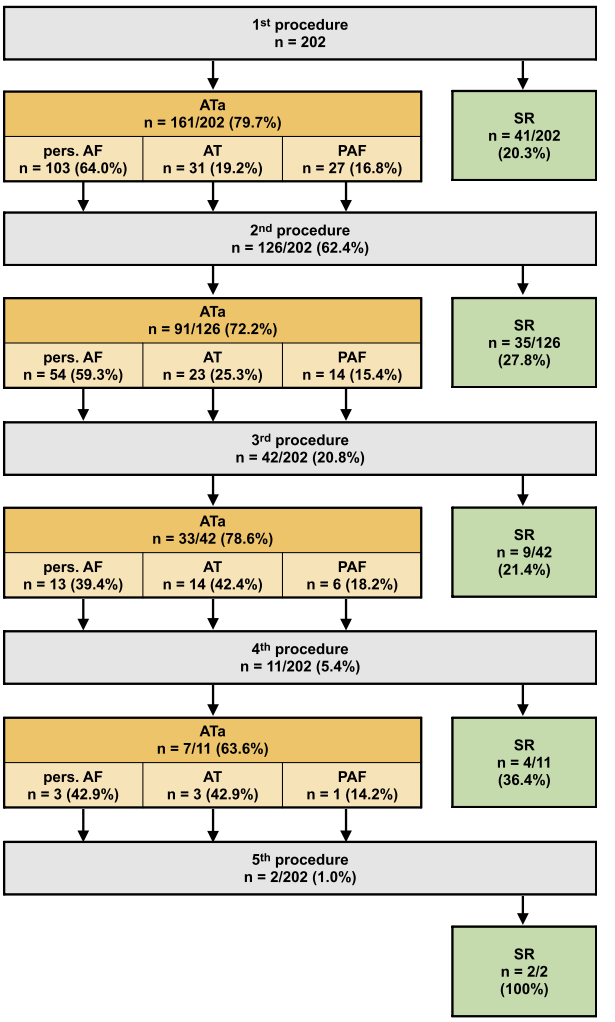

Figure 2 Flowchart Demonstrating Arrhythmia Outcome

AT = atrial tachycardia; PAF = paroxysmal atrial fibrillation; Pers. AF = persistent atrial fibrillation; SR = sinus rhythm.

Isolation of LAA occurred in 10 of 97 (10.3%) patients undergoing PVI and additional ablation (acute PVI nonresponder): this affected no patient during the first, 4 patients during the second, 3 during the third, and 3 at the fourth procedure.

The following complications occurred in 18 (4.7%) of 383 procedures: ischemic stroke (n = 2), transient ischemic attack (n = 1), femoral hematoma requiring blood transfusion (n = 11) and vascular surgery (n = 3 of 11), pneumothorax (n = 1), aspiration pneumonia (n = 1), transient pulmonary edema (n = 1), and cardiac tamponade (n = 1).

Cerebrovascular events occurred during follow-up as follows: cerebral hemorrhage (n = 1), stroke (n = 9), and transient ischemic attack (n = 4) including 3 periprocedural

Downloaded From: http://content.onlinejacc.org/ on 01/20/2014

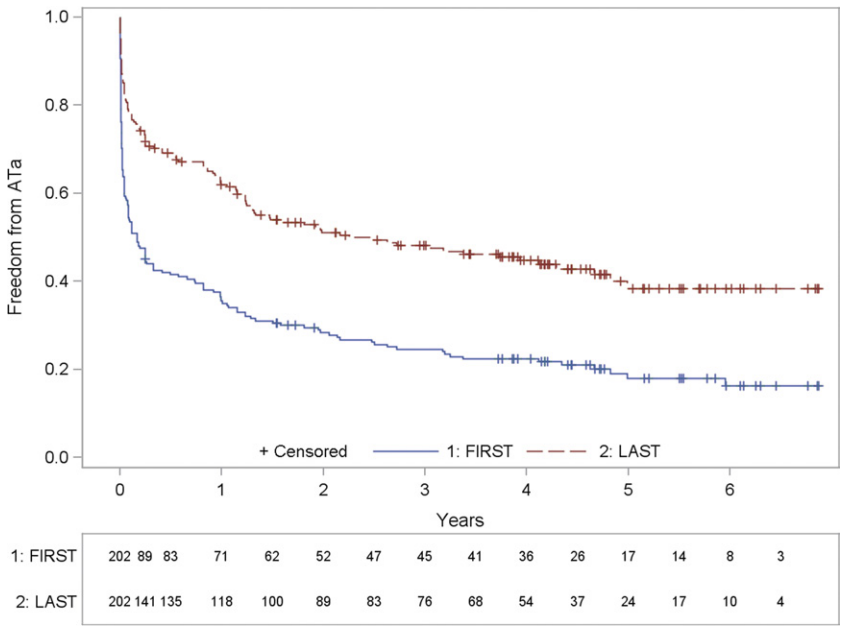

Figure 3 **Single and Multiple Procedure Outcomes**

Kaplan-Meier event-free survival curve after the first procedure **(blue line)** and after the last procedure **(red line)**. Plus sign **(+)** indicates censored. **Numbers at bottom** indicate patients at risk. ATa = atrial tachyarrhythmia.

events as stated above. Thromboembolic events occurred in 2 patients without ATa recurrence and in 1 patient with his first ATa episode after ablation. The latter 3 patients had $CHADS_2$ scores of 1, 2, and 3, respectively, and were not receiving OAC therapy at the time of the event.

Five deaths occurred during follow-up due to myocardial infarction (n = 1), leukemia (n = 1), non-Hodgkin's lymphoma (n = 1), gallbladder cancer (n = 1), and unknown cause (n = 1).

PVI as the sole ablative strategy. At the first procedure, 165 of 202 (81.7%) patients were acute PVI responders (Tables 2, 3), and therefore received PVI as the sole ablation strategy. Arrhythmia recurrence occurred in 132 of 165 (80.0%) patients. By the last procedure, PVI was the sole ablation strategy in 105 of 202 (52.0%) patients (acute PVI responder).

In the overall population, PVI alone was able to establish long-term SR in 24.3% (49 of 202) of the patients and in 46.7% (49 of 105) of acute PVI responders. Regression of AF was noted in another 27 of 105 (25.7%) acute PVI responders (SR after readministration of AADs in 21 and change to PAF in 6 patients).

The only significant difference between patients who maintained SR after PVI alone and the remaining patients was the mean duration of persistent AF (35.2 ± 22.5 months vs. 53.5 ± 48.5 months; p = 0.045).

Acute PVI responders at the first procedure had a significantly lower risk for arrhythmia recurrence (HR: 0.54 [95% CI: 0.39 to 0.74]; p < 0.001) than acute PVI nonresponders. Patients undergoing PVI plus additional ablation had a nonsignificantly higher risk for procedural complications compared to patients undergoing PVI

Table 2 **Summary of Ablation Procedures**

		PVI and Additional Ablation		
Procedure	**PVI Only Until This Procedure**	**CFAE**	**LA Line**	**SVC/AES**
First procedure (n = 202)	**165** (165)	**29** (29)	**12** (12)	**7** (7)
Second procedure (n = 126)	**0** (60)	**15** (21)	**24** (26)	**13** (0)
Third procedure (n = 42)	**0** (5)	**15** (20)	**21** (26)	**1** (0)
Fourth procedure (n = 11)	**0** (0)	**1** (2)	**3** (6)	**0** (0)
Fifth procedure (n = 2)	**0** (0)	**0** (0)	**0** (2)	**0** (0)
Ablation summary (last procedure)	**105**	**60**	**60**	**21**

Bold values indicate patients in whom this ablation strategy was performed for the first time. Values in parentheses indicate patients in whom this ablation strategy was performed either for the first time or in whom it was repeated.

AES = atrial extrasystoles; CFAE = complex fractionated atrial electrogram; LA = left atrial; PVI = pulmonary vein isolation; SVC = superior caval vein.

Downloaded From: http://content.onlinejacc.org/ on 01/20/2014

JACC Vol. 60, No. 19, 2012
November 6, 2012:1921–9

Table 3 Clinical, Ablation, and Outcome Characteristics Between Acute PVI Responder and Acute PVI Nonresponder by the Final Procedure

Parameter	Acute PVI Responder (n = 105)	Acute PVI Nonresponder (n = 97)	p Value
Age, yrs	61 ± 9	62 ± 9	0.103
Male	83 (79)	77 (79)	0.953
Total AF duration, months	95 ± 56	105 ± 72	0.260
Total AF duration <2 yrs	8 (8)	9 (9)	0.671
Persistent AF duration, months	44 ± 33	55 ± 53	0.077
Amiodarone	55 (52)	60 (62)	0.174
Structural heart disease	17 (16)	15 (15)	0.888
LA diameter, mm	48 ± 5	50 ± 6	0.023
Hypertension	80 (76)	75 (77)	0.850
LVEF, %	60 ± 6	60 ± 7	0.834
CHADS2 score	1 ± 1	1 ± 1	0.572
Number of procedures	1.5 ± 0.6	2.4 ± 2.2	<0.001
Procedure duration, min	223 ± 66	238 ± 64	0.107
Fluoroscopy duration, min	30 ± 14	31 ± 11	0.380
Complications	7 (7)	11 (11)	0.244
LAA isolation	0 (0)	10 (10)	0.001
Sinus rhythm	49 (47)	42 (43)	0.631

Values are mean ± SD or n (%).

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack; LAA = left atrial appendage; other abbreviations as in Tables 1 and 2.

alone (6.7% vs. 11.3%; p = 0.244). Additionally, a 10% incidence of LAA isolation was noted in the latter group.

Predictors of arrhythmia recurrence. After a single procedure, univariate predictors of recurrence were persistent AF duration, total AF duration, and PVI as the sole ablative strategy. For each additional year of persistent AF, the risk of arrhythmia recurrence increased by 10.0% (HR: 1.10 [95% CI: 1.05 to 1.14]; p < 0.001). For each additional year of total AF duration, the risk for arrhythmia recurrence increased by 4.9% (HR: 1.05 [95% CI: 1.01 to 1.07]; p = 0.002). PVI performed alone was associated with a significantly reduced risk of relapse. In multivariate analyses, persistent AF duration (HR: 1.09 [95% CI: 1.04 to 1.13]; p < 0.001) and PVI as the sole ablative strategy (HR: 0.57 [95% CI: 0.41 to 0.78]; p < 0.001) independently predicted arrhythmia recurrences.

Univariate predictors of arrhythmia recurrence after the last ablation procedure were persistent AF duration (HR: 1.07 [95% CI: 1.04 to 1.13]; p < 0.001) and total AF duration (HR: 1.06 [95% CI: 1.02 to 1.09]; p < 0.001). In multivariate analyses, only total AF duration (HR: 1.06 [95% CI: 1.02 to 1.09]; p < 0.001) predicted arrhythmia recurrence. Interestingly, when considering overall procedures, PVI alone was no longer a significant parameter of maintenance of long-term SR.

Patients with a total AF duration of <2 years had a significantly higher success rate compared to other patients (76.5% vs. 42.2% in SR, p = 0.033) (Fig. 4). Patients with a total AF duration of >2 years were almost 3 times more likely to relapse after the last ablation (HR: 2.81 [95% CI: 1.04 to 7.63]; p = 0.042).

Discussion

In this study, we found that: 1) circumferential PVI alone was sufficient to restore SR in 24% of patients with LS-AF; 2) 5-year outcomes of LS-AF ablation remain mediocre with a 45% multiple-procedure success rate; 3) AF regression is a common phenomenon found in 23% of patients; and 4) persistent AF duration independently predicted arrhythmia recurrences whereas acute PVI responders had a reduced risk of relapse after the first ablation.

Pulmonary vein isolation in LS-AF. PVI is an effective therapy for PAF patients, with success rates ranging from 57% to 80% at up to 5 years of follow-up (13–16). For patients with LS-AF, there is conflicting evidence about the long-term efficacy of PVI as the first-line ablative strategy (17,18). In this study, using the sequential approach, PVI was the first-line therapy for all patients. Additional ablative strategies, for example, CFAEs, were only applied in PVI nonresponders—if DC cardioversion failed after PVI or at repeat ablation procedures when patients demonstrated no PV reconnection.

In patients with LS-AF, observed >5 years after ablation, PVI alone was sufficient to restore and maintain SR in 24% of patients. Regression of AF was noted in another 13% of those patients, resulting in clinical improvement. This finding suggests that the PVs and the antrum are important substrates in patients with LS-AF. Interestingly, after the first procedure, PVI alone was associated with a 46% relative risk reduction in arrhythmia recurrence compared to acute PVI nonresponders. Thus, successful DC cardioversion after PVI may identify patients who have a less diseased LA.

For the majority of patients, repeat ablation and additional ablation strategies are required to maintain SR in 45% of patients. Interestingly, success rates were similar between patients undergoing PVI alone and PVI nonresponder undergoing additional ablation strategies.

Procedural success was 37.6% after 1 or 2 procedures as compared to 45% after as many as 5 procedures. More than 2 procedures were performed in 42 of 202 (22.3%) patients. Although the patient number is not large enough to draw a definite conclusion, these data indicate that the success rate beyond the second procedure is reasonable. Importantly, in patients undergoing >1 redo procedure, ablation strategies in addition to PVI are required in the majority of patients, and the incidence of ATs as the clinical arrhythmia increases. The ATs are usually clinically worse tolerated but more amenable to ablation than AF. The relatively high incidence of redo procedures of LA linear lesions in this study indicates the difficulty of obtaining durable complete lines.

Complication rates in this study were in keeping with previous publications (9). In PVI nonresponders, more extensive ablation and more procedures were required. That

Downloaded From: http://content.onlinejacc.org/ on 01/20/2014

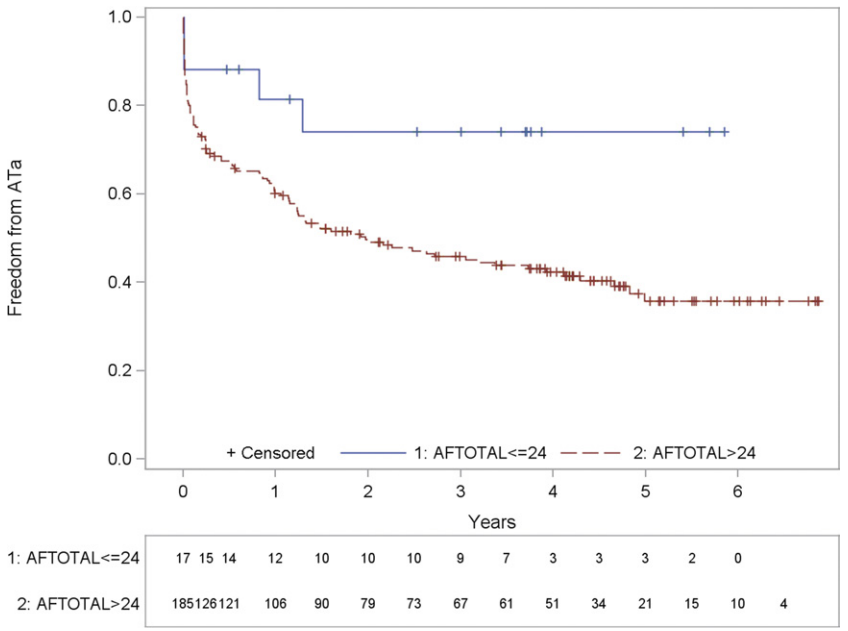

Figure 4 **Multiple Procedure Success for Patients With Total AF Duration <2 Years Versus ≥2 Years**

Kaplan-Meier event-free survival curves for patients with total atrial fibrillation (AF) duration of <2 years **(blue line)** versus ≥2 years **(red line)** after the last procedure. Plus sign **(+)** indicates censored. Arrhythmia-free survival was significantly higher among patients with AF duration <2 years (77% vs. 42% in sinus rhythm, p = 0.033). ATa = atrial tachyarrhythmia.

may have resulted in an increased complication rate per patient, although it did not reach statistical significance.

Comparison with previous studies. Our study evaluated a sequential approach to AF ablation while reserving additional ablative strategies for PVI nonresponders. That makes this study unique and comparison with other studies difficult. In all other studies, either PVI or additional ablative strategies were performed, and DC cardioversion after PVI was not attempted.

A recently published systematic review of the literature evaluated the impact of ablation strategies on the outcomes of LS-AF ablation (17). A total of 32 studies, including 4 randomized controlled trials, were analyzed. The meta-analysis found that with respect to single-procedure and drug-free success: 1) PVI is a superior approach compared to PV ablation alone; 2) CFAE ablation alone is an inferior strategy compared to PV ablation plus linear ablation at the roof and mitral isthmus; and 3) CFAE ablation may or may not provide incremental benefit when added to PVI (17). The researchers concluded that, because of variation in success within and between techniques, the optimal ablation technique for LS-AF remains unclear.

A recent meta-analysis evaluated the efficacy of PVI versus PVI plus CFAE ablation after a single procedure without AADs (18); a total of 660 patients enrolled in 7 controlled trials were analyzed. The investigators found that CFAE ablation in addition to PVI increases the rate of SR maintenance in nonparoxysmal AF after a single procedure (relative risk: 1.35 [95% CI: 1.04 to 1.75]; p = 0.022), but does not provide additional clinical benefit in PAF patients. However, direct comparison of studies evaluating LS-AF ablation is difficult, not only because of the different ablative approaches but also because of heterogeneous patient populations. For example, in several studies, patients with a continuous AF duration of <12 months were included and terms like "nonparoxysmal AF" or "chronic AF" used (17).

Despite the relatively conservative ablation strategy used in this study, the single-procedure outcomes concur with prior reports utilizing a more aggressive ablation protocol (19), and at first procedure, PVI as the sole ablative strategy was associated with a lower risk for arrhythmia recurrence. Termination of AF at the first procedure as well as at the last procedure did not influence outcomes. In this study, AF termination was only attempted in acute PVI nonresponders; these patients may, therefore, represent a subgroup of patients with a more diseased LA, and thus explain why, in contrast to other studies, AF termination did not influence outcomes.

A recent study demonstrated that the LAA can be trigger site of AF, and that LAA isolation may improve clinical outcomes (20). However, the clinical impact and long-term thromboembolic risk after LAA isolation is uncertain, and it is important to balance the risks and benefits of additional ablation as they may increase the incidence of potential complications and adverse events such as LAA isolation and the occurrence of iatrogenic AT (2,19,21).

Downloaded From: http://content.onlinejacc.org/ on 01/20/2014

Finally, PV reconduction is found in approximately 75% of patients after the initial procedure (22). Since the PVs are an important trigger and substrate in some patients with LS-AF, achieving durable lesions may improve outcomes. As long as durable isolation of the PVs cannot be established with a single procedure, the final conclusion about the value of PVI will remain uncertain.

There is still conflicting evidence about the efficacy of additional ablation strategies used with PVI in patients with LS-AF. CFAE ablation may improve outcomes but also increases the risk of adverse events. To avoid overtreatment of as many as a quarter of patients who can be successfully treated with PVI only, we believe that PVI as the first-line treatment is a reasonable approach, with further ablation reserved for PVI nonresponder.

Time to arrhythmia recurrence. In the majority of patients arrhythmias recurred within the first year; however, late recurrences (>12 months) were noted in 15.3% of patients. These results raise the question as to whether cure for a heterogeneous and complex condition such as LS-AF is feasible, or whether AF recurrence is only a matter of time.

Three patients in whom OAC therapy was discontinued because of apparently stable SR sustained thromboembolic events. Although there is some evidence that OAC therapy may be discontinued after AF ablation in patients at moderate thromboembolic risk, data are sparse and nonrandomized (23). Therefore, the indication for lifelong anticoagulation therapy after ablation should be exclusively based upon the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke/transient ischemic attack/thromboembolism, vascular disease, age 65 to 74, sex category female).

Study limitations. Because of AF regression and symptom improvement in a significant number of patients, some patients with recurrence did not undergo repeat ablation. A higher rate of reablation may have resulted in improved outcomes. Follow-up assessment of AF recurrence consisted of 24-h Holter monitoring. As implantable loop recorders or 7-day Holter monitoring were not used before ablation, the longest continuous AF duration may have been overestimated, particularly in patients in whom infrequent Holter monitoring was performed. The overall success may, therefore, have been overestimated. This study is descriptive and nonrandomized; its results require confirmation in larger randomized controlled trials. During this study, AF procedures were restricted to patients with a body mass index <35 kg/m^2. Unfortunately, therefore, we were unable to evaluate the clinical impact of body mass index.

Conclusions

In patients with LS-AF, single procedure success is poor during 5-year follow-up. Repeat ablation and additional ablation strategies are often required to maintain SR in 45%. For patients with a total AF duration of <2 years, the outcome appears to be favorable.

Reprint requests and correspondence: Dr. Roland Tilz, Department of Cardiology, Asklepios Klinik St. Georg, Lohmuehlenstr 5, Hamburg 20099, Germany. E-mail: tilz6@hotmail.com.

REFERENCES

1. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace 2012;14:528–606.
2. Elayi CS, Verma A, Di Biase L, et al. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. Heart Rhythm 2008;5:1658–64.
3. Cheema A, Dong J, Dalal D, et al. Circumferential ablation with pulmonary vein isolation in permanent atrial fibrillation. Am J Cardiol 2007;99:1425–8.
4. Oral H, Chugh A, Yoshida K, et al. A Randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. J Am Coll Cardiol 2009;53:782–9.
5. Tilz RR, Chun KR, Schmidt B, et al. Catheter ablation of long-standing persistent atrial fibrillation: a lesson from circumferential pulmonary vein isolation. J Cardiovasc Electrophysiol 2010; 21:1085–93.
6. Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004;43:2044–53.
7. Oral H, Chugh A, Lemola K, et al. Noninducibility of atrial fibrillation as an end point of left atrial circumferential ablation for paroxysmal atrial fibrillation: a randomized study. Circulation 2004; 110:2797–801.
8. O'Neill MD, Wright M, Knecht S, et al. Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. Eur Heart J 2009;30:1105–12.
9. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–429.
10. Ouyang F, Antz M, Ernst S, et al. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. Circulation 2005;111:127–35.
11. Ouyang F, Bansch D, Ernst S, et al. Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. Circulation 2004;110: 2090–6.
12. Jais P, Hocini M, Hsu LF, et al. Technique and results of linear ablation at the mitral isthmus. Circulation 2004;110:2996–3002.
13. Medi C, Sparks PB, Morton JB, et al. Pulmonary vein antral isolation for paroxysmal atrial fibrillation: results from long-term follow-up. J Cardiovasc Electrophysiol 2010;22:137–41.
14. Ouyang F, Tilz R, Chun J, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation 2010;122:2368–77.
15. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol 2011;57:160–6.
16. Tzou WS, Marchlinski FE, Zado ES, et al. Long-term outcome after successful catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:237–42.
17. Brooks AG, Stiles MK, Laborderie J, et al. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart Rhythm 2010;7:835–46.
18. Li WJ, Bai YY, Zhang HY, et al. Additional ablation of complex fractionated atrial electrograms after pulmonary vein isolation in patients with atrial fibrillation: a meta-analysis. Circ Arrhythm Electrophysiol 2011;4:143–8.

Downloaded From: http://content.onlinejacc.org/ on 01/20/2014

19. Rostock T, Salukhe TV, Steven D, et al. Long-term single- and multiple-procedure outcome and predictors of success after catheter ablation for persistent atrial fibrillation. Heart Rhythm 2011;8:1391–7.
20. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. Circulation 2010;122:109–18.
21. Haissaguerre M, Sanders P, Hocini M, et al. Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. J Cardiovasc Electrophysiol 2005;16:1125–37.
22. Willems S, Steven D, Servatius H, et al. Persistence of pulmonary vein isolation after robotic remote-navigated ablation for atrial fibrillation and its relation to clinical outcome. J Cardiovasc Electrophysiol 2010;21:1079–84.
23. Themistoclakis S, Corrado A, Marchlinski FE, et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J Am Coll Cardiol 2010;55:735–43.

Key Words: catheter ablation ■ long-standing persistent atrial fibrillation ■ long-term outcome.

Downloaded From: http://content.onlinejacc.org/ on 01/20/2014