Stand-Alone Pulmonary Vein Isolation Versus Pulmonary Vein Isolation With Additional Substrate Modification as Index Ablation Procedures in Patients With Persistent and Long-Standing Persistent Atrial Fibrillation

The Randomized Alster-Lost-AF Trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation)

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Background—Pulmonary vein isolation (PVI) for persistent atrial fibrillation is associated with limited success rates and often requires multiple procedures to maintain stable sinus rhythm. In the prospective and randomized Alster-Lost-AF trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation), we sought to assess, in patients with symptomatic persistent or long-standing persistent atrial fibrillation, the outcomes of initial ablative strategies comprising either stand-alone PVI (PVI-only approach) or a stepwise approach of PVI followed by complex fractionated atrial electrogram ablation and linear ablation (Substrate-modification approach).

Methods and Results—Patients were randomized 1:1 to stand-alone PVI or PVI plus substrate modification. The primary study end point was freedom from recurrence of any atrial tachyarrhythmia, outside a 90-day blanking period, at 12 months. A total of 124 patients were enrolled, with 118 patients included in the analysis (61 in the PVI-only group, 57 in the Substrate-modification group). Atrial tachyarrhythmias recurred in 28 PVI-only group patients and 24 Substrate-modification group patients, for 1-year freedom from tachyarrhythmia recurrence after a single ablation procedure of 54% (95% confidence interval, 43%–68%) in the PVI-only and 57% (95% confidence interval, 46%–72%) in the Substrate-modification group (P=0.86). Twenty-four patients in the PVI-only group (39%) and 18 in the Substrate-modification group (32%) were without arrhythmia recurrence and off antiarrhythmic drug therapy at the end of the 12-month follow-up.

Conclusions—In patients with persistent and long-standing persistent atrial fibrillation, no significant difference was observed in 12-month freedom from atrial tachyarrhythmias between an index ablative approach of stand-alone PVI and a stepwise approach of PVI plus complex fractionated atrial electrogram and linear ablation.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00820625.

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Key Words: atrial fibrillation ■ catheter ablation ■ recurrence ■ tachycardia

Catheter ablation has become a routine treatment option for patients experiencing symptomatic paroxysmal atrial fibrillation (AF). Long-term clinical success rates of ≤80% after 5 years have been reported for the treatment of paroxysmal AF by initial stand-alone pulmonary vein isolation (PVI) as the accepted cornerstone of all AF ablation strategies; however, to achieve permanent PVI, multiple procedures are often required.[1,2] In contrast, the results for ablation of persistent AF are less convincing.[3] The optimal strategy for persistent AF is not known, and previous studies investigating more extensive ablation strategies in addition to PVI demonstrated heterogeneous results.[4–12] The recently published STAR AF 2 trial (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial) compared initial stand-alone PVI to PVI with additional ablation of complex fractionated atrial electrograms (CFAEs) or additional linear ablation and could not demonstrate a superior outcome for the additional ablation strategies.[13] The prospective and randomized Alster-Lost-AF

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WHAT IS KNOWN

- Pulmonary vein isolation (PVI) is the cornerstone of catheter ablation for both paroxysmal and persistent symptomatic atrial fibrillation (AF).
- Ablation of complex fractionated atrial electrograms (CFAEs) and the creation of various lines of conduction block (linear ablation) in the left atrium are alternative approaches to catheter ablation of AF.

WHAT THE STUDY ADDS

- The prospective and randomized Alster-Lost-AF study sought to assess, in patients with persistent and long-standing persistent AF, the midterm outcomes after index ablation strategies of stand-alone PVI or a stepwise approach of PVI followed by CFAE and linear ablation.
- No difference was observed between the 2 study arms in the primary end point of recurrence-free survival outside a 90-day blanking period at 1 year.
- It is concluded that reconduction through gaps in the circumferential PVI lines overpowers any beneficial effect that additional substrate modification may have and that the impact of CFAE and linear ablation at the time of PVI cannot be assessed as long as durable PVI is not convincingly achieved.

study (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation) sought to assess, in patients with persistent and long-standing persistent AF, the midterm outcomes after stand-alone PVI versus a stepwise approach of PVI followed by CFAE ablation and linear ablation.

Methods

Study Design

The Alster-Lost-AF study was designed as a prospective, randomized, single-center trial. Patients with persistent or long-standing persistent AF underwent 1:1 randomization to an index AF ablation strategy consisting of either stand-alone PVI (PVI-only group) or PVI followed by biatrial CFAE and linear ablation (Substrate-modification group; Figure 1). Periprocedural atrial flutter (AFL) was treated by linear ablation in both groups; patients in whom AF did not convert during ablation underwent direct current (DC) cardioversion.

The primary study end point was freedom from recurrence of any atrial tachyarrhythmia (>30 s duration), outside a blanking period of 90 days,[2] at 12 months. Secondary end points were the assessment of procedural parameters and the incidence of procedure-related complications. The term major complication was applied according to previously published criteria.[2]

Inclusion and Exclusion Criteria

Patients between 18 and 75 years of age experiencing symptomatic persistent (duration >6 months but <12 months) or long-standing persistent AF (duration ≥12 months) with a maximum duration of 5 years and with an indication to undergo catheter ablation were enrolled into the study. All patients had at least 1 failure of antiarrhythmic (class I or III) drug therapy before ablation. Exclusion criteria were a documented intracardiac thrombus, a diameter of the left atrium (LA) >55 mm assessed by echocardiography, acute or chronic renal failure (Kidney Disease: Improving Global Outcomes stage ≥II), pregnancy, life expectancy <12 months, previous catheter ablation for AF, contraindication to systemic anticoagulation, and a known reversible cause of AF. The study was approved by the Hamburg Ethics Committee (trial number: PV 2961), and the trial design has been published online. All participants provided written informed consent.

Electrophysiological Procedures

All patients underwent transesophageal echocardiography before the ablation procedure to exclude intracardiac thrombi and to assess the LA diameter, valvular status, and left ventricular function. Oral anticoagulation with vitamin-K antagonists was stopped at least 3 days before the ablation procedure and replaced with low-molecular-weight heparin (LMWH) therapy. In cases of an International Normalized Ratio <2.0, LMWH was administered postprocedurally until a therapeutic International Normalized Ratio of 2 to 3 was achieved. Preexisting therapy with novel oral anticoagulants was stopped 24 hours before the ablation procedure and reinitiated 6 hours afterward. All procedures were performed under deep sedation using midazolam, sufentanil, and continuous propofol infusion.

A standard diagnostic catheter was advanced into the coronary sinus. Transseptal puncture was performed using a modified

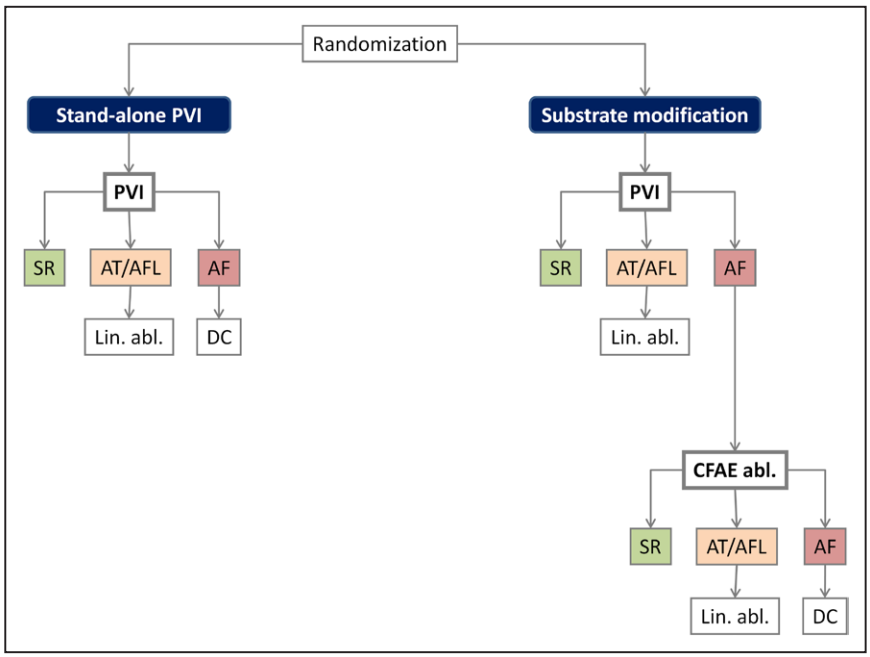

Figure 1. Study design. AF indicates atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; CFAE, complex fractionated atrial electrogram; DC, direct current cardioversion; Lin. abl., linear ablation; PVI, pulmonary vein isolation; and SR, sinus rhythm.

Brockenbrough technique and transseptal sheaths (SL1; St. Jude Medical, Minneapolis, MN), followed by selective pulmonary vein (PV) angiographies. After LA access, intravenous heparin was administered targeting an activated clotting time of 250 to 300 s. Three-dimensional reconstruction of the LA using an electroanatomical mapping system (CARTO; Biosense Webster, Diamond Bar, CA) was conducted, and the PV ostia were tagged according to the selective PV angiographies and local electric signals. Ablation was performed using a 3.5 mm tip irrigated radiofrequency current catheter (NaviStar ThermoCool; Biosense Webster). A spiral mapping catheter (LASSO NAV; Biosense Webster) was placed at the ostium of each PV to record electric PV potentials. All patients underwent wide area circumferential ablation PVI guided by the lasso catheter as previously described.[1,3] The procedural end point for PVI was defined as the absence of all PV potentials after a 30-minute waiting period.

In case of AF termination during PVI, the procedure was stopped. In case of AF persistence, patients randomized to the PVI-only group underwent DC cardioversion. Patients randomized to the Substrate-modification group underwent additional ablation of CFAEs in the LA, the right atrium, and the coronary sinus. CFAE ablation was performed for a maximum of 2 hours or until conversion to sinus rhythm (SR) or atrial tachycardia (AT)/AFL.

CFAE ablation was conducted according to previously defined criteria (fractionated electrograms with ≥1 continuous deflections of a prolonged atrial activation complex or atrial electrograms with a cycle length <120 ms over a period of at least 5 s).[14] If no conversion was achieved within 2 hours of CFAE ablation, the patient underwent DC cardioversion. In case of conversion to AT or AFL, additional linear lesion sets were applied in the form of an anterior, posterior, roof, or mitral isthmus line to terminate AT or creation of a cavotricuspid isthmus (CTI) line to terminate AFL. Bidirectional block of all linear lines was assessed in SR using electrophysiological maneuvers.

Repeat Procedures

The ablation target during repeat procedures was at the operator's discretion and independent of the patient's randomization. In all procedures, electric reconduction of previously isolated PVs was assessed. Repeat procedures comprised reisolation of reconnected PVs and additional substrate modification, if necessary.

Postprocedural Care

All patients underwent postprocedural transthoracic echocardiography to rule out a pericardial effusion and chest X-ray to exclude a pneumothorax in case of puncture of the subclavian vein. In patients on vitamin-K antagonists and an International Normalized Ratio <2.0, LMWH was administered until an International Normalized Ratio of 2.0 to 3.0 was achieved. Novel oral anticoagulants were reinitiated 6 hours post-ablation. Anticoagulation was continued in all patients for 3 months and thereafter based on the individual $CHADS_2$/CHA_2DS_2-VASc score. Antiarrhythmic drug therapy was recommended to continue for 3 months after the ablation procedure. All patients were treated with proton pump inhibitors twice daily for 6 weeks.

Clinical Follow-Up

Follow-up was performed at 3, 6, and 12 months and comprised a clinical examination, 12-lead ECG, and 24-hour Holter ECG. In addition, regular telephone interviews were performed to assess subjective arrhythmia recurrence and adverse events at 1, 3, 6, and 12 months. Additional Holter ECGs were initiated in patients with symptoms suggestive of arrhythmia recurrence.

Statistics

We expected 35% event-free patients in the PVI-only group and 60% in the Substrate-modification group in the first year. The survival curves were examined with a 2-sided log-rank test at a significance level of 5%. The sample size calculation led to a total number of 118 patients to detect differences between the ablation groups with a power of 80%. Assuming a 5% rate of patients lost to follow-up increased the total number of patients to 124.

Continuous data are summarized as mean and SD or median plus first (Q1) and third quartile (Q3). Categorical data are presented as absolute and relative frequencies. The primary study end point was freedom from any atrial tachyarrhythmia after the index procedure. The statistical analyses were based on the intention-to-treat principle. Differences in procedure time, ablation time, fluoroscopy time, and area dose product between the ablation groups were compared with a 2-sample *t* test or Mann–Whitney *U* test. Categorical data were compared using Fisher exact test. The recurrent event data were analyzed with Kaplan–Meier survival curves and life tables stratified by the number of procedures and the ablation group. Survival curves were compared with the log-rank test.

All analyses were conducted using R version 3.3.1 (www.r-project.org). A P value <0.05 was considered statistically significant.

Table 1. Baseline Patient Characteristics

Variable	All Patients, (n=118)	PVI-Only, (n=61)	Substrate Modification, (n=57)
Age, y	61.5±9.7	62.1±9.9	60.9±9.6
Female sex	34 (29)	19 (31)	15 (26)
BMI	27.9±4.0	28.1±3.8	27.8±4.2
Duration of AF, mo	12 [7, 24]	12 [7, 24]	12 [7, 24]
Type of AF			
Persistent	69 (59)	35 (57)	34 (60)
Long-standing persistent	49 (42)	26 (43)	23 (40)
CAD	11 (9)	5 (8)	6 (11)
Valvular disease	14 (12)	8 (13)	6 (11)
Hypertension	64 (54)	35 (57)	29 (51)
Diabetes mellitus	9 (8)	5 (8)	4 (7)
$CHADS_2$ score	1 [0, 1]	1 [0, 1]	1 [0, 1]
0–1	103 (87)	52 (85)	51 (90)
2–3	14 (12)	8 (13)	6 (11)
>3	1 (1)	1 (2)	0 (0)
CHA_2DS_2-VASc score	2 [1, 2]	2 [1, 2]	1 [1, 2]
0–1	58 (49)	26 (43)	32 (56)
2–3	52 (44)	31 (51)	21 (37)
>3	8 (7)	4 (7)	4 (7)
LVEF ≥55%	100 (85)	50 (82)	50 (88)
LA diameter, mm	47.0±4.4	47.3±4.5	46.7±4.3

Values are mean±SD, median [first quartile, third quartile], or n (%).

AF indicates atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; $CHADS_2$, stroke risk score based on congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism; CHA_2DS_2-VASc, stroke risk score based on congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism, vascular disease, age 65-74 years, sex; LA, left atrium; and LVEF, left ventricular ejection fraction.

Results

Patients

A total of 124 patients were consecutively enrolled. Six (5%) of the 124 patients withdrew their consent during follow-up and were excluded from the study, resulting in a total of 118

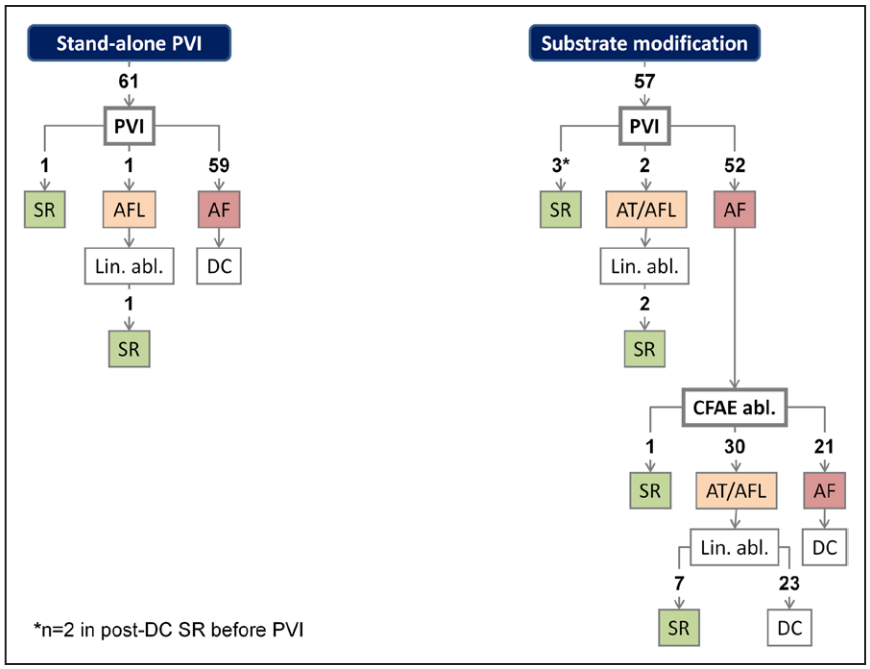

Figure 2. Acute outcomes of index ablation procedures according to randomization. AF indicates atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; CFAE, complex fractionated atrial electrogram; DC, direct current cardioversion; Lin. abl., linear ablation; Numbers, numbers of patients; PVI, pulmonary vein isolation; and SR, sinus rhythm.

patients included in the intention-to-treat analysis. Sixty-one patients were randomized to the PVI-only group and 57 patients to the Substrate-modification group. Baseline and procedural patient data are shown in Table 1. The median duration of AF persistence before randomization was 12 months [Q1, Q3: 7, 24 months] in both groups. AF was categorized as persistent in 69 patients (58%) and long-standing persistent in 49 patients.

Index Catheter Ablation in the PVI-Only Group

During the index ablation procedure, 1 patient (2%) in the PVI-only group converted to SR during PVI, and another patient converted to typical AFL, which was successfully terminated by linear ablation of the CTI; the other 59 patients (97%) underwent successful DC cardioversion (Figure 2).

Index Catheter Ablation in the Substrate-Modification Group

In the Substrate-modification group, 2 patients (4%) presented in SR after DC cardioversion before hospital admission for ablation. PVI in the remaining patients resulted in SR, AT, and AFL in 1 patient each (Figure 2); AT and AFL were successfully terminated by an anterior line and a CTI line, respectively.

CFAE ablation was subsequently performed in the 52 patients (91%) still in AF after PVI. CFAEs were ablated in the LA in all 52 patients, additionally in the right atrium in 27 patients (47%), and in the coronary sinus in 33 patients (58%). During CFAE ablation, 1 patient (2%) converted to SR, and 30 patients (53%) converted to AT (n=27) or typical AFL (n=3);

Table 2. Procedural Characteristics of Linear Ablation in the 57 Patients Randomized to Substrate Modification

	n	%
Procedures with linear ablation	32	56
Left atrial linear ablation (total)	28	49
Anterior line	13	23
Mitral isthmus line	17	30
Roof line	3	5
Posterior line	1	2
CTI block	14	25
Conversion to sinus rhythm during linear ablation	9/32	28

CTI indicates cavotricuspid isthmus.

Table 3. Procedural Data

	PVI-Only (n=61)	Substrate Modification (n=57)	*P* Value
Ablation time, min	39 [31, 52]	82 [60, 99]	<0.0001
Procedure duration, min	162±56	218±53	<0.0001
Fluoroscopy time, min	19.5±8.9	23.5±8.5	0.0151
Radiation dose, cGy·cm^2	2918±2005	3976±2641	0.0162
Major complications	3 (5)	7 (12)	0.19
Cardiac tamponade	0 (0)	2 (4)	
Stroke	1 (2)	1 (2)	
Transient ischemic attack	1 (2)	0 (0)	
Groin bleeding requiring transfusion	1 (2)	2 (4)	
Groin bleeding requiring surgical therapy	0 (0)	2 (4)	
Minor complications	8 (13)	5 (9)	0.56
Minor groin complication	8 (13)	4 (7)	
Mediastinal hematoma, conservative treatment	0 (0)	1 (2)	

Values are mean±SD, median [first quartile, third quartile], or n (%).

AF could not be terminated within 2 hours in the remaining 21 patients (37%) who all underwent successful DC cardioversion (Figure 2). In the 27 patients converted to AT during CFAE ablation, a total of 39 ATs occurred. Tachycardia mapping revealed perimitral flutter in 19 cases, roof-dependent AT in 4 cases, and focal AT in 3 cases. In the remaining 13 cases, the tachycardia mechanism was not mappable because of instability of the AT. In these patients, no additional linear ablation was performed.

All 27 patients with conversion to AT and the 3 patients with conversion to AFL during CFAE ablation underwent ablation with sets of linear lesions in the LA and across the CTI, respectively. In the 19 patients with perimitral flutter, ablation was achieved by way of a mitral isthmus line in 11 cases, an anterior line in 6 cases, a mitral isthmus line plus an anterior line in 1 case, and a mitral isthmus line plus a posterior line in 1 case. The roof-dependent and focal ATs were treated by the creation of roof lines and by focal ablation, respectively. Empirical linear ablation (delivery of a mitral isthmus line in 4 cases and an anterior line in another 4 patients) was performed in 8 patients in whom conversion to AT during PVI or CFAE ablation was not achieved. In total, 48 linear ablations comprising 34 LA lesions and 14 CTI blockades were performed in 32 patients (56%) of the Substrate-modification group (Table 2). All left and right atrial linear lesions proved to be bidirectionally blocked except for 1 mitral isthmus line. All 3 AFL patients and 4 AT patients converted to SR during linear ablation; the remaining 23 AT patients underwent successful DC cardioversion (Figure 2).

At the end of all ablation attempts, 2 patients (3%) in the PVI-only group and 11 patients (19%) in the Substrate-modification group had converted from AF to SR (P=0.007).

Procedural Parameters and Complications

With median ablation times of 82 minutes in the Substrate-modification group and 39 minutes in the PVI-only group (P<0.0001), procedure duration was significantly longer in the former (218±53 versus 162±56 minutes, P<0.0001). Accordingly, fluoroscopy time (23.5±8.5 versus 19.0±8.5 minutes, P=0.0151) and radiation dose (3976±2641 versus 2918±2005 cGy·cm^2, P=0.0162) were significantly higher in patients undergoing substrate modification (Table 3).

Major complications were observed in a total of 10 patients (9%; Table 3). In detail, major complications occurred in 3 PVI-only patients (5%; 1 stroke, 1 transient ischemic attack, and 1 groin complication requiring transfusion) and 7 Substrate-modification patients (12%; 1 stroke, 2 cardiac tamponades requiring subxiphoidal drainage, 2 groin bleedings requiring transfusion, and 2 groin bleedings requiring surgical intervention).

The stroke in the PVI-only group occurred 2 hours after the procedure in the form of aphasia with partial remission until discharge. The stroke in the Substrate-modification group occurred on the fourth postprocedural day with hemiplegia because of an embolism to the right midcerebral artery, which persisted until the end of follow-up. The transient ischemic attack occurred 8 hours post-procedure in the form of aphasia with complete remission. In 2 of these 3 patients with cerebrovascular events, activated clotting time was <300 s at least at 1 measurement during the procedure. The stroke patients were on periprocedural heparin bridging therapy (1 on LMWH, 1 on unfractionated heparin therapy with subtherapeutic partial thromboplastin time); the transient ischemic attack patient was on LMWH bridging therapy.

Minor groin complications without the need for specific therapy were observed in 8 PVI-only patients (13%) and 5 Substrate-modification patients (9%; Table 3). No atrioesophageal fistula or PV stenosis occurred in either group. The overall incidences of major and minor complications were statistically not different between the groups (P=0.19 and 0.56, respectively).

Primary End Point

Twelve-month clinical follow-up was available in a total of 113 patients (96%), in 59 (97%) of the PVI-only group

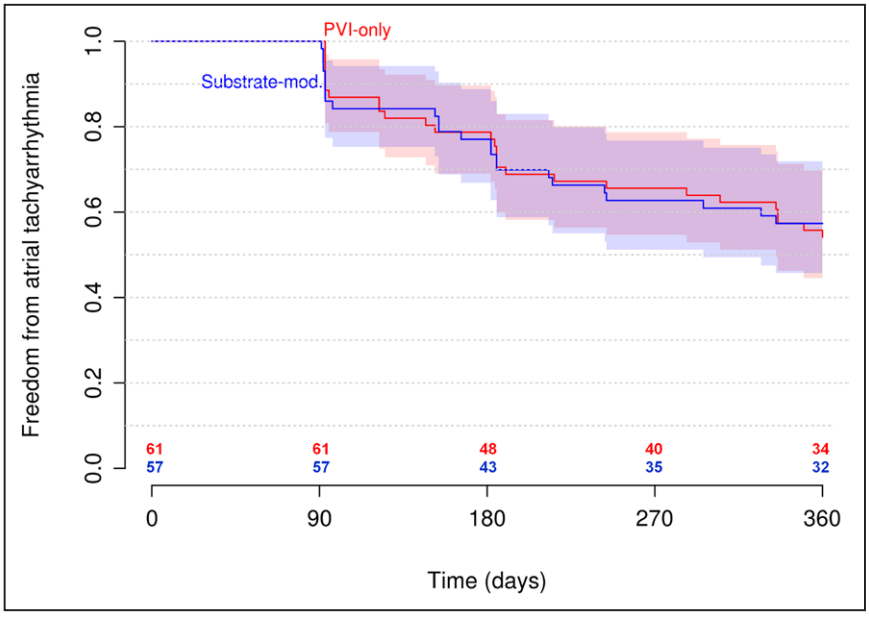

Figure 3. Freedom from recurrence of atrial tachyarrhythmias after a single procedure. One-year Kaplan–Meier estimates are 54% (95% confidence interval [CI], 43%–68%) in the pulmonary vein isolation (PVI)-only group and 57% (95% CI, 46%–72%) in the Substrate-modification group (P=0.86).

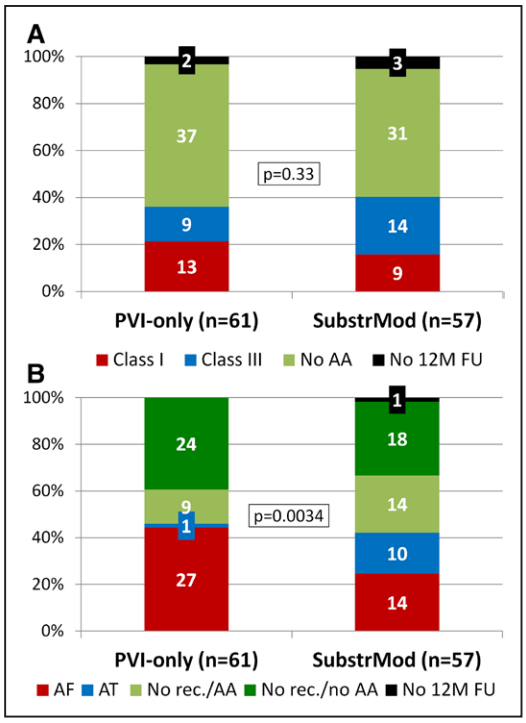

Figure 4. **A**, Antiarrhythmic (AA) medication at 12 mo in the 2 study groups. The distributions are statistically not different. **B**, Arrhythmia recurrence outside the 90-d blanking period in the 2 study groups. The statistically significant difference between the distributions is primarily driven by the difference in atrial tachycardia (AT) recurrence. AF indicates atrial fibrillation; FU, follow-up; Numbers, numbers of patients; PVI, pulmonary vein isolation; and SubstrMod, substrate modification.

patients and 54 (95%) of the Substrate-modification group patients. Two patients in the PVI-only group and 3 patients in the Substrate-modification group did not complete 12-month clinical follow-up, of which 4 patients dropped out of the study after having reached the primary study end point.

With recurrence of atrial tachyarrhythmias outside the 90-day blanking period documented in 28 patients of the PVI-only group and 24 patients of the Substrate-modification group, Kaplan–Meier estimates of 12-month recurrence-free survival after a single ablation procedure were 54% (95% confidence interval [CI], 43%–68%) and 57% (46%–72%), respectively (P=0.86; Figure 3).

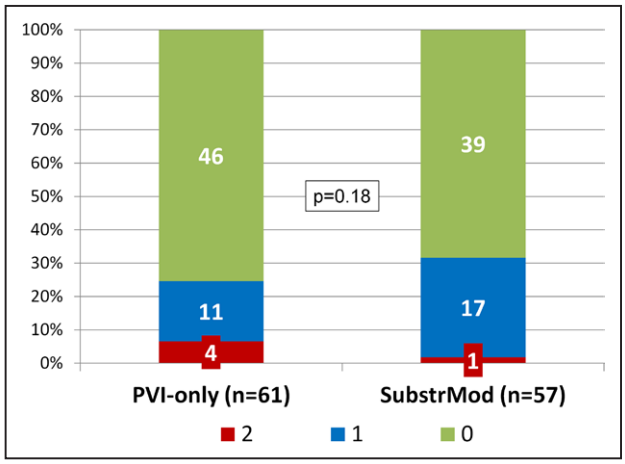

Figure 5. Number of repeat ablation procedures in the 2 study groups. The distributions of 0, 1, or 2 repeat ablation procedures are statistically not different. Numbers in columns denote numbers of patients. PVI indicates pulmonary vein isolation; and SubstrMod, substrate modification.

A subgroup analysis according to the underlying type of AF revealed no difference between ablation modalities in recurrence-free survival, neither for patients with persistent AF (57%; [PVI-only] versus 61% [Substrate-modification]; P=0.80) nor for patients with long-standing persistent AF (50%; [PVI-only] versus 52% [Substrate-modification]; P=0.99).

Type of Arrhythmia Recurrence

In the PVI-only group, recurrent AF was documented in 27 (96%) of the 28 patients, and AT was the recurrent arrhythmia in the remaining patient. The type of arrhythmia recurring in the 24 Substrate-modification group patients was AF in 14 (58%) and AT in 10 patients (42%; P=0.0013 for the between-group difference in types of recurrent arrhythmia).

Antiarrhythmic Medication

At 12 months, 22 PVI-only (36%) and 23 Substrate-modification patients (40%) were on antiarrhythmic drug therapy (13 on class I, 9 on class III in the PVI-only group; 9 on class I, 14 on class III in the Substrate-modification group; Figure 4A).

Twenty-four patients in the PVI-only group (39%) and 18 in the Substrate-modification group (32%) were without arrhythmia recurrence and off antiarrhythmic drug therapy at the end of the 12-month follow-up (Figure 4B).

Repeat Ablation Procedures

Fifteen patients (25%) in the PVI-only group and 18 patients (32%) in the Substrate-modification group underwent repeat ablation procedures during follow-up (P=0.40); 4 of the former patients and 1 of the latter underwent 2 repeat ablation procedures (Figure 5). One-year Kaplan–Meier estimates of event-free survival after multiple ablation procedures were 69% (95% CI, 57%–82%) in the PVI-only group and 86% (95% CI, 77%–96%) in the Substrate-modification group (P=0.09; Figure 6).

Electric reconduction from the PV to the LA was demonstrated during the repeat procedures in 12 PVI-only patients (80%) and 14 Substrate-modification patients (78%). Exclusive reisolation of reconnected PVs was performed in 7 (47%) of the former and 3 (17%) of the latter patients; additional substrate modification was performed in the remaining patients of either group. Substrate modification specifically for tachycardia termination in cases of spontaneous or inducible AT was performed in 3 PVI-only patients (20%) and 7 Substrate-modification patients (39%).

Impact of Conversion to SR on Arrhythmia Recurrence

In the Substrate-modification group, conversion of AF to SR or AT during the procedure was not associated with a lower risk of arrhythmia recurrence than lack of conversion (1-year estimates of event-free survival [95% CI] were 64% [95%

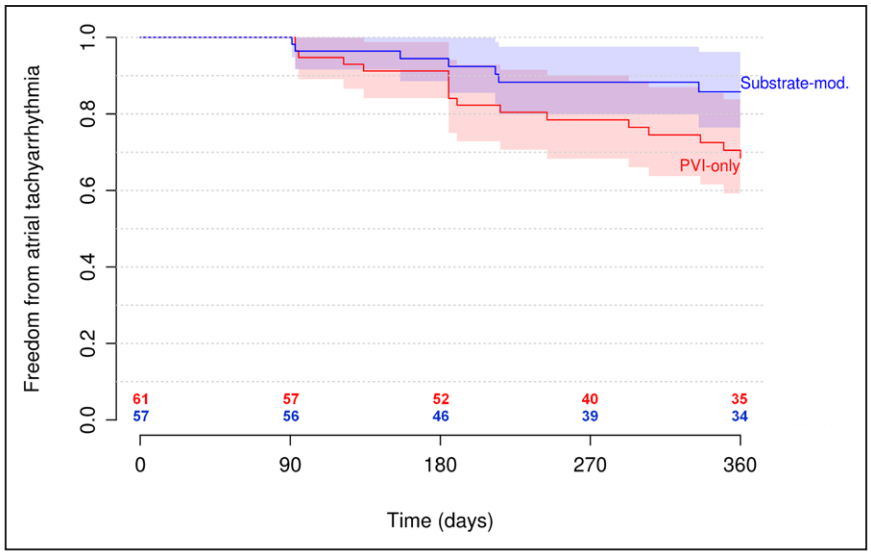

Figure 6. Freedom from recurrence of atrial arrhythmias after multiple procedures. One-year Kaplan–Meier estimates of event-free survival are 69% (95% confidence interval [CI], 57%–82%) in the pulmonary vein isolation (PVI)-only group and 86% (95% CI, 77%–96%) in the Substrate-modification group (*P*=0.09).

CI, 50%–83%] and 48% [95% CI, 31%–73%], respectively [*P*=0.25]; Figure 7).

Discussion

Major Findings

Our study hypothesis of PVI plus substrate modification as the index procedure being superior by a 25% reduction in arrhythmia recurrence to an index PVI-only ablation strategy in patients with persistent or long-standing persistent AF could not be confirmed. The Kaplan–Meier estimates of freedom from atrial tachyarrhythmias at 1 year, outside a 90-day blanking period, of 54% in the PVI-only group and 57% in the Substrate-modification group were statistically not different. The type of atrial tachyarrhythmia recurring during follow-up was predominantly (98%) AF in the PVI-only group, whereas AF recurred in only 58% of the Substrate-modification group patients and AT was the recurrent type of arrhythmia in 42%. The Substrate-modification strategy was associated with significantly longer procedure duration and fluoroscopy time and, accordingly, a higher radiation dose.

Current Ablation Strategies for Chronic AF

Although PVI is the widely accepted cornerstone in ablation of AF, additional substrate-based ablation strategies failed to demonstrate clear and reproducible clinical benefit in previous randomized trials. Ablation of CFAEs for the treatment of AF was introduced by Nademanee et al.[14] In 3 randomized trials, predominantly with smaller patient cohorts, ablation of CFAEs in addition to PVI demonstrated lower rates of recurrence of atrial tachyarrhythmias than stand-alone PVI.[5,8,10] Furthermore, additional linear ablation demonstrated better clinical outcomes in another 3 randomized trials.[6,7,12] Nonetheless, results of other trials did not show a clinical benefit of additional CFAE ablation,[4,9] and the recently published STAR AF II trial revealed no difference in clinical outcomes when comparing stand-alone PVI to PVI plus additional CFAE or linear ablation in a large cohort of patients with persistent AF.[13]

The stepwise ablation approach was first investigated by Haïssaguerre et al[15] and consisted of the sequential combination

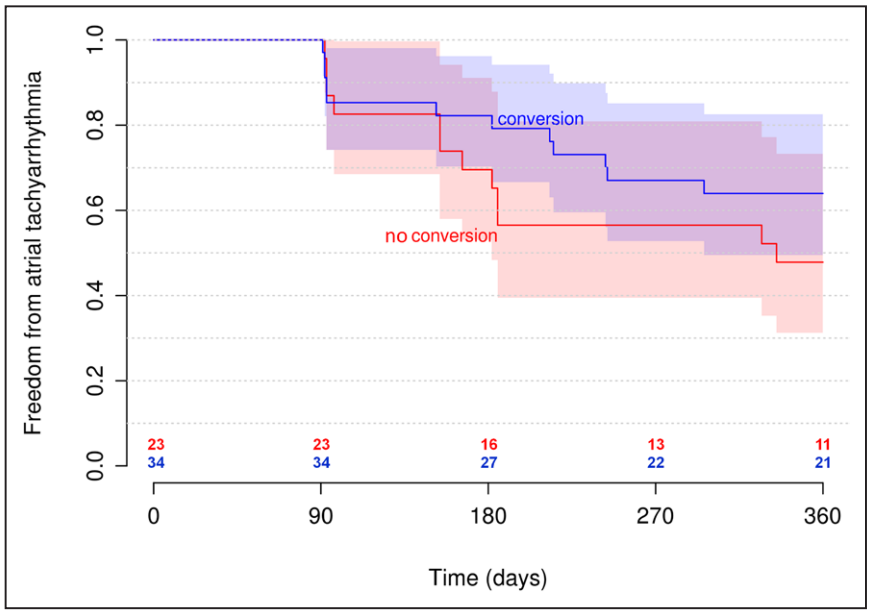

Figure 7. Freedom from recurrence of atrial arrhythmias according to the conversion of atrial fibrillation to sinus rhythm or atrial tachycardia during substrate-modification procedures. One-year Kaplan–Meier estimates of event-free survival are 48% (95% confidence interval [CI], 31%–73%) in the no-conversion subgroup and 64% (95% CI, 50%–83%) in the conversion subgroup (*P*=0.25).

of PVI and additional ablation of CFAEs and, in case of conversion to AT during the ablation procedure, linear ablation; in that original study, 95% of patients were in SR after 1 year and multiple ablation procedures. In contrast, 2 large registries reported single-procedure success rates of only 35.3% and 47.8% at 12 months.[16,17]The recently published single-center randomized CHASE-AF trial (Randomized Catheter Ablation of Persistent Atrial Fibrillation Study) investigated the stepwise approach (termed full defragmentation) versus stand-alone PVI in patients with persistent AF. The trial could not demonstrate a difference in arrhythmia recurrence during 12 months of follow-up; a higher incidence of AT as the mode of recurrence was observed in the full defragmentation group.[11]

The Substrate-Modification Strategy Failed to Reduce Arrhythmia Recurrence

This study is the first to investigate in a randomized manner the clinical outcome of the stepwise substrate-modification ablation approach in patients with a high prevalence (42%) of long-standing persistent AF; in our cohort, continuous AF had persisted for a median of 12 months. The STAR AF II trial did not assess a complete stepwise approach but rather randomized the patients into 3 groups to PVI, PVI plus additional CFAE ablation or PVI plus linear ablation.[13] In addition, only 75.6% of the patients included in STAR AF II had persistent AF of >6 months duration.[13] The CHASE-AF trial investigated a patient population with mainly persistent AF defined as AF lasting for at least 7 days or a history of DC cardioversion.[11] The median duration of persistent AF in CHASE-AF patients randomized to full defragmentation was 5 months (152 days [65, 236] days) and thus significantly shorter than the median AF persistence of 12 months in the present trial. Patients undergoing full defragmentation in CHASE-AF also had smaller mean LA diameters than patients in our Substrate-modification cohort (43.7±5.2 versus 46.7±4.3 mm, respectively).

Compared with CHASE-AF, the Alster-Lost-AF stepwise approach used a more extensive linear ablation approach. In CHASE-AF, only 22 of 75 patients (29%) randomized to full defragmentation received linear ablation, and only 12 (16%) of these patients were treated with a mitral isthmus line or an anterior line. In the remaining patients, only conduction block along a roof line or across the CTI was achieved. In our trial, a total of 28 patients in our Substrate-modification group (49%) underwent linear ablation in the LA with the creation of at least an anterior line or a mitral isthmus line after the failure of PVI and additional CFAE ablation.

Nevertheless, our study failed to demonstrate a clinical benefit for the patients in the Substrate-modification group. In our patient cohort, recurrence of atrial tachyarrhythmias was common (overall 44%), and a high proportion of patients (28% total) had to undergo repeat ablation procedures. In addition, we did not observe a difference in the clinical outcomes of patients with persistent and long-standing persistent AF.

One may wonder why additional substrate modification at the time of PVI fails to show additional clinical benefit. Surgical studies on the cut-and-sew maze technique[18] have shown that substrate modification at the time of (surgical) PVI almost always eliminates AF, including patients with persistent forms of AF. The difference between the surgical and the radiofrequency current ablation approach is that surgical PVI is permanent, whereas radiofrequency current–induced PVI at the index procedure is associated with a high likelihood of reconduction from the PVs to the LA through gaps in the circumferential ablation lines.[19] In this study, conduction gaps were found in 80% of patients undergoing repeat ablation, indicating that the development of conduction gaps along the ablation lines is the dominant mechanism of AF recurrence after radiofrequency current–induced PVI in both ablation strategies. Therefore, the demonstration of a potential long-term benefit of additional substrate modification at the time of PVI is prevented by the high reconduction rate through gaps in the PVI lines. The clinical value of substrate modification can only be assessed in the presence of durable PVI.

Types of Recurrent Atrial Tachyarrhythmia

In the 28 PVI-only patients with recurrences, AF was the predominant type of recurrent arrhythmia, with AT recurring in only 1 patient (4%). In contrast, AT was the recurrent arrhythmia in 42% of the 24 Substrate-modification patients with recurrences. The difference in the type of atrial arrhythmia recurrence after stand-alone PVI versus PVI plus substrate modification is explained by the different ablation techniques. It was well described in the original article by Haïssaguerre et al[15] introducing the stepwise approach that AT was the dominant arrhythmia during follow-up, occurring in 23 of 52 patients, with AF recurring in only 2 patients. This finding was confirmed in a more recent article by the same group,[16] with 72.7% of 150 patients requiring repeat procedures (36.5% for AF and 63.5% for AT). The high incidence of AT recurrence is because of the creation of extensive ablation within the LA and right atrium, creating incomplete lines of conduction block or scars, which then serve as the substrate for AT. In contrast, gaps in the circumferential ablation lines after stand-alone PVI lead to recurrence of AF but only rarely to gap-related ATs.

Procedural Characteristics

Our patients treated with the stepwise ablation approach had longer procedural durations, longer fluoroscopy durations, and thus a higher radiation exposure than patients undergoing stand-alone PVI; these findings corroborate previous trials comparing PVI to more extensive ablation strategies.[4,7,11]

Conversion of AF and Arrhythmia Recurrence

Several single-arm registries reported that conversion of AF (to SR or AT) during ablation impacted positively on long-term clinical success,[16,17,20–22] whereas others, including the randomized CHASE-AF trial, did not demonstrate a beneficial impact of AF conversion.[11,15] In our analysis, conversion of AF was not associated with a superior clinical outcome. Of note, we observed only a modest rate (about 60%) of patients in whom AF terminated during ablation,[11] although most of the studies which document a positive influence of AF termination had a higher conversion rate (66%–84%).[16,20–22] Our low rate of AF termination might be explained by the high number of patients with long-standing persistent AF in our cohort because a long persistence of AF is considered a negative predictor for AF termination during ablation.[22]

Limitations

Ours is a single-center study. In retrospect, the study hypothesis of a 25% improvement by the substrate-modification approach in the 1-year primary outcome seems optimistic; we cannot exclude that a smaller improvement might be present. Contact force–sensing catheters were not used. The EFFICAS I and II studies (TactiCath Prospective Effectiveness) have shown a reduction in gap formation around the PVs when ablation was guided by contact force sensing,[23,24] but, to date, a randomized controlled trial showing better clinical outcomes associated with contact force–guided ablation is lacking. Follow-up did not use loop recorder systems. We therefore cannot exclude that asymptomatic episodes of AF have been missed. A relatively high proportion (40%) of our patients was on antiarrhythmic drug therapy at the end of follow-up. Although it seems unlikely that asymptomatic, paroxysmal arrhythmias have recurred unrecognized in a substantial number of patients and the prevalence of antiarrhythmic drug therapy throughout follow-up was not different between the study arms, true recurrence rates may have been higher than observed, but the difference between ablation strategies in recurrence rates would not have been affected.

Conclusions

In this study, additional CFAE and linear ablation at the time of initial PVI in patients with symptomatic persistent or long-standing persistent AF did not result in different 1-year clinical outcomes compared with stand-alone PVI, but was associated with longer ablation, procedure and fluoroscopy times, and higher radiation exposure. On the basis of our findings, and as long as durable PVI cannot be convincingly achieved at the time of the index ablation procedure, we feel that stand-alone PVI should be the primary ablative strategy for patients with persistent or long-standing persistent AF; subsequent linear ablation should only be performed in cases where clinical ATs require treatment. Future studies need to focus on the development and investigation of new strategies to achieve durable PVI by catheter ablation. Only then can randomized trials assess the clinical value of additional substrate modification.

Disclosures

Dr Kuck reports having received consulting fees/honoraria from Biosense Webster, Medtronic, Boston Scientific, and St. Jude Medical. Dr Metzner received speaker's honoraria from Medtronic. The other authors report no conflicts.

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Stand-Alone Pulmonary Vein Isolation Versus Pulmonary Vein Isolation With Additional Substrate Modification as Index Ablation Procedures in Patients With Persistent and Long-Standing Persistent Atrial Fibrillation: The Randomized Alster-Lost-AF Trial (Ablation at St. Georg Hospital for Long-Standing Persistent Atrial Fibrillation)

Thomas Fink, Michael Schlüter, Christian-Hendrik Heeger, Christine Lemes, Tilman Maurer, Bruno Reissmann, Johannes Riedl, Laura Rottner, Francesco Santoro, Boris Schmidt, Peter Wohlmuth, Shibu Mathew, Christian Sohns, Feifan Ouyang, Andreas Metzner and Karl-Heinz Kuck

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