JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 24, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.09.088

Pulmonary Vein Isolation Versus Defragmentation

The CHASE-AF Clinical Trial

Julia Vogler, MD,* Stephan Willems, MD,* Arian Sultan, MD,† Doreen Schreiber, MD,‡ Jakob Lüker, MD,† Helge Servatius, MD,§ Benjamin Schäffer, MD,* Julia Moser, MD,* Boris A. Hoffmann, MD,* Daniel Steven, MD†

ABSTRACT

BACKGROUND Long-term success rates using ablation for persistent atrial fibrillation (AF) are disappointing and usually do not exceed 60%.

OBJECTIVES This study sought to compare arrhythmia-free survival between pulmonary vein isolation (PVI) and a stepwise approach (full defrag) consisting of PVI, ablation of complex fractionated electrograms, and additional linear ablation lines in the setting of atrial tachycardias (AT) in patients with persistent AF after PVI.

METHODS From November 2010 to February 2013, 205 patients (151 men; 61.7 ± 10.2 years of age) underwent de novo ablation for persistent AF. Subsequently, patients were prospectively randomized to either PVI alone (n = 78) or full defrag (n = 75), with 52 patients not randomized due to AF termination with the original PVI. The primary endpoint was recurrence of any AT after a blanking period of 3 months.

RESULTS During the entire study, 241 ablations were performed (mean: 1.59 in the PVI-alone group, 1.55 in the full-defrag group). With the stepwise approach, termination of AF occurred in 45 (60%) patients. However, arrhythmia-free survival did not differ whether patients underwent single or multiple procedures (p = 0.468). Procedure duration, fluoroscopy time, and radiofrequency duration were significantly longer in the full-defrag group (all p < 0.001).

CONCLUSIONS A stepwise approach aimed at AF termination does not seem to provide additional benefit over PVI alone in patients with persistent AF, but it is associated with significantly longer procedural and fluoroscopic duration as well as radiofrequency application time. (The Randomized Catheter Ablation of Persist End Atrial Fibrillation Study [CHASE-AF]; NCT01580124) (J Am Coll Cardiol 2015;66:2743–52)

A well-established therapy for paroxysmal atrial fibrillation (PAF), pulmonary vein isolation (PVI), is associated with encouraging long-term results and has proven to be superior to antiarrhythmic therapy for long-term rhythm stability (1–3). However, PVI alone appears to be insufficient for treating persistent AF (persAF), with disappointing long-term results (4–10). Therefore, additional ablation strategies targeting the modification and elimination of the AF-sustaining atrial substrate have been developed, including ablation of complex fractionated atrial electrograms (CFAEs) (6,11) in both atria and the coronary sinus (CS), isolation of the left atrial appendage (LAA), and

From the *Department of Electrophysiology, University Heart Center Hamburg, University Hospital Eppendorf, Hamburg, Germany; †Department of Electrophysiology, University Heart Center Cologne, University Hospital Cologne, Cologne, Germany; ‡Department of Electrophysiology, Clinic Hirslanden-Heart Center, Zurich, Switzerland; and the §Department of Cardiology Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland. The study was funded with 154,000 € by St. Jude Medical GmbH, Eschborn, Germany. St. Jude Medical is not responsible for any specific role within the trial. The University Heart Center Hamburg and Dr. Willems were completely in charge of the design and implementation of the trial, collection, management, analysis, and interpretation of the data, as well as preparation of the manuscript. Dr. Willems is a member of the speakers bureau for St. Jude Medical, Biosense Webster, Boston Scientific, Boehringer Ingelheim, and Bayer Vital; and has received research grants from St. Jude Medical, Biosense Webster, Boehringer Ingelheim, and Bayer Vital. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 29, 2015; revised manuscript received September 7, 2015, accepted September 24, 2015.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drugs
AF = atrial fibrillation
AT = atrial tachycardia
CFAE = complex fractionated atrial electrograms
CS = coronary sinus
DC = direct current
ECG = electrocardiogram
LA = left atrium
LAA = left atrial appendage
PAF = paroxysmal atrial fibrillation
persAF = persistent atrial fibrillation
PVI = pulmonary vein isolation
RA = right atrium

deployment of linear lesions in the left atrium (LA) (12–14). Despite these strategies, arrhythmia recurrence is common in patients with persAF, often leading to repeat ablation.

The CHASE-AF (Catheter Ablation of Persistend Atrial Fibrillation) study was designed to compare a strategy for AF termination using a stepwise approach consisting of PVI followed by biatrial ablation of CFAEs and linear ablation lines in the case of atrial tachycardias (AT) versus PVI alone in patients with persAF in whom AF does not terminate with a single PVI.

METHODS

We enrolled 205 patients (61.7 ± 10.2 years) with persAF at the University Heart Center Hamburg, Hamburg, Germany. PersAF was defined as an episode lasting >7 days (documented on an electrocardiogram [ECG]) or a history of electrical cardioversion (regardless of the time in AF before cardioversion, but with a history consistent with persAF). Exclusion criteria were age <18 or >80 years, previous operative or interventional treatment of AF, PAF, pregnancy, contraindication for oral anticoagulation or heparin administration, transient factors causing AF, drug and/or alcohol abuse, and severe underlying heart disease with LA enlargement of >60 mm. The study was approved by the local institutional review board and ethics committee, and funded by St. Jude Medical, Inc. (St. Paul, Minnesota). All patients provided written informed consent.

SEE PAGE 2753

STUDY DESIGN. Following PVI, patients were randomized 1:1 to PVI alone or a stepwise ablation approach (full-defrag group). To rule out patients with PV-dependent AF, patients whose AF was terminated with PVI were excluded before randomization. The index procedure in the PVI-alone group consisted of a circumferential PVI, including optional right atrial (RA) isthmus ablation followed by direct current (DC) cardioversion. Entrance block evaluated by a circumferential mapping catheter during sinus rhythm at the procedure's end defined the endpoint. Patients in the full-defrag group received additional CFAE ablation in both atria, the CS, and linear ablation in the setting of AT as previously described (**Figure 1**) (15–18). We checked all linear ablation lines for bidirectional block after attaining sinus rhythm. If AF termination was not achieved, the procedure was stopped after a maximum of 6 h or if a maximum of 5 l of fluid had been administered to the patient (17). DC cardioversion was performed. Intraprocedural antiarrhythmic drugs (AADs) were used at the operator's discretion. Previous AAD treatment was continued for a maximum of 6 months after the index procedure, but de novo AADs were not allowed.

The primary endpoint was recurrence of any documented atrial arrhythmia that lasted >30 s between 3 and 12 months after the first procedure (including a blanking period of 3 months). Secondary outcomes included procedure and fluoroscopy duration, radiofrequency (RF) application time, number of procedures, incidence of peri-procedural complications, antiarrhythmic therapy, and achieving the primary endpoint after a single ablation.

Transesophageal echocardiography was performed in all patients to rule out LA thrombus. Oral anticoagulation was stopped at least 3 days before ablation and replaced by low-molecular-weight heparin. The electrophysiological study was performed under deep sedation. The catheter setting consisted of a steerable 6-F 10-polar CS catheter, a circumferential 7-F 10-polar mapping catheter for PV mapping, one 4-polar catheter for mapping of the RA, and a 7-F externally irrigated catheter for mapping and ablation. All catheters were introduced via femoral access. A single trans-septal puncture was performed for the mapping and ablation catheters placed into the LA. Intravenous heparin was administered after the trans-septal puncture, targeting an activated clotting time between 250 and 300 s (ACT controls every 30 min). Trans-septal sheaths were continuously flushed with heparinized saline. In all patients, the 3-dimensional mapping system (EnSite NavX, St. Jude Medical) provided electroanatomical reconstruction of the LA. RF current was applied with a maximum power of 30 W, using an irrigation rate of 10 to 30 ml/min for the PVs, 35 W, and an irrigation rate between 30 and 60 ml/min in the LA, and up to 30 W in the RA. RF power was limited to 25 W for ablation within the CS, with the irrigation rate manually adjusted to keep the tip temperature below 42°C.

We saw all patients every 3 months in our outpatient clinic. Follow-up visits included a detailed history, ECG, 24-h Holter recording at least every 3 months, and 72-h Holter monitoring at the 12-month follow-up visit. In the event of arrhythmia recurrence, patients underwent a repeat procedure between 3 and 6 months after the first procedure. To avoid crossover between the 2 groups, the approach for the repeat procedure was the same as the index procedure. In case of a complete entrance block or insignificant slow passive conduction of 1 PV (cycle length in the PV is longer than in the RA, LAA, and CS), patients initially randomized to the PVI-alone

group underwent substrate modification as in the other group.

STATISTICAL ANALYSIS. Assuming an absolute risk reduction of 30% for the stepwise approach compared with PVI in the primary outcome, the estimated sample size per group was 65 patients to provide 95% power with an alpha error of 5%. To account for a potential dropout rate of 10%, 160 patients were planned for inclusion. Baseline patient characteristics, procedure-related data, and arrhythmia-free survival were compared using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher exact test (if the expected frequencies were low) for categorical variables. Continuous variables are expressed as mean ± SD for normal distribution or as median and interquartile ranges in the case of other distribution. Categorical variables are summarized as counts and percentages. Event-free survival was displayed with Kaplan-Meier curves and compared by the log-rank test. Throughout all calculations, a 2-tailed p value of 0.05 was considered statistically significant. Alpha adjustment for multiple testing was not applied; therefore, results are of an exploratory and descriptive character. An independent statistician performed all analyses using SPSS version 22 (IBM Corporation, Armonk, New York).

RESULTS

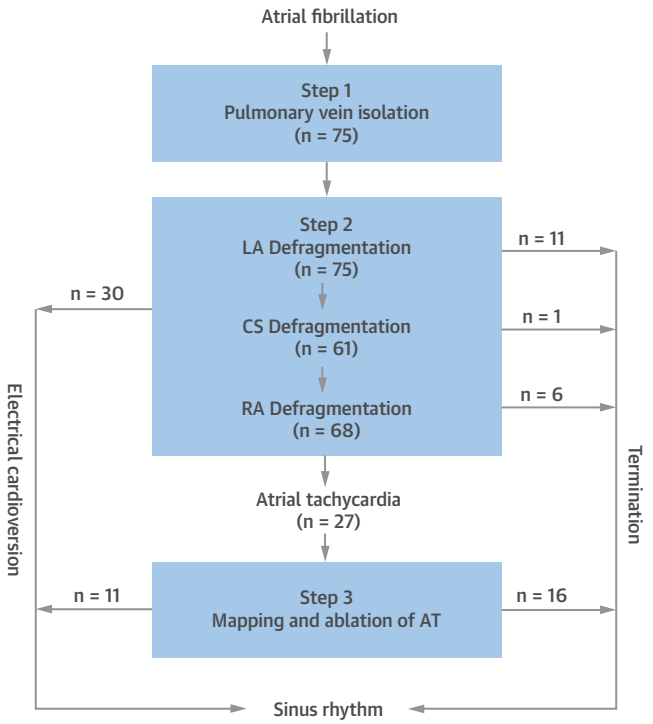
From November 2010 to February 2013, 205 patients with persAF (mean age: 61.7 ± 10.2 years; 151 men) were enrolled and assigned to PVI alone (n = 78), full defrag (n = 75), or not randomized (n = 52) due to termination of AF with PVI (Figure 2). There were no differences in baseline characteristics except for the longest episode of continuous AF, which was longer in the PVI-alone group (Table 1). An equal number of patients in the PVI and defrag groups were on antiarrhythmic therapy before ablation (Table 1).

A total of 142 patients were eligible for rhythm outcome analysis; 11 patients (7 in the PVI-alone group, 4 in the full defrag group) were lost to or had incomplete follow-up. In the PVI-alone group, 10 patients were treated with a stepwise approach during the repeat procedure (second or third ablation) due to isolated PVs and excluded from rhythm outcome analysis to avoid bias by crossover. No patient died during follow-up.

All patients were in spontaneous AF at the beginning of the procedure. Baseline AF cycle length did not differ (Table 2). In the PVI-alone group, sinus rhythm was achieved by DC cardioversion. In the full-defrag group, mean AF cycle length progressively increased during CFAE ablation (Figure 3). AF termination was achieved in 45 (60%) patients: 18 patients converted to sinus rhythm during ablation of CFAE in the LA, RA, or CS. In 27 patients, AF was converted to AT; 11 of these patients required cardioversion because AT could not be terminated by ablation. Failure to terminate was mainly due to unstable AT combined with prolonged procedure duration, high volume load, and barely mappable electrograms after extensive ablation. AF was not terminated in the remaining 30 patients. Procedure duration, fluoroscopy time, and RF duration were longer in the full-defrag group, and patients had a higher fluid intake (Table 2).

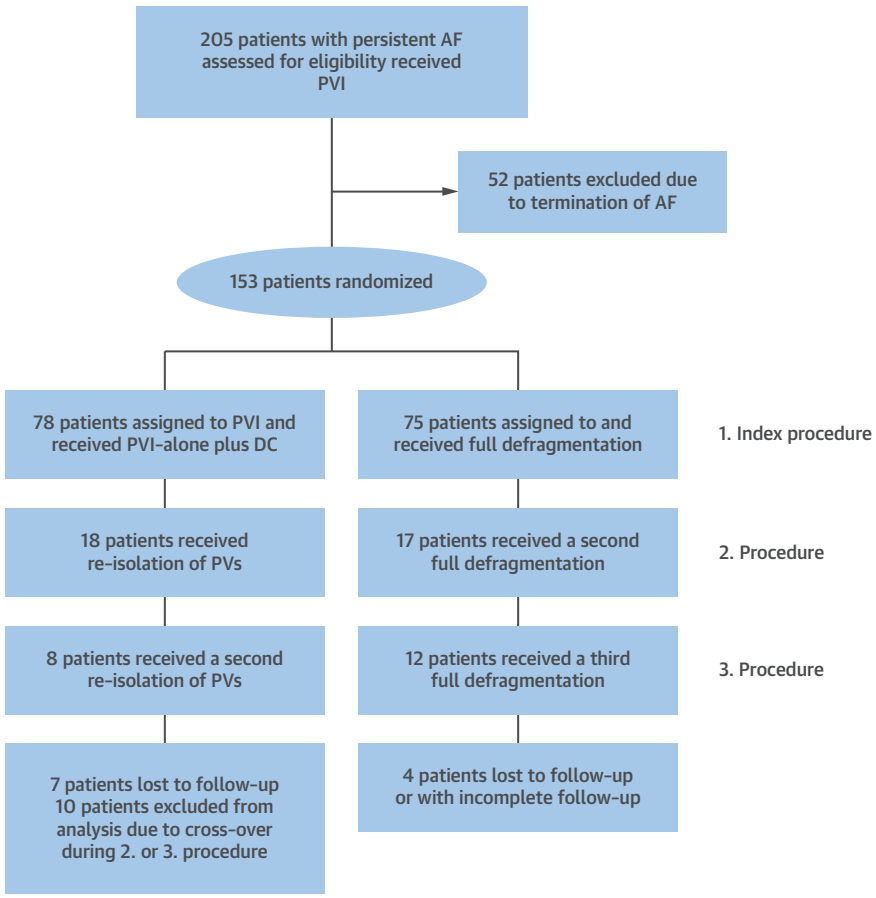
In the full-defrag group, 22 patients underwent linear ablation: mitral isthmus line in 6 patients; mitral isthmus line plus ablation at the cavotricuspid isthmus in 2 patients; mitral isthmus line plus LA roof line in 2 patients; anterior line in 1 patient; anterior line plus linear ablation at the cavotricuspid isthmus in 1 patient; LA roof line and linear ablation at the cavotricuspid isthmus in 1 patient; and ablation at the cavotricuspid isthmus in 8 patients. Bidirectional block was achieved in 20 of these 22 patients. The remaining 2 patients showed an incomplete block at the mitral isthmus line.

FIGURE 1 Stepwise Ablation Approach



The subsequent ablation steps used with the stepwise approach. AT = atrial tachycardia; CS = coronary sinus; LA = left atrium; RA = right atrium.

FIGURE 2 Study Flowchart



Patients with persistent atrial fibrillation (AF) that did not terminate after initial pulmonary vein isolation (PVI) were randomized to subsequent PVI or full defragmentation (full defrag). DC = direct current cardioversion; PV = pulmonary vein.

RHYTHM OUTCOME. During the entire study, 241 ablations were performed in 153 patients (mean: 1.59 in the PVI-alone group, 1.55 in the full-defrag group). Single ablation was performed in 88 patients, 2 ablations in 41 patients, and 3 ablations in 24 patients. (As discussed earlier, 10 patients in the PVI group required the stepwise approach.) After single (**Figure 4**) and multiple procedures (**Central Illustration**), arrhythmia-free survival (on drug therapy) did not differ between the 2 groups: by per-protocol analysis, sinus rhythm was maintained in 39 of 61 (63.9%) patients in the PVI-alone group versus 41 of 71 (57.7%) patients in the full-defrag group ($p = 0.468$). By intention-to-treat analysis, arrhythmia-free survival was also similar (61.4% in the PVI group vs. 58.3% in the full-defrag group; $p = 0.707$). The drug-free overall 1-year multiple procedure success rate was 51.4% in the PVI-alone group compared with 50.0% in the full-defrag group ($p = 0.865$). PAF recurred in 4 (6.6%) patients in the PVI-alone group and in 8 (11.3%) patients in the full-defrag group; for persAF, the corresponding numbers were 18 (29.5%) and 19 (26.8%) patients ($p = 0.635$), respectively. No difference was seen in the rate of ATs: 5 (8.2%) patients in the PVI-alone group, and 6 (8.5%) in the full-defrag group ($p > 0.999$). Termination of AF during the first procedure was not associated with better arrhythmia-free survival; 13 patients (21.3%) in the PVI group and 20 patients (28.2%) in the full-defrag group were still or once again on antiarrhythmic medication at the last follow-up visit ($p = 0.364$).

A subanalysis that evaluated the arrhythmia-free survival after 12 months according to the number of ablations within the follow-up period was consistent with the results of the overall study population (**Table 3**). There was no difference between the 2 treatment groups, and there was no trend toward a difference for either group. With few patients who

underwent 2 or 3 ablations, statistical analysis was limited. Arrhythmia-free survival (on drugs) in patients who required single ablation was higher than expected in patients with persAF, but was not superior with the stepwise approach (75% vs. 73.8%; p = 0.904) (Table 3). Baseline characteristics were similar in both treatment groups.

Amiodarone was the AAD most commonly used in both groups, followed by flecainide. Twenty-nine (19.9%) patients were started on AADs within the first 3 months due to symptomatic AF. After 12-month follow-up, 104 (73.2%) patients were off AADs, whereas 38 (26.8%) patients were still or once again on antiarrhythmic medication.

ADVERSE EVENTS. Major procedure-related complications (patient-related, pericarditis excluded) did not differ significantly between the 2 groups (PVI 5.1% vs. full defrag 13.3%; p = 0.078). In the full-defrag group, 1 patient had a procedure-related stroke with minimal residual neurological impairment and 1 patient developed cardiac tamponade. The incidence of pericardial effusion with symptoms of pericarditis was higher in the full-defrag group (5.3% vs. 23.3%; p = 0.002; odds ratio: 5.46, 95% confidence interval: 1.74 to 17.15). No difference was seen in the rate of vascular access complications between the 2 groups. The relatively high overall incidence of procedure-related complications was mainly due to vascular complications.

TABLE 1 Baseline Characteristics

	PVI (n = 78)	Full Defragmentation (n = 75)	p Value
Patient demographics			
Age, yrs	63.0 ± 9.6	61.1 ± 10.9	0.43
Male	56 (71.8)	60 (80.0)	0.24
Body mass index, kg/m^2	27.2 ± 4.7	27.5 ± 3.2	0.78
Baseline dates concerning AF			
History of AF, months	52.1 ± 47.7	64.4 ± 61.2	0.56
Longest episode of AF, days	324.0 ± 435.8 184.3 (121.7–365.2)	167.0 ± 130.9 152.2 (64.93–235.9)	0.03
CHA_2DS_2-VASc score	2.1 ± 1.3	1.7 ± 1.3	0.10
Medical history			
Coronary artery disease	21 (26.9)	12 (16.0)	0.10
Valvular heart disease	5 (6.4)	2 (2.7)	0.44
Arterial hypertension	65 (83.3)	57 (76.0)	0.26
Dyslipidemia	39 (50.0)	26 (34.7)	0.06
Baseline echocardiographic measurements			
LVEF, %	60.0 ± 7.1	59.8 ± 7.1	0.99
LA diameter, mm	44.5 ± 6.6	43.7 ± 5.2	0.30
Antiarrhythmic therapy before ablation	35 (46.1)	35 (46.7)	0.94
Amiodarone	20 (26.3)	17 (22.7)	
Flecainide/propafenone	9 (11.6)/1 (1.0)	9 (12)/0 (0.0)	
Dronedarone	4 (5.3)	8 (10.7)	

Values are mean ± SD, n (%), or median (interquartile range).

AF = atrial fibrillation; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65-74 years, sex; LA = left atrium; LVEF = left ventricular ejection fraction; PVI = pulmonary vein isolation.

DISCUSSION

Our study showed that: 1) sole PVI was comparable to a stepwise approach aimed at terminating persAF after a 12-month follow-up (Central Illustration); 2) arrhythmia-free survival was higher than anticipated in both treatment groups for those patients who required single ablation; and 3) a stepwise approach was associated with a longer procedure duration, fluoroscopy time, and RF duration, but did not result in a higher rate of major complications.

This is one of the first studies to directly compare PVI and a stepwise approach in patients with persAF in whom AF did not terminate after PVI. Based on previous studies of patients with persAF (10,16,19–21) and our own experiences with such patients (15), which showed improved success rates with a stepwise approach, we hypothesized that the stepwise approach would produce a benefit.

Why did the stepwise approach fail in this regard? Most patients in previous studies had chronic persAF. The definition of chronic AF, however, has not been uniform, ranging from a minimum of 1 month (10,16) up to >12 months (the official definition for long-standing persAF by the European Heart Rhythm Association). This entity of AF seems to be associated with more advanced disease. Therefore, PVI alone may be insufficient to restore sinus rhythm in these patients. However, in our study, the longest episode of continuous AF had been <12 months in most patients, and continuous AF episodes ranged widely,

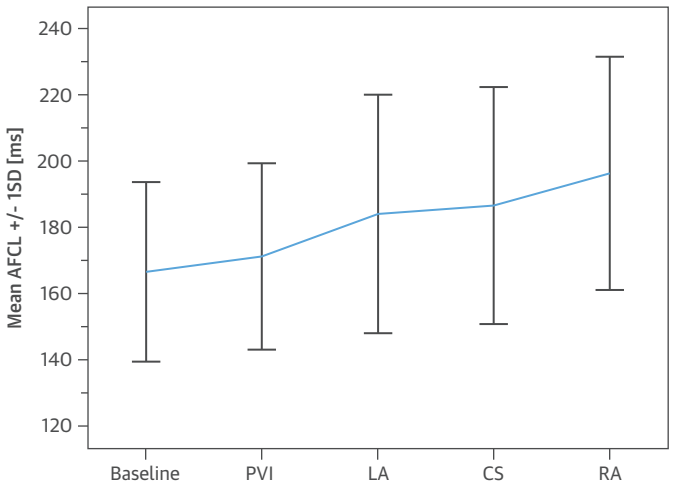
TABLE 2 Procedural Data

Variable	PVI	Full Defragmentation	p Value
Baseline AFCL, ms			
LAA	171.9 ± 28.8	168.4 ± 34.8	0.73
RAA	172.7 ± 31.3	173.0 ± 37.0	0.62
CS	180.9 ± 123.0	166.7 ± 32.8	0.38
LSPV	177.6 ± 32.4	175.0 ± 36.7	0.87
LIPV	176.6 ± 30.9	175.9 ± 28.8	0.93
RSPV	181.5 ± 34.3	188.4 ± 33.3	0.16
RIPV	182.3 ± 29.8	183.0 ± 26.9	0.65
Procedure duration, min	124.9 ± 36.5	220.6 ± 58.2	<0.001
Radiofrequency application time, min	45.0 ± 22.5	99.9 ± 36.2	<0.001
Fluoroscopy time, min	26.9 ± 12.3	52.7 ± 18.3	<0.001
Fluid intake, ml	1,356.9 ± 600.5	2,821.1 ± 942.3	<0.001

Values are mean ± SD.

AFCL = atrial fibrillation cycle length; CS = coronary sinus; LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; PVI = pulmonary vein isolation; RAA = right atrial appendage; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

FIGURE 3 Mean AFCL Progression

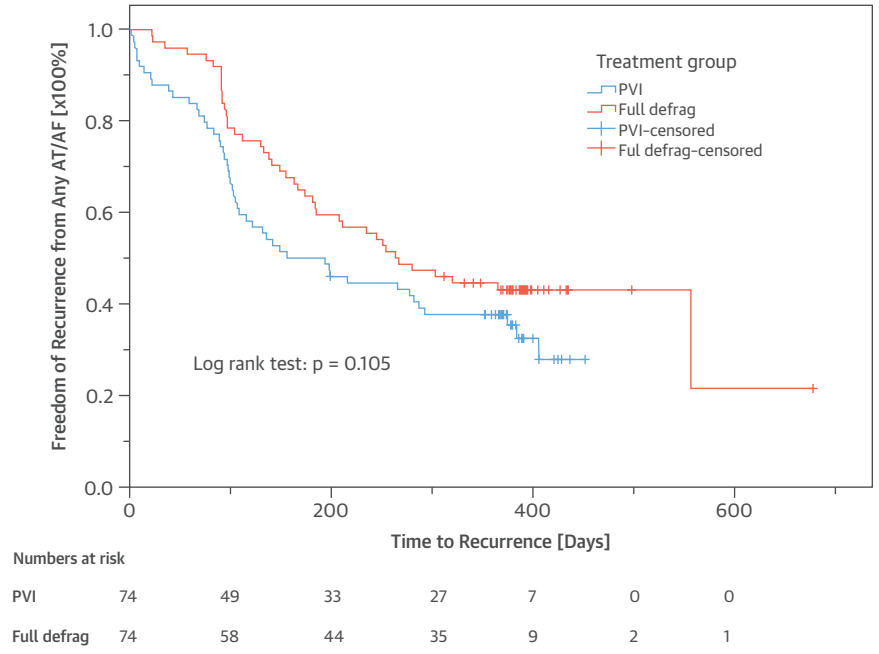


The mean atrial fibrillation cycle length (AFCL) is shown during ablation in the full-defrag group, starting from baseline to the end of ablation in the right atrium. Abbreviations as in Figures 1 and 2.

from 1 day to >12 months. This suggests a different population of patients with a less advanced type of AF compared with previous studies. A subset of patients might have had AF of paroxysmal character. Additional CFAE ablation is not beneficial for sinus rhythm maintenance in these patients (20,22–25); consequently, PVI might have been comparable to the stepwise approach in our study. AF termination rate in the full-defrag group was lower than in the Bordeaux group studies (16,26). However, compared with other studies (27–29), including STAR AF II (the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II) (30) and our own experience, a termination rate of 60% is reasonable if patients with successful AF termination following PVI are excluded and if linear ablation lines are only performed in cases of ATs. Assuming that AF termination during the procedure is 1 of the strongest predictors of procedure outcome, as shown in some previous studies (15,31), arrhythmia-free survival should have been superior in patients with AF termination. However, the results of the STAR AF II trial and our study do not support that assumption (1,28,32). There is conflicting evidence as to whether AF termination during ablation influences long-term outcome. Therefore, the outcome value of AF termination remains controversial in a "real-world scenario."

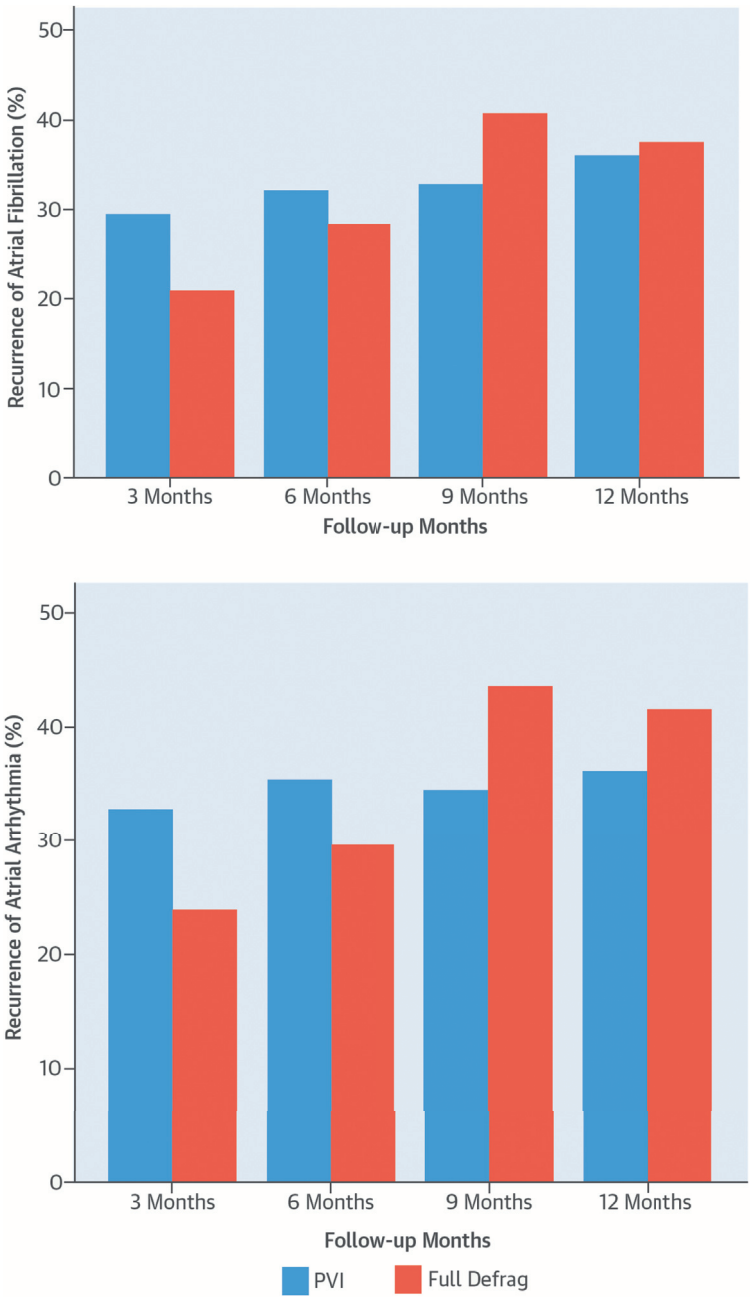
PATIENT CHARACTERISTICS. Long-term efficacy of PVI as the first-line ablative strategy in persAF is questionable. However, Tilz et al. (8,9) reported that 43.2% of patients were arrhythmia free after a

FIGURE 4 Rhythm Outcome After Single Ablation



Kaplan-Meier event-free survival curve demonstrates arrhythmia-free survival after a single ablation. Abbreviations as in Figures 1 and 2.

CENTRAL ILLUSTRATION **Catheter Ablation of Persistent Atrial Fibrillation: Pulmonary Vein Isolation Versus Defragmentation**



Vogler, J. et al. J Am Coll Cardiol. 2015; 66(24):2743–52.

In comparing pulmonary vein isolation (PVI) to defragmentation (full defrag), recurrence per treatment group after a follow-up of 3, 6, 9, and 12 months is shown for **(top)** atrial fibrillation (AF), including both paroxysmal and persistent AF patients, and **(bottom)** any atrial arrhythmia (10 crossover patients excluded). The stepwise approach (full defrag) did not appear to provide additional benefit over PVI alone in these patients.

TABLE 3 12-Month Rhythm Outcome According to Number of Ablations

No. of Ablations	Rhythm Outcome	PVI	Full Defragmentation	p Value
1 (PVI: n = 36; full defrag: n = 42)	Survival free of atrial arrhythmia	27 (75.0)	31 (73.8)	0.90
	Recurrence of PAF/persAF	3 (8.3)/6 (16.7)	3 (7.1)/7 (16.7)	0.98
2 (PVI: n = 18; full defrag: n = 17)	Survival free of atrial arrhythmia	10 (55.6)	5 (29.4)	0.12
	Recurrence of PAF/persAF	1 (5.6)/7 (38.9)	3 (17.6)/8 (47.1)	0.36
3 (PVI: n = 7; full defrag: n = 12)	Survival free of atrial arrhythmia	2 (28.6)	5 (41.7)	0.57
	Recurrence of PAF/persAF	0 (0)/5 (71.4)	2 (16.7)/4 (33.3)	0.22

Values are n (%).
full defrag = full defragmentation; PAF = paroxysmal atrial fibrillation; persAF = persistent atrial fibrillation; PVI = pulmonary vein isolation.

follow-up of 19 ± 11 months, and only one-quarter of patients were arrhythmia free after 5 years following PVI as the sole ablative strategy. In contrast to their study, we excluded patients with AF termination following PVI. PVI responders in the study by Tilz et al. (9) had a smaller LA diameter and a shorter total AF duration compared with PVI nonresponders. The average LA diameter in both of our treatment groups was smaller, and AF duration was substantially shorter than that in their study, as well as in the Bordeaux studies, which indicated a less advanced AF phenotype. Therefore, a considerable amount of our patients may have been PVI responders, resulting in PVI noninferiority.

Finally, permanent electrical isolation of all PVs by creation of durable lesions is critical because recurrence of atrial arrhythmias after ablation of persAF is also related to reconnected PVs. Newer techniques like contact force, recognition of dormant conduction by adenosine, or PVI guided by loss of pace capture on the ablation line (33), as well as the new generation of cyroballoons, can help reduce the problem of PV reconduction.

INTERPRETATION OF CFAES. Since the promising study of Nademanee (11), the addition of CFAE ablation has been suggested to improve long-term freedom from AF. However, different trials results have been highly variable, and extensive ablation may have unintentionally created new substrates responsible for additional atrial arrhythmias. Patients in our study did not seem to benefit from extensive biatrial defragmentation. This finding is consistent with increasing evidence that CFAEs might not represent critical sites for AF perpetuation, but might correspond to areas of normal atrial voltage and conduction (34–36). More recent evidence suggests that stable rotors and focal sources may sustain human AF (36). Furthermore, the exact mechanism by which CFAE ablation could improve arrhythmia-free outcome remains unclear, the definition of CFAEs varies in different centers, and CFAE stability has been questioned (37).

Like earlier results in catheter ablation of persAF, our data underline a trend toward being even more selective in treating patients with persAF. AF termination during ablation, which has been identified as a predictor of success in some previous studies (15,17,18,31), does not seem to correlate with better arrhythmia-free survival. The termination rate in our study (60%) is consistent with those presented in previous multicenter trials, such as STAR AF II (30). Nevertheless, the STAR AF II trial, the RASTA study (Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation) (27), and a recently published meta-analysis (29) did not demonstrate a benefit of CFAE ablation. The results favored lone PVI at least as an initial approach, and our results underline the presumption that less may be more in selected patients with persAF. However, the long-term success rates of lone PVI, even after multiple procedures, are low (9), indicating additional ablation is needed in some patients. Whether these approaches in the future will rely more on a substrate-based approach or a phased mapped-derived rotor concept needs to be determined and requires a better understanding of AF pathophysiology (35,36,38,39).

STUDY LIMITATIONS. Compared with other studies, our follow-up period may have been too short to detect differences in arrhythmia outcome between the 2 treatment groups. In addition, in patients who were on amiodarone for up to 6 months, a follow-up of 12 months might have been too short to determine the drug-free success rate. Patients in the CHASE-AF study received the recommended minimum assessment of AF documentation (1) during follow-up. Due to the nature of AF, assessment by an implantable loop recorder is superior to Holter ECGs; therefore, the overall success rate may have been overestimated. Some patients with AF recurrence did not undergo re-ablation because of symptom improvement or complete symptom relief, which might have decreased our success rate. The definition of persAF as a history of at least 1 DC cardioversion,

regardless of the time in AF before cardioversion, is critical; patients with short-lasting (<48 h) paroxysmal AF might have been included in our study. However, we think we addressed that issue by excluding patients with PV-dependent AF before randomization.

Suppressing potential triggers due to previous antiarrhythmic therapy can reduce recurrence of atrial arrhythmias (40). Continuing amiodarone right up to the ablation and up to 6 months afterwards may have improved our acute AF termination rate. It also may have affected our recurrence rates. Nevertheless, our approach of ongoing amiodarone treatment, and thus our results, are comparable to those of other studies (e.g., the STAR AF II trial [30] and a study by Scherr et al. [26]). Our fluoroscopy times are in line with earlier studies, but were longer than expected when using new image integration modules and pressure sensor catheters. Without these newer techniques, and due to the problem of map stability in impedance-based, 3-dimensional mapping, operators used fluoroscopy more intensively, especially at certain catheter positions at the roof or the LAA.

CONCLUSIONS

A stepwise approach, aimed at AF termination, did not seem to provide additional benefit over PVI alone in patients with persAF. The risk of major complications was not increased, but patients who underwent substrate modification using the stepwise approach were exposed to significantly longer procedure time and fluoroscopy duration, as well as increased RF application time.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Julia Vogler, Department of Electrophysiology, University Heart Center Hamburg, University Hospital Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. E-mail: j.vogler@uke.de.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A substrate-based, extensive ablation approach (stepwise) to patients with persistent AF does not improve arrhythmia-free survival compared with PVI alone over 12 months of post-procedural follow-up.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: PVI should be the initial strategy in patients with persistent AF undergoing catheter ablation, because more extensive ablation is associated with longer procedure duration, fluoroscopy, and radiofrequency exposure without better rhythm control outcomes.

TRANSLATIONAL OUTLOOK: Further studies are needed to define the safety and efficacy of ablation of AF rotors and other focal sources to improve outcomes in patients with persistent AF.

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. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012;367:1587–95.

3. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA 2014;311:692–700.

4. Lim TW, Jassal IS, Ross DL, Thomas SP. Medium-term efficacy of segmental ostial pulmonary vein isolation for the treatment of permanent and persistent atrial fibrillation. Pacing Clin Electrophysiol 2006;29:374–9.

5. Oral H, Knight BP, Tada H, et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation 2002;105:1077–81.

6. 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.

7. 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.

8. 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.

9. Tilz RR, Rillig A, Thum AM, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J Am Coll Cardiol 2012;60:1921–9.

10. 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.

11. 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.

12. Sanders P, Jais P, Hocini M, et al. Electrophysiologic and clinical consequences of linear catheter ablation to transect the anterior left atrium in patients with atrial fibrillation. Heart Rhythm 2004;1:176–84.

13. Ernst S, Ouyang F, Lober F, Antz M, Kuck KH. Catheter-induced linear lesions in the left atrium in patients with atrial fibrillation: an electroanatomic study. J Am Coll Cardiol 2003;42:1271–82.

14. Willems S, Klemm H, Rostock T, et al. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. Eur Heart J 2006;27:2871–8.

15. 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.

16. 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.

17. Rostock T, Steven D, Hoffmann B, et al. Chronic atrial fibrillation is a biatrial arrhythmia: data from catheter ablation of chronic atrial fibrillation aiming arrhythmia termination using a sequential ablation approach. Circ Arrhythm Electrophysiol 2008;1:344–53.

18. O'Neill MD, Jais P, Takahashi Y, et al. The stepwise ablation approach for chronic atrial fibrillation–evidence for a cumulative effect. J Interv Card Electrophysiol 2006;16:153–67.

19. Haissaguerre M, Hocini M, Sanders P, et al. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. J Cardiovasc Electrophysiol 2005;16:1138–47.

20. 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.

21. Estner HL, Hessling G, Ndrepepa G, et al. Acute effects and long-term outcome of pulmonary vein isolation in combination with electrogram-guided substrate ablation for persistent atrial fibrillation. Am J Cardiol 2008;101:332–7.

22. Nuhrich JM, Steven D, Berner I, et al. Impact of biatrial defragmentation in patients with paroxysmal atrial fibrillation: results from a randomized prospective study. Heart Rhythm 2014;11:1536–42.

23. Hayward RM, Upadhyay GA, Mela T, et al. Pulmonary vein isolation with complex fractionated atrial electrogram ablation for paroxysmal and nonparoxysmal atrial fibrillation: a meta-analysis. Heart Rhythm 2011;8:994–1000.

24. Wu SH, Jiang WF, Gu J, et al. Benefits and risks of additional ablation of complex fractionated atrial electrograms for patients with atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol 2013;169:35–43.

25. Deisenhofer I, Estner H, Reents T, et al. Does electrogram guided substrate ablation add to the success of pulmonary vein isolation in patients with paroxysmal atrial fibrillation? A prospective, randomized study. J Cardiovasc Electrophysiol 2009;20:514–21.

26. Scherr D, Khairy P, Miyazaki S, et al. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. Circ Arrhythm Electrophysiol 2015;8:18–24.

27. Dixit S, Marchlinski FE, Lin D, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. Circ Arrhythm Electrophysiol 2012;5:287–94.

28. Elayi CS, Di Biase L, Barrett C, et al. Atrial fibrillation termination as a procedural endpoint during ablation in long-standing persistent atrial fibrillation. Heart Rhythm 2010;7:1216–23.

29. Wynn GJ, Das M, Bonnett LJ, Panikker S, Wong T, Gupta D. Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. Circ Arrhythm Electrophysiol 2014;7:841–52.

30. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812–22.

31. 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.

32. Komatsu Y, Taniguchi H, Miyazaki S, et al. Impact of atrial fibrillation termination on clinical outcome after ablation in relation to the duration of persistent atrial fibrillation. Pacing Clin Electrophysiol 2012;35:1436–43.

33. Steven D, Sultan A, Reddy V, et al. Benefit of pulmonary vein isolation guided by loss of pace capture on the ablation line: results from a prospective 2-center randomized trial. J Am Coll Cardiol 2013;62:44–50.

34. Viles-Gonzalez JF, Gomes JA, Miller MA, et al. Areas with complex fractionated atrial electrograms recorded after pulmonary vein isolation represent normal voltage and conduction velocity in sinus rhythm. Europace 2013;15:339–46.

35. Jadidi AS, Cochet H, Shah AJ, et al. Inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation: combined magnetic resonance imaging and high-density mapping. J Am Coll Cardiol 2013;62:802–12.

36. Narayan SM, Shivkumar K, Krummen DE, Miller JM, Rappel WJ. Panoramic electrophysiological mapping but not electrogram morphology identifies stable sources for human atrial fibrillation: stable atrial fibrillation rotors and focal sources relate poorly to fractionated electrograms. Circ Arrhythm Electrophysiol 2013;6:58–67.

37. Lau DH, Maesen B, Zeemering S, Verheule S, Crijns HJ, Schotten U. Stability of complex fractionated atrial electrograms: a systematic review. J Cardiovasc Electrophysiol 2012;23:980–7.

38. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation 2014;130:530–8.

39. Narayan SM, Baykaner T, Clopton P, et al. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). J Am Coll Cardiol 2014;63:1761–8.

40. Di Biase L, Santangeli P, Mohanty P, et al. Amiodarone increases the AF termination during ablation but reduces the long-term success rate of patients undergoing ablation of long-standing persistent atrial fibrillation: preliminary results from the SPECULATE study (abstr). Heart Rhythm 2012;9 Suppl:S37.

KEY WORDS **atrial tachycardia, complex fractionated atrial electrogram, paroxysmal, stepwise**