Original Article

Is There Still a Role for Complex Fractionated Atrial Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and Persistent Atrial Fibrillation?

Meta-Analysis of 1415 Patients

Rui Providência, MD, MSc; Pier D. Lambiase, PhD; Neil Srinivasan, MD; Girish Ganesh Babu, MD; Konstantinos Bronis, MD; Syed Ahsan, MD; Fakhar Z. Khan, MD; Anthony W. Chow, MD; Edward Rowland, MD; Martin Lowe, MD, PhD; Oliver R. Segal, MD

Background—Ablation of complex fractionated atrial electrograms (CFAEs) has been proposed as a strategy to improve outcomes in atrial fibrillation (AF) catheter ablation, but the use of this technique remains contentious. We aimed to assess the impact of CFAE ablation in addition to pulmonary vein isolation (PVI) in patients undergoing ablation for AF.

Methods and Results—We performed a random effects meta-analysis of studies comparing PVI versus PVI+CFAE ablation. The outcomes of freedom from AF/atrial tachycardia after 1 or several ablation procedures and acute procedural–related complications were assessed. Studies were searched on MEDLINE, EMBASE, COCHRANE, and clinicaltrials.gov, and sensitivity analyses were performed. Thirteen studies including a total of 1415 patients were considered eligible. Additional ablation of CFAEs resulted in no improvement in mid-term procedural outcome or freedom from AF or atrial tachycardia (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.58–1.10; *P*=0.17). Sensitivity analysis of 398 paroxysmal AF ablation procedures showed no incremental benefit of CFAE ablation (OR, 0.80; 95% CI, 0.46–1.38; *P*=0.42). PVI+CFAE ablation versus PVI alone did not improve the overall rate of freedom from AF or atrial tachycardia in patients with persistent AF (OR, 1.01; 95% CI, 0.63–1.64; *P*=0.96) or longstanding persistent AF (OR, 0.84; 95% CI, 0.24–2.96; *P*=0.79). There was no increase in procedural-related adverse events (OR, 1.06; 95% CI, 0.41–2.75; *P*=0.91).

Conclusions—Despite the apparent safety of this technique, CFAE ablation did not improve freedom from AF/atrial tachycardia in patients with paroxysmal or persistent AF. The role of CFAE ablation in addition to PVI should be questioned and other alternatives assessed to improve the outcome of AF ablation. **(*Circ Arrhythm Electrophysiol*. 2015;8:1017-1029. DOI: 10.1161/CIRCEP.115.003019.)**

Key Words: atrial fibrillation ■ catheter ablation ■ electrophysiology ■ pulmonary veins ■ tachycardia

Catheter ablation is now an established treatment for patients with symptomatic drug-refractory atrial fibrillation (AF; class I, level of evidence A).[1,2]

Editorial see p 999

After the seminal work of Haïssaguerre et al[3] demonstrating that AF could be triggered by pulmonary ectopy, strategies targeting the pulmonary veins have become the cornerstone for AF catheter ablation procedures.[4]

However, those studies also showed that relapses occur in ≤30% of paroxysmal AF patients in the first year and 70% of patients with persistent AF even when all the pulmonary veins are successfully isolated.[5] The focus has subsequently shifted to targeting areas of abnormal left atrial tissue which may act as a substrate for sustaining AF episodes in addition to pulmonary vein isolation. Complex fractionated atrial electrograms (CFAEs) have emerged as one of the possible sources for sustaining AF and CFAE ablation has become a widespread adjuvant strategy in ablation.[6]

Despite joint Heart Rhythm Society, European Heart Rhythm Association and European Cardiac Arrhythmia Society Consensus recommendations endorsing more extensive ablation for persistent AF, including targeting CFAEs±linear ablation,[4] evidence to support the incremental benefit of CFAE ablation remains largely absent.[7,8] This meta-analysis aims to assess the impact of additional CFAE ablation in patients undergoing pulmonary vein isolation (PVI) for ablation of AF.

Received March 24, 2015; accepted June 5, 2015.

From the Department of Electrophysiology, The Heart Hospital and Institute of Cardiovascular Sciences, University College London, London, United Kingdom.

The Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.115.003019/-/DC1.

Correspondence to Oliver R. Segal, MD, Department of Electrophysiology, The Heart Hospital, 16–18 Westmoreland St, London W1G 8PH, United Kingdom. E-mail oliver.segal@uclh.nhs.uk

WHAT IS KNOWN

- Complex fractionated atrial electrograms (CFAEs) have emerged as one of the possible sources for sustaining atrial fibrillation, and CFAE ablation has become a widespread adjuvant strategy in ablation.
- The impact of CFAE ablation in addition to pulmonary vein isolation in patients undergoing catheter ablation of atrial fibrillation is still controversial.

WHAT THE STUDY ADDS

- CFAE ablation seems to be safe.
- We failed to confirm the overall benefit of CFAE ablation in addition to pulmonary vein isolation.

Methods

Study Selection

We performed searches on MEDLINE (via PubMED), EMBASE, clinicaltrials.gov, and COCHRANE databases (from inception to November 30, 2014) using the following search string: AF and catheter ablation and (CFAE or complex fractionated atrial electrograms).

Reference lists of all accessed full-text articles were further searched for sources of potentially relevant information. The authors of full-text papers and congress abstract authors were also contacted by e-mail to retrieve additional information.

Only longitudinal studies performed in humans were considered for inclusion. The population, intervention, comparison and outcome (PICO) approach was used.[9] The population of interest included patients with AF and the intervention was catheter ablation of AF, consisting of PVI and optional CFAE ablation. Comparisons were performed between patients receiving PVI versus PVI plus CFAE ablation. The outcomes were freedom from AF or atrial tachycardia (AT) recurrence; ablation-related complications.

Minimum follow-up duration was 6 months. Both registries and randomized trials were considered eligible for analysis. Empirical ablation of lines was allowed if this was performed as part of the ablation protocol in both treatment groups. The Methods section of evaluated studies was reviewed to confirm the suitability and composition of the reported end point.

To be eligible, studies needed to present matched control-groups and the only difference in the treatment strategy had to be performing CFAE ablation in 1 group and no CFAE ablation in the comparator. If other differences between treatment groups were observed in the study protocol (eg, use of different mapping or imaging systems; comparisons of patients with persistent AF converting to sinus rhythm while having their PVI versus patients remaining in AF after PVI), the study was not considered appropriate for inclusion. If at least 3 treatment groups were present in the study, and only 1 of them was considered inadequate, the study could still be considered eligible and data of the 2 appropriate treatment groups included. Full-text articles remaining unpublished >3 years after initial congress abstract presentation were not considered appropriate for inclusion.

The definitions of AF or AT relapse, blanking period, and methods used for monitoring during follow-up were collected in all studies. The following events were considered ablation-related complications and their incidence in both treatment groups was assessed: cardiac tamponade or pericardial effusion requiring pericardiocentesis, stroke or transient ischemic attack, atrio-oesophageal fistula, and pulmonary vein stenosis.

Three independent reviewers (R.P., N.S., and G.B.) screened all abstracts and titles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated to determine the eligibility of the study for the review and meta-analysis. Agreement of at least 2 reviewers was required for decisions about inclusion or exclusion of studies. Study quality was formally evaluated using the Delphi Consensus criteria for randomized controlled trials[10] and a modified Newcastle–Ottawa Quality Assessment Scale for Cohort Studies[11] by 3 reviewers (R.P., N.S., and G.B.). An agreement between the 3 reviewers was mandatory for the final classification of studies.

Data extraction and presentation for the preparation of this article followed the recommendations of the PRISMA group.[12] The following data were extracted for characterizing each patient sample in the selected studies, whenever available: demographics and sample characterization, AF duration, presence of structural heart disease, atrial size, ablation technique and criteria for defining CFAE, location of ablated CFAE, follow-up duration, number of procedures, monitoring of AF relapse, and use of antiarrhythmic agents.

Statistical Analysis

Data were pooled using random effects, according to the Mantel–Haenszel model, through Review Manager (RevMan), version 5.1. (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2011). The odds ratio (OR) and respective 95% confidence interval (95% CI) were used as a measurement of treatment effect. Pairwise comparisons were performed for the end points: AF/AT relapse and ablation-related complications.

To assess study design–related factors potentially interfering with the results of the meta-analysis, several sensitivity analyses were performed to assess the impact of baseline differences in the population, study design, CFAE mapping and treatment approaches, and follow-up in the AT or AF relapse outcomes. Sensitivity analyses were only performed for conditions fulfilled by at least 2 studies and gathering at least 15% of the whole meta-analysis population.

Statistical heterogeneity on each outcome of interest was quantified using the I^2 statistic. The I^2 statistic describes the percentage of total variation across studies because of heterogeneity rather than chance. Values of <25%, 25% to 50%, and >50% are by convention classified low, moderate, and high degrees of heterogeneity, respectively.

Funnel plots and meta-regression analyses were obtained using Comprehensive Meta-Analysis software (version 2). Funnel plots were used for evaluating the presence of publication bias and traced for comparisons including >10 studies (minimum number for assuring the appropriateness of the method).[13] A meta-regression (using the unrestricted maximum likelihood method) was performed for comparisons involving >10 studies for assessing the possible association of modulator variables with the end point AF or AT relapse.

Heterogeneity-adjusted trial sequential analysis was applied to the meta-analysis to reduce the risk of random error because of repetitive testing of accumulating data.[14] The optimal information size with adaptation of monitoring boundaries, and the cumulative Z statistics after each trial were assessed. This was based on an α significance level of 5% and a β of 20% (80% power), an expected reduction in AT or AF relapse of 30% and a 50% increase in complications, the observed incidence rate in the control group, and the variation across trials (I^2).

Results

Search Results

A total of 398 entries were retrieved for analysis of titles and abstracts. Of these, 374 were excluded as they were either duplicates or deemed unsuitable for the purpose of our meta-analysis (editorials, letters, reviews, or case reports). The remaining 24 results were carefully screened, and after analysis of their full-text, only 8 were considered adequate for the purpose of our meta-analysis.[7,15–21] A careful review of their reference list provided 4 more entries that were selected after revision of the full text.[22–25] Manual searches also provided 1 last entry, a randomized controlled trial recently published in a Hot-Line Session at a major cardiovascular meeting.[8] The selection process is illustrated in Figure 1. There was an excellent agreement between investigators on the inclusion of the selected trials.

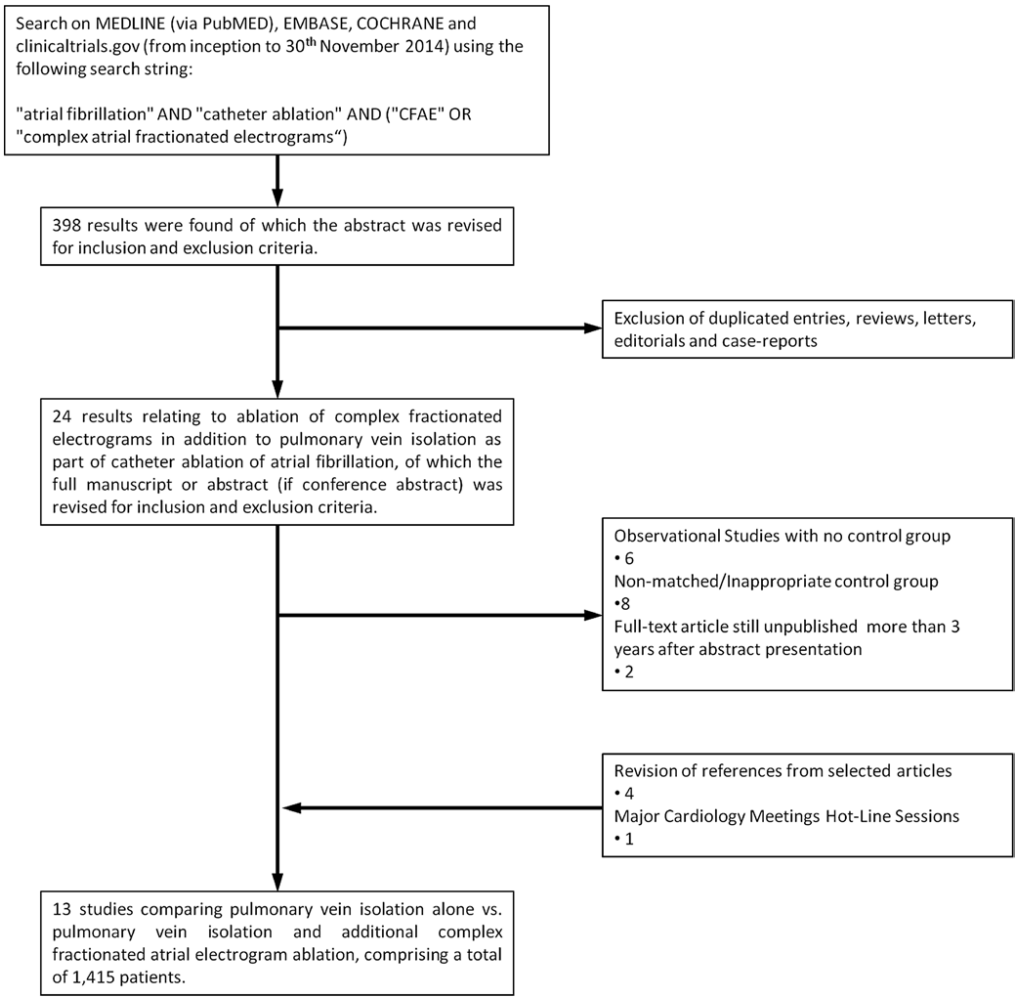


Figure 1. Flowchart diagram illustrating study selection methodology.

Baseline data and the design of selected trials are summarized in Tables 1 and 2. The final population for this meta-analysis included 1415 patients (815 treated with PVI+CFAE ablation and 600 with PVI).

Nine studies were randomized controlled trials.[7,8,17,19–24] Of the 5 multicenter trials,[7,8,16,17,22] only 1[16] was nonrandomized. Quality assessment of the included studies is shown in Table I in the Data Supplement. Two randomized controlled studies had ≥6 Delphi criteria[7,8] and all cohort studies had a Newcastle–Ottawa score of ≥7.

Treatment groups were balanced at baseline (Table 1). Most studies had small patient samples, usually <100 participants. The percentage of persistent AF patients markedly differed between studies. In most studies, patients were in their fifties and AF had been diagnosed <5 to 6 years before ablation. In 1 study, the mean left atrium (LA) size was in the normal range,[20] whereas in the remainder a mild to moderate LA dilation was observed. In all studies, LA size was characterized according to a single linear dimension (diameter). Eligibility/patient selection criteria for each study are illustrated in Table 2.

CFAE definition and the approach used for CFAE mapping and ablation in each trial are presented in Table 2 and Table II in the Data Supplement. Some studies used automatic algorithms incorporated into 3-dimensional mapping systems,[7,8,16,18,20,24] whereas others relied on operator-guided analysis of electrograms.[15,17,19,21–23,25]

Data about outpatient treatment, relapse definition, and follow-up in the different studies are shown in Table 3. Mean follow-up duration was >12 months in the majority of studies. Most studies relied on clinical appointments, 12-lead ECG, and 24- or 48-hour Holter monitors for follow-up purposes. Some studies used external loop recorders[7,15–19,22,23] or transtelephonic monitoring.[7,8,21,24] Interrogation of existing cardiac devices was used in 3 studies,[7,16,22] but implantable loop recorders were not used routinely in any of the studies. During follow-up, patients underwent a mean of 1 to 1.4 ablation procedures.

Role of Additional CFAE Ablation and Outcomes

The pooled data of studies comparing PVI alone versus PVI+CFAE ablation showed a lack of significant benefit in favor of any treatment strategy in terms of freedom from AF or AT (PVI=29.7% versus PVI+CFAE=31.3%; OR, 0.80; 95% CI, 0.58–1.10; *P*=0.17). Only 2 studies showed benefits of the PVI+CFAE ablation strategy,[7,25] whereas the remainder were neutral (Figure 2A). While in Nam et al[25] data on AF duration was not provided and only persistent AF patients were treated, the Substrate and Trigger Ablation for Reduction of

Table 1. Selected Studies for the Systematic Review: Baseline Information

Author	Study Design, Acronym	Sample Size, Pts		Persistent AF		Age		Women		AF Duration, Y		LA Size, mm		LA Size, mm		Structural Heart Disease	
		PVI	PVI+CFAE	PVI	PVI+CFAE	PVI	PVI+CFAE	PVI	PVI+CFAE	PVI	PVI+CFAE	PVI	PVI+CFAE	PVI	PVI+CFAE	PVI	PVI+CFAE
Verma et al[15]	Single-center cohort	100	100	40%	40%	57±12	56±9	37%	37%	5.3±3.0	5.1±2.0	42±9	43±10	53±12	53±11	31%	34%
Elayi et al[22]	Multicenter RCT	48	49	100%	100%	58±10	59±11	31%	35%	5.5±3.5	6.3±2.5	45±7	46±6	52	55	46%	47%
Verma et al[16]	Multicenter cohort	35	35	40%	40%	60	61	23%	26%	4.9±4.5	5.5±4.0	43±9	41±10	53±8	53±7	29%	34%
Deisenhofer et al[23]	Single-center RCT	48	50	0%	0%	58±10	55±10	31%	18%	4±3	4±4	43±6	44±5	*	*	58%	68%
Di Biasi et al[17]	Multicenter RCT	35	34	0%	0%	57±8	58±8	17%	12%	5.3±5.7	5.3±5	43±6	44±6	55±8	55±6	…	…
Lin et al[18]	Single-center cohort	30	30	100%	100%	49±12	49±10	13%	20%	5.4±6.4	8.4±7.2	40±5	41±8	56±8	54±8	23%	17%
Oral et al[19]	Single-center RCT	50	50	100%	100%	58±10	62±8	18%	18%	6±5	5±4	47±6	46±6	53±12	54±9	72%	74%
Verma et al[7] STAR-AF	Multicenter RCT	32	34	34%	35%	55±11	59±10	25%	26%	6.4±6.6	7.6±9.4	43±5	41±6	62±7	59±12	NA	NA
Chen et al[20]	Single-center RCT with crossover	35	58	0%	0%	52±13	56±11	29%	33%	4.4±1.9	4.3±3.9	35±4	34±4	66±4	64±3	5%†	3%
Dixit et al[24] RASTA	Single-center RCT	55	51	100%	100%	59±8	60±9	13%	10%	4.7±5.4	3.6±3.3	48±7	49±8	56±9	56±14	…	…
Nam et al[25]	Prospective single-center cohort	35	35	0%	0%	51±11	54±11	14%	14%	…	…	40±5	40±5	61±5	59±6	…	…
Nürich et al[21]	Single-center RCT	33	35	0%	0%	59±2	63±2	39%	37%	3.0	4.0	40±1	40±1	67±1	68±1	6%†	9%
Verma et al[8] STAR-AF 2	Multicenter RCT	64	254	100%	100%	58±10	60±9	22%	18%	4.3±6.3	4.2±5.0	44±6	44±6	55±11	57±10	…	…

AF indicates atrial fibrillation; CFAE, complex fractionated atrial electrograms; LA, left atrium; LV, left ventricle; NA, not available; PVI, pulmonary vein isolation; Pts, patients; RCT, randomized controlled trial; and STAR-AF, Substrate and Trigger Ablation for Reduction of Atrial Fibrillation.

*LV ejection fraction <35% was an exclusion criterion.

†Only history of coronary artery disease. Most patients with structural heart disease were excluded.

Atrial Fibrillation (STAR AF)[7] study included patients with longer AF duration from diagnosis and also a third of patients had high-burden paroxysmal AF.

The incidence of severe complications was low, usually <1 to 1.5%. More extensive ablation did not lead to an increase in procedural complications (PVI=1.5% versus PVI+CFAE=1.5%; OR, 1.06; 95% CI, 0.41–2.75; *P*=0.91; Figure 2B).

The observed I^2 values showed moderate heterogeneity for freedom from AF/AT (I^2=32%). Conversely, heterogeneity of procedural complications was low (I^2=0%). Funnel plots (Figure I in the Data Supplement) for the 2 main end points do not suggest the presence of selection bias.

Figure 3A and 3B illustrates the necessary sample power to demonstrate a 30% reduction in AF or AT relapse and a 50% increase in complications in patients having CFAE ablation performed in addition to PVI. Despite failing to show a significant reduction in this end point, this meta-analysis was sufficiently powered to show a 30% reduction in AF or AT relapse using a more extensive ablation strategy (1011 patients needed). From a safety perspective, and despite the apparently reassuring data, a sample of 4891 patients would be required to statistically confirm that additional CFAE ablation does not lead to an increase in complications because of the low incidence of complications.

Sensitivity Analyses

Several scenarios were assessed to find specific subsets of patients or treatment approaches that could show the benefit of additional CFAE ablation in patients undergoing PVI (Table 4).

When separately pooling data on nonrandomized studies, benefit was found in favor of PVI+CFAE ablation with a statistically significant almost 50% lower likelihood of AF or AT relapse: PVI+CFAE=15.0% versus PVI=25.5%; OR, 0.52; 95% CI, 0.31 to 0.86; *P*=0.01.

A trend for a 38% reduction in relapses in patients undergoing PVI+CFAE ablation who also had empirical linear ablation (at least 1 of the following: mitral isthmus, left atrial roof, cavotricuspid isthmus, or superior vena cava isolation) was also observed: PVI+CFAE±linear ablation=14.6% versus PVI±linear ablation=14.6%; OR, 0.62; 95% CI, 0.37 to 1.03; *P*=0.07. Sensitivity analysis of the remaining studies (those without empirical linear ablation) revealed no benefit of CFAE ablation: PVI+CFAE=37.2% versus PVI=34.1%; OR, 0.87; 95% CI, 0.57 to 1.31; *P*=0.49. All remaining assessed scenarios demonstrated no clear benefit of CFAE ablation.

Meta-Regression: Assessment of Moderator Variables

The assessment of potential moderator variables through meta-regression is shown in Table III in the Data Supplement. A

Table 2. Selected Studies for the Systematic Review: Procedure Information

Author	Patient Selection	CFAE Mapping and Definition	CFAE Location % of PVI	Ablation Details (Lines+Imaging)
Verma et al[15]	Consecutive patients with drug-resistant AF referred for first ablation procedure vs matched controls treated in the previous 3 mo	AF induced if pts in SR. Mapping using the circular mapping catheter: (1) rapid atrial electrograms with a short cycle length (<120 ms) averaged over a 10-s period or (2) fractionated atrial electrograms composed of 2 deflections or more and perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-s recording period	LA septum and anterior wall CFAE ablated in 90% of pts PVI=100%	ICE-guided ablation SVC line
Elayi et al[22]	One hundred forty four consecutive pts with longstanding persistent and drug-resistant AF referred for first procedure of AF ablation	Mapping using the ablation catheter: (1) atrial electrograms with fractionation and composed of 2 deflections or more and with continuous activity of the baseline or (2) atrial electrograms with a cycle length ≤120 ms	LA, right atrium, and CS PVI=100%	CARTO or NavX mapping system SVC line (if PV-like potentials) CTI ablation line when an isthmus-dependent flutter was documented. Mapping and ablation was attempted if AF organized into AT
Verma et al[16]	Thirty-five consecutive patients with symptomatic drug-refractory AF, with no prior open-heart surgery and with LA <55 mm, undergoing a first catheter ablation procedure. Matched controls treated in the previous 6 mo	AF induced if pts in SR. CFAE mapping using the circular mapping and the ablation catheter. The NavX mapping system automated algorithm for CFAE mapping was used: regions with a mean CL <120 ms were defined as CFAE and were targeted for ablation	LA and CS PVI=100%	NavX mapping system If AF regularized to an atrial flutter/tachycardia, which did not terminate after all CFAE sites were ablated, the flutter/ tachycardia was electrically cardioverted without specifically targeting the flutter/tachycardia circuit/focus
Deisenhofer et al[23]	Pts with drug-resistant paroxysmal AF having ≥4 episodes per month and referred for a first ablation procedure	AF induced if pts in SR. Mapping with ablation catheter: (1) atrial electrograms with fractionated electrograms composed of 2 deflections or more, and perturbation of baseline with continuous deflection of a prolonged activation complex over a 10-s recording period, or (2) atrial electrograms with a short cycle length (120 ms) averaged over a 10-s recording period	LA, right atrium, and CS CFAE ablated in only 60% of pts PVI=98% (both treatment arms)	CARTO mapping system Additional lines in the LA if AF organized into AT
Di Biasi et al[17]	Pts with drug resistant paroxysmal AF diagnosed for ≥1 y, referred for a first ablation procedure and presenting with spontaneous AF in the laboratory	If AF terminated before CFAE ablation or before all CFAEs were ablated, induction of AF was performed. Mapping with ablation catheter: (1) atrial electrograms with 2 deflections or more or with fractionated baseline complexes with continuous activity over a 10-second recording time or (2) atrial electrograms with a cycle length ≤120 ms over a 10-s recording period	Left and the right atrium, including the CS PVI=100%	CARTO or NavX mapping system SVC line (if PV-like potentials) When AF organized into AT, an attempt to map and terminate the AT during ablation was performed
Lin et al[18]	Sixty consecutive pts with drug-resistant nonparoxysmal AF referred for a first AF ablation procedure. Controls were ablated before the availability of the automatic algorithm.	CFAE mapping using the ablation catheter. The NavX mapping system automated algorithm for CFAE mapping was used. Only continuous CFAEs were ablated and were defined as: continuous CFAEs (>8 s) by an averaged fractionated interval of <50 ms over a 5-s recording period	LA and proximal CS PVI=100%	NavX mapping system Linear ablation of the LA roof, mitral isthmus and CTI When AF organized into AT, an attempt to map and terminate the AT during ablation was performed Focal AT or sites of atrial ectopics were mapped and ablated (the SVC was ablated if these arose from that structure)

(*Continued*)

Table 2. Continued

Author	Patient Selection	CFAE Mapping and Definition	CFAE Location % of PVI	Ablation Details (Lines+Imaging)
Oral et al[19]	Pts with longstanding persistent AF referred for a first AF ablation procedure	If AF terminated after pulmonary vein isolation, pts were not randomized to 1 of the 2 strategies and therefore were not included in this meta-analysis. Mapping with ablation catheter: (1) electrograms with a cycle length ≤120 ms or shorter than the AF cycle length in the coronary sinus, or (2) fractionated electrograms or displayed continuous electric activity	LA and CS PVI=100%	CARTO mapping system Linear ablation in the LA or RA not performed
Verma et al[7]	Pts with drug-refractory, high-burden paroxysmal (episodes >6 h, >4 in 6 mo) or persistent AF undergoing a first catheter ablation procedure	AF induced if pts in SR. CFAE mapping using a circular mapping and ablation catheter. The NavX automated algorithm for CFAE mapping was used: regions with mean CL <120 ms defined as CFAE and were targeted for ablation	LA, RA and CS PVI=94% (both treatment arms)	NavX mapping system If AF regularized to an AT or flutter, which did not terminate after all CFAE sites were ablated, the tachycardia was mapped and ablated or cardioverted electrically at the discretion of the investigator
Chen et al[20]	Pts with drug-refractory paroxysmal AF and self-terminating episodes lasting <7 days and occurring in the 6 mo before the procedure	AF induced if pts in SR. CFAE mapping using the ablation catheter. The NavX automatic algorithm for CFAE mapping was used: Regions with a mean CL <120 ms were defined as CFAE and were targeted for ablation	LA and CS PVI=100% of PVI+CFAE group 98% of PVI group	NavX mapping system All AT or flutters that occurred spontaneously or were induced were mapped and ablated accordingly
Dixit et al[24]	Pts >30 y old with drug-refractory persistent AF referred for a first procedure of AF ablation	AF induced if pts in SR. CFAE mapping using a circular mapping and ablation catheter (NavX) or the ablation catheter (CARTO). The NavX and CARTO automated algorithms for CFAE mapping were used: CFAEs considered present when mean FI <120 ms	LA PVI=100%	CARTO or NavX mapping system CTI-line if typical atrial flutter was known or induced If AF regularized to an AT or flutter, the tachycardia was mapped and ablated
Nam et al[25]	Pts with drug-refractory AF remaining inducible after PVI and nonrandomly assigned to 1 of 2 treatment arms	AF induced if pts in SR. CFAE mapping with ablation catheter. CFAEs defined visually as highly fractionated or continuous electrograms with little isoelectric baseline.	LA, RA and CS PVI=100%	NavX mapping system used in 71% of pts If AF regularized to an AT or flutter, the tachycardia was mapped and ablated
Nürich et al[21]	Pts with drug-refractory paroxysmal AF referred for first catheter ablation procedure and remaining in AF after PVI	CFAE mapping with ablation catheter. CFAEs were characterized as: (1) continuous electric activity without an interspersing isoelectric line, (2) high-frequency complex fractionated activity (multiple, high-frequency deflections of a single electrogram), (3) locally short AF cycle length or intermittent local burst activity, (4) activation gradient between the electrogram recorded by the distal bipole in relation to the proximal bipole of the ablation catheter and (5) local spreading of centrifugal activation	LA, RA and CS PVI=100%	CARTO or NavX mapping system Linear ablation was performed only in cases of conversion to AT with a macroreentrant mechanism
Verma et al[8]	Pts with drug-refractory persistent AF referred for first procedure of catheter ablation. Exclusion criteria: sustained AF episode >3 y and LA diameter >60 mm	CFAE mapping using a circular mapping and ablation catheter. The NavX automated algorithm for CFAE mapping was used: regions with mean CL <120 ms defined as CFAE and targeted for ablation	LA, RA, and CS PVI=97% (both treatment arms)	NavX mapping system If AF regularized to an AT or flutter, which did not terminate after all CFAE sites were ablated, the tachycardia was mapped and ablated or cardioverted electrically at the discretion of the investigator

AF indicates atrial fibrillation; AT, atrial tachycardia; CARTO, CARTO mapping system (Biosense-Webster, Diamond Bar, CA); CFAE, complex fractionated atrial electrograms; CL, cycle length; CS, coronary sinus; CTI, cavotricuspid isthmus; FI, fractionated interval; ICE, intracardiac echo; LA, left atrium; NavX, EnSite NavX Navigation and Visualization Technology (St Jude Medical, Austin, TX); PV, pulmonary vein; PVI, pulmonary vein isolation; Pts, patients; RA, right atrium; RCT, randomized controlled trial; SR, sinus rhythm; and SVC, superior vena cava.

Table 3. Selected Studies for the Systematic Review: Follow-Up Data and Study Assessment

Author	Follow-Up Duration	No. of Ablation Procedures per Patient	Blanking Period Duration	Use of AAD	Definition of Relapse	Monitoring During Follow-Up
Verma et al[15]	12 mo	1	2 mo	Only in the first 2 mo	AF or atypical AFL occurring beyond 2 mo post procedure	Rhythm transmitters in the first 3 mo; appointments, 12-lead ECG and 48-h Holter monitor at 3, 6, and 12 mo
Elayi et al[22]	16±1 mo	1.2	2 mo	Only in the first 2 mo or if relapse. Amiodarone: never	AF/AT lasting >1 min occurring after the 2-mo blanking period	Event recorder used 4 times a wk in the first 6 mo; outpatient visits, 12-lead ECG and 48-h Holter at 3, 6, 9, 12, and 15 mo Device interrogation in patients with implanted devices
Verma et al[16]	13±4 mo	1	2 mo	Only in the first 2 mo	AF/AT recurrence >2 mo postablation off antiarrhythmic medication	ECG, 48-h Holter recording and clinical appointment 3, 6, and 12 mo post ablation; external loop recorders (>2 wk) if symptoms; interrogation of implanted devices
Deisenhofer et al[23]	19±8 mo	1.3	3 mo	Only β-blockers were allowed	AF/AT >30-s duration on a 7-d Holter ECG 3 mo after the procedure or symptomatic AF/AT≥3 mo after ablation	Appointments every 3 mo; 24-h Holter 1 mo after the procedure; 7-d Holter ECG 3 mo after the procedure
Di Biasi et al[17]	14±2 mo	1.1	2 mo	Only in the first 2 mo or if relapse	Episodes of AF/AT with or without AADs lasting >1 min occurring beyond the blanking period	Appointments every 3 mo; event recorder used 4 times a week in the first 5 mo; 24-h Holter at 3, 6, 9, 12, and 15 mo after the procedure
Lin et al[18]	19±11 mo*	1.4*	2 mo	Allowed in the first 8 wk after the procedure	AF/AT episode lasting >1 min and confirmed by ECG, occurring >2 mo after ablation	Appointment and ECG at 2 wk and then every 1–3 mo for at least 1–2 y; 24-h Holter monitoring and 7-d cardiac event recording if symptoms suggestive of tachycardia
Oral et al[19]	Single procedure 10±3 mo repeat procedure 9±4 mo after last ablation	1.4	12 wk	For 8–12 wk if already being previously treated	Any episode of AF/AT ≥30 s in duration beyond 12 wk after ablation	Appointment at 3 mo and then every 3 or 6 mo; 30-d autotriggered event monitor at 6 mo; Pts contacted the clinical coordinator if symptoms of AF/AT
Verma et al[8]	12 mo	1.2	3 mo	Allowed in the first 2 mo after the procedure	Any episode of AF/AT lasting >30-s (symptomatic or asymptomatic)	ECG, 48-h Holter recording, and clinical appointment 3, 6, and 12 mo post ablation; monthly telephone interviews; external loop recorders (>2 wk) and transtelephonic monitors if symptoms; interrogation of implanted devices
Chen et al[20]	23±6 mo	1	3 mo	All pts treated with AADs in first 3 mo	Any episode of AT >30 s, as detected by ECG or Holter monitor, occurring after the blanking period was considered a recurrence	ECG and 48-h Holter monitor performed 3 days after the procedure and repeated at 1, 3, 6, and 12 mo; Pts contacted the clinical coordinator if symptoms of AF/AT
Dixit et al[24]	22±9 mo	1.4	6 wk	AADs discontinued 3–6 mo after ablation if no relapse	Any symptomatic or asymptomatic AF or AT episode lasted for >30 s	ECG, clinical appointment +30 day transtelephonic monitoring at 6 wk, 6 and 12 mo, or more often if suggestive symptoms; telephonic contact every 3 mo after the first year
Nam et al[25]	24±12 mo	1.1	3 mo	Reinitiated if symptomatic AF recurred after the procedure	ECG recorded AF or AFL occurring after the blanking period	Monthly clinical appointments and ECG until the third month, and every 3 mo thereafter; 24-h Holter every 6 mo; additional ECGs during crisis if symptomatic
Nürich et al[21]	21±1 mo	1.3	3 mo	AADs discontinued 1–3 mo after ablation	Any AT >30 s after the blanking period of 3 mo	Regular appointments and 24-h Holter every 1 to 3 mo; if symptoms, an additional tele-ECG recording was obtained
Verma et al[8]	18 mo	1.3	3 mo	Pts could be treated with AADs in the first 3 mo after the procedure	Any AF or AT >30 s after a blanking period of 3 mo	12-lead ECG, 24-h Holter monitor, and clinical appointments at 3, 6, 9, 12, and 18 mo; transtelephonic ECG monitor used if symptoms

AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; and pts, patients.

*Three pts in the pulmonary vein isolation (PVI) group had complex fractionated atrial electrogram (CFAE) ablation performed in a repeat procedure. Also, follow-up duration was longer in PVI (27±9 mo) vs PVI+CFAE (10±7 mo).

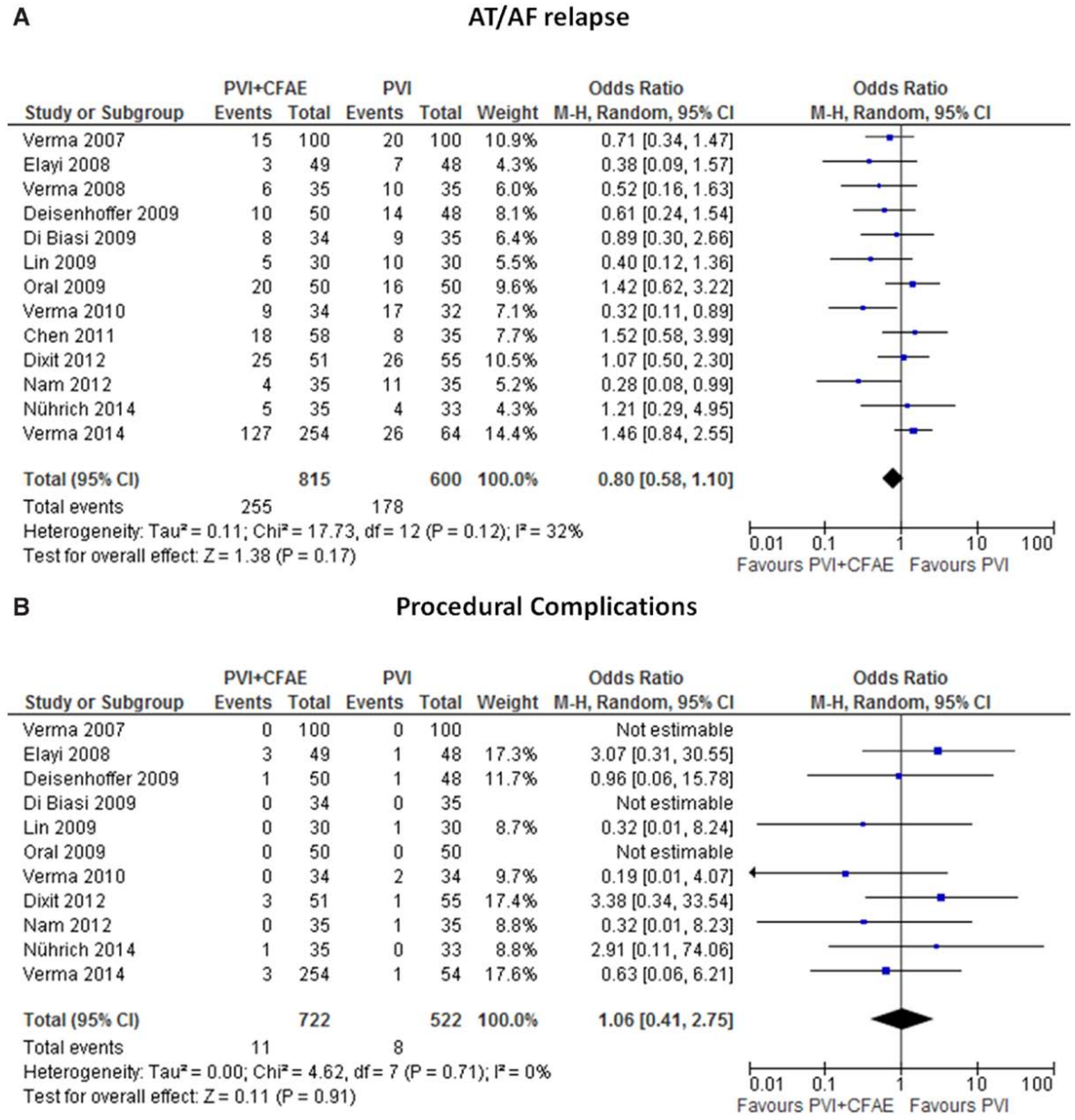


Figure 2. Forest plots comparing pulmonary vein isolation (PVI) vs PVI+complex fractionated atrial electrogram (CFAE) ablation about atrial tachycardia (AT)/atrial fibrillation (AF) relapse and procedural complications. **A**, AT/AF relapse. **B**, Procedural complications. CI indicates confidence interval.

moderate association was found between longer duration AF (years since diagnosis) and greater clinical benefit from CFAE ablation performed in addition to PVI (r=0.38, Model Q=6.94, df=1, P=0.008; Figure 4). No other variables were associated with procedural outcomes.

Discussion

Two main conclusions can be drawn from this meta-analysis: (1) pooled results failed to confirm the overall benefit of CFAE ablation in addition to PVI in patients undergoing catheter ablation of AF; (2) CFAE ablation was associated with a low incidence of adverse effects, comparable with PVI alone, with the caveat that this meta-analysis was not sufficiently powered to definitively infer this.

Increasing evidence suggests that PVI with durable lesion formation (either using contact-force sensing catheters or the cryoballoon) seems to be a key in paroxysmal AF ablation, with success rates (freedom from AT or AF after a blanking period) of >80% at 12 months.[26] However, ablation of persistent AF still remains a challenge. A recent multicenter randomized controlled trial showed that catheter ablation was more effective than drug therapy as a rhythm control strategy, but almost 40% of patients presented with AF or AT relapses in the first 12 months.[27] In this trial, CFAE or linear ablation could be performed at the operators' discretion. We think this means there is considerable scope for improvement in overall success rates for persistent AF ablation.

Why Is CFAE Ablation of No Benefit?

There are several explanations for the observed lack of benefit of additional CFAE ablation.

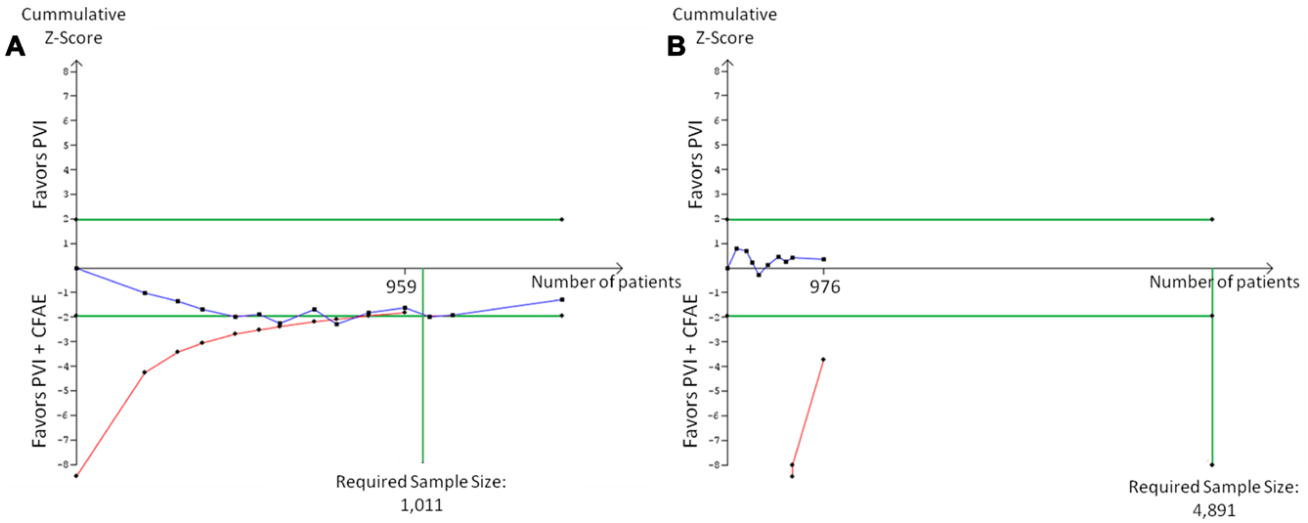


Figure 3. Heterogeneity-adjusted trial sequential analysis with estimation of optimal information size cumulative *Z*-statistics after each trial for (**A**) 30% reduction in atrial tachycardia/atrial fibrillation relapse and (**B**) 50% increase in procedural complications. The blue line is the *Z* curve; horizontal green lines highlight *Z* values of 1.96 and −1.96. The red line illustrates the O'Brien–Fleming boundaries. The vertical green line marks the required sample size.

Table 4. Sensitivity Analyses About AT/AF Relapse in Patients Undergoing Catheter Ablation of AF

Sensitivity Analysis	AF/AT relapse		OR	95% CI	*P* Value	Heterogeneity Analysis (I^2)
	PVI	PVI+CFAE				
Only patients with paroxysmal AF	24.7% (46/186)	21.2% (45/212)	0.80	0.46–1.38	0.42	20%
Only patients with persistent AF	34.4% (85/247)	41.5% (180/434)	1.01	0.63–1.64	0.96	35%
Only longstanding persistent AF	23.2% (23/99)	23.5% (23/98)	0.84	0.24–2.96	0.79	59%
Only single-center studies	28.2% (109/386)	24.9% (102/409)	0.84	0.58–1.22	0.37	19%
Only multicenter studies	32.2% (69/214)	37.7% (153/406)	0.68	0.35–1.33	0.26	56%
Only randomized controlled studies	32.6% (119/365)	37.2% (207/557)	0.91	0.61–1.34	0.62	32%
Only cohort studies	25.5% (51/200)	15.0% (30/200)	0.52	0.31–0.86	0.01	0%
Randomized controlled studies with Delphi criteria ≥6	44.8% (43/96)	47.2% (136/288)	0.73	0.16–3.23	0.67	85%
Only using the NavX mapping system	36.2% (71/196)	40.1% (165/411)	0.75	0.38–1.48	0.40	62%
When either NavX or CARTO mapping systems used in same study	26.9% (46/171)	24.3% (41/169)	0.90	0.53–1.54	0.71	0%
Studies without empirical additional ablation lines	34.1% (132/387)	37.2% (224/602)	0.87	0.57–1.31	0.49	44%
Studies with empirical additional ablation lines	21.6% (46/213)	14.6% (31/213)	0.62	0.37–1.03	0.07	0%
Studies using automated CFAE-mapping systems	38.6% (97/251)	41.1% (190/462)	0.82	0.48–1.41	0.47	53%
Studies where CFAEs were operator-defined	23.2% (81/349)	18.4% (65/353)	0.75	0.51–1.11	0.15	4%
Mapping with a circular mapping catheter±ablation catheter	34.6% (99/286)	38.4% (182/474)	0.80	0.47–1.34	0.39	52%
Mapping performed only with the ablation catheter	25.2% (79/314)	21.4% (73/341)	0.78	0.50–1.21	0.26	24%
Studies with CFAE mapping and ablation in both atria	29.8% (88/295)	33.8% (166/491)	0.67	0.38–1.16	0.15	50%
Studies with CFAE ablation only in the left atrium or CS	29.5% (90/305)	27.5% (89/324)	0.91	0.62–1.34	0.63	9%
Studies using 8-mm ablation catheters	29.7% (46/155)	26.5% (40/151)	0.86	0.51–1.47	0.59	0%
Studies using only 3.5- to 4-mm irrigated catheters	29.7% (132/445)	32.4% (215/664)	0.76	0.51–1.13	0.17	42%
Studies allowing Class I and III AADs during the blanking period	29.6% (153/517)	33.0% (241/730)	0.88	0.63–1.22	0.44	28%
Relapse defined as >1-min AT/AF episode	23.0% (26/113)	14.2% (16/113)	0.55	0.27–1.12	0.10	0%
Relapse defined as >30-s AT/AF episode	35.0% (111/317)	40.2% (214/532)	1.03	0.69–1.53	0.89	33%
Use of external loop recorders or transtelephonic ECG monitoring	32.3% (129/399)	36.0% (212/589)	0.85	0.57–1.27	0.44	38%
No external loop recorders or transtelephonic ECG monitoring	24.4% (49/201)	19.0% (43/226)	0.68	0.38–1.21	0.19	27%

AADs indicates antiarrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; CI, confidence interval; CFAE, complex fractionated atrial electrograms; CS, coronary sinus; OR, odds ratio; and PVI, pulmonary vein isolation.

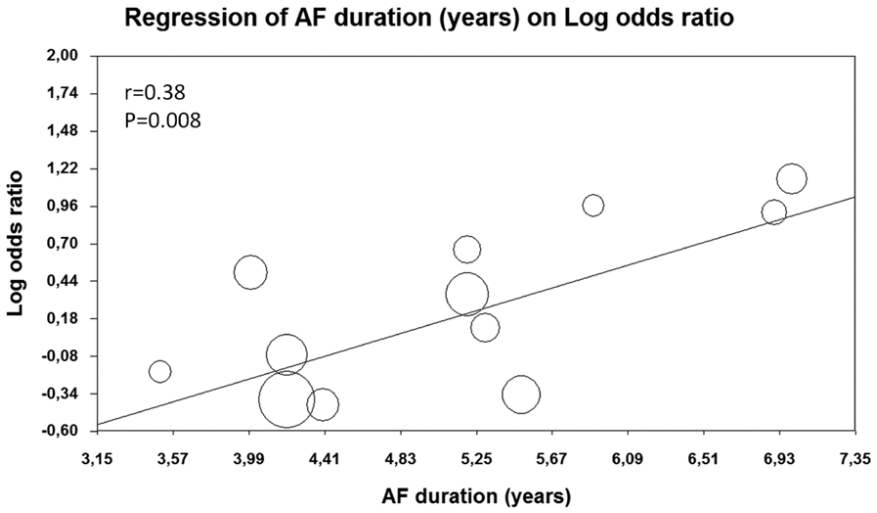


Figure 4. Meta-regression plot assessing the association of atrial fibrillation (AF) duration (years since diagnosis) with atrial tachycardia or AF relapse according to the used treatment strategy.

First, patients included in most studies often present with milder forms of AF (paroxysmal AF and recently diagnosed persistent AF), in which PVI alone by itself may be sufficient both in terms of treating triggers and reducing the critical mass of atrial tissue to maintain AF.[28] In most trials, the duration of AF episodes in persistent AF patients ranged from 7 days to >1 year. Such a broad definition is likely to include patients with different mechanisms and substrate for AF, and therefore likely variable potential for benefit from more extensive ablation strategies. Even though our meta-analyses lacked sufficient statistical power to confirm this hypothesis (only 2 studies[19,22] focused on patients with long-standing persistent AF and no subanalyses are available regarding the duration of AF episodes), there was a moderate association between AF duration and benefit of additional CFAE ablation, implying that the longer AF has persisted, the more atrial remodelling has occurred and the greater benefit may be accrued by CFAE ablation.

Second, data in this study suggest that CFAE mapping and ablation is performed in a highly heterogeneous manner in different centers with subjective interoperator variance in the targeting of CFAEs.[29] Centers may also treat different forms of AF in similar ways, for example, patients with long-standing persistent AF being offered PVI alone, similar to those with true PAF. It is possible, therefore, that we are simultaneously targeting different types of signals which play different roles in AF perpetuation. Even when automatic mapping systems are used, there are differences in their set up and algorithms for classifying fractionated electrograms (Table II in the Data Supplement) and this is even more heterogeneous and subjective in manually derived CFAE definitions with fractionation intervals ranging from <50 to <120 ms and with no consensus on how CFAE signals should be mapped/acquired. It has been shown, using a rigorously defined visual scale for assessing progressive degrees of fractionation, that not all types of atrial fractionated signals have the same influence in AF maintenance, and that targeting zones of continuous activity can lead to more pronounced increases in AF cycle length.[30] However, a consensus definition of CFAEs and which type of electrograms should be ablated are yet to be defined. Similarly, there is evidence that CFAEs may vary temporally and spatially,[31] and the timeframe over which CFAEs should be acquired is not defined and varies between studies. The type of catheters used and the contact force used is also variable without a standardized approach.

Third, it is still not known whether CFAEs represent areas of atrial myocardium critical to AF maintenance or simply areas of passive activation because of wavebreak. Thus, is CFAE ablation merely an exercise in atrial debulking or does it really hit the eye of the storm, removing critical elements involved in the triggering or sustaining AF and result in electric organization into re-entrant ATs and eventually sinus rhythm? It is possible that common locations for CFAEs (atrial septum, close to the pulmonary veins, and left atrial appendage) are coincidentally adjacent to parasympathetic ganglia[32] or that CFAE ablation causes AF termination just by chance. However, Hunter et al think that CFAE ablation is not merely debulking the atria and have proposed that grading CFAEs according to the degree of fractionation may be of importance, as not all CFAEs seem to play the same role in AF perpetuation.[30] The results of that study, and the recent SELECT-AF trial,[33] seem to show that selectively targeting areas of complex continuous fractionated electrograms may impact positively AF ablation results in the acute and midterm setting. However, this technique requires further investigation and confirmation from large randomized studies, especially in light of the results of this meta-analysis. Understanding the true mechanism of CFAEs is probably the only way to confirm the rationale to continue targeting them or a good reason to stop.

Despite the results of the present meta-analysis, it is intriguing that adjunctive CFAE ablation increases the chances of organization into AT or conversion to sinus rhythm.[19] Data also suggest that termination of persistent AF during catheter ablation is a predictor of long-term success.[34] It would therefore be expected that CFAE ablation in addition to PVI might result in better long-term outcomes. However, the seemingly helpful acute results of CFAE ablation are not borne out on long-term follow-up. It is possible that in failing to produce transmural lesions, gap formation and recovery occur, or that relapses are related to PVI reconnection rather than unsuccessful CFAE elimination. It is possible that contact force–sensing catheters may lead to an improvement in outcomes. These catheters have already shown to be effective in improving lesion formation[35] and the outcomes of paroxysmal AF

ablation.[36] Another explanation is that recurrence occurs because of progression of atrial disease, with development of further fibrosis and arrhythmogenic triggers leading to arrhythmia relapse requiring further ablation.

Is CFAE Ablation of Any Interest?

Evidence suggests that additional CFAE ablation leads to an increase in procedure duration (procedures last at least 1 hour longer).[8] On this basis, the results of this meta-analysis, probably it is not necessary to perform CFAE ablation in every patient undergoing AF ablation. CFAE ablation is, however, safe and should be considered in patients where a high likelihood of AF relapse is expected with PVI alone. Our data suggest that patients with longer AF duration may be most likely to benefit the most from more extensive ablation. Whether they should have additional CFAE ablation in addition to PVI or linear ablation using the step-wise Bordeaux approach[37] is unclear. Our data show a trend in favor of this approach, with CFAE ablation being apparently more beneficial if performed alongside PVI and lines, but this needs to be investigated in a randomized clinical trial.

Whether or not, performing CFAE ablation can be of benefit in patients with a more severe substrate or dilated left atria is still an open question. Data provided in the included studies did not allow us to perform a sensitivity analyses on this matter. On meta-regression, LA size (in mm) was not associated with procedural success. However, LA diameter is known to be an inappropriate and outdated method, and the current recommendations of the European Association of Echocardiography and American Society of Echocardiography support measuring LA biplane volume using either the area–length formula or the modified Simpson's rule as the preferred method for assessing LA size.[38] Therefore, it is still to be clarified if we found no association between a possible benefit of additional CFAE according to LA size simply because it does not exist or just because we have used an inexact way to assess the LA.

Role of Other Treatment Strategies

Targeting rotors,[39] ganglia,[40] or using other mapping algorithms based on electrograms, like dominant frequency[41] or different signal processing algorithms for accessing CFAEs,[42] needs to be ascertained.

In patients with advanced forms of AF, a combined treatment approach is required, targeting not only substrate and triggers but also optimization of medical therapy,[43] in a similar manner to the treatment of hypertension and heart failure with combination therapy, whereas addressing risk factors[44] and focusing on the correction of diseases triggering AF, such as sleep apnoea.

More studies are needed to address the questions raised by this meta-analysis. Four questions deserve special attention: (1) Do CFAEs play a role in the maintenance of AF? (2) What is the best method to detect and eliminate CFAEs? (3) Which patients benefit most from CFAE ablation (if any)? and (4) Are there more effective alternatives?

Limitations

Several limitations are commonly linked to the methodology of meta-analyses, principally heterogeneity between studies analyzed. In this case, however, heterogeneity, assessed through the I^2 test, was low for the pooled analysis of complications and low to moderate for AT or AF relapse. This supports the notion that the majority of the included studies share many commonalities. Also, to address this limitation, we assessed the modulating effect of baseline differences in the different study populations through meta-regression. Some other limitations should be highlighted. First, this meta-analysis was not sufficiently powered to show differences about complication rate. In spite of this, these initial data seem reassuring in this context. The observed low incidence of complications in both treatment groups implies studies of several thousand patients would be necessary to clearly demonstrate the safety of CFAE ablation. Second, only a minority of studies presented data allowing sensitivity analysis of patients with long-standing persistent AF. Therefore, we were not able to provide conclusive evidence of benefit of CFAE ablation in this group of patients, who are likely to be the subgroup to benefit most from this intervention. Third, overall study quality can be considered low, as only 2 randomized controlled trials with a Delphi score of ≥6 were identified and included for analysis. Fourth, the definition of CFAE varied widely among the different studies. This heterogeneity in methodology could have influenced the results of the analysis but likely reflects current real-world practice highlighting the lack of consensus on what a CFAE is. We attempted to assess this through a sensitivity analysis on visual inspection methods and automated algorithms (Table 4) and found no significant differences in these approaches. Finally, the CFAE ablation protocol (Table II in the Data Supplement) differed among studies. The extent of CFAE ablation may have a role in procedural outcomes and needs to be addressed further in a randomized study.

Conclusions

Although associated with a low incidence of adverse events, adjunctive CFAE ablation in patients undergoing PVI was not associated with an increase in the overall medium-term success rate of catheter ablation for paroxysmal or persistent AF.

Our data suggest a possible benefit of this intervention in patients with more advanced forms of AF (those with longer AF duration). However, this requires confirmation in randomized controlled trials.

Other alternatives should be assessed to improve the outcome of AF ablation.

Disclosures

None.

References

1. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation–developed with the special contribution of the European Heart Rhythm Association. *Europace*. 2012;14:1385–1413. doi: 10.1093/europace/eus305.

2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104. doi: 10.1161/CIR.0000000000000040.
3. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659–666. doi: 10.1056/NEJM199809033391003.
4. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 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. doi: 10.1093/europace/eus027.
5. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F Jr, Strickberger SA, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation*. 2002;105:1077–1081.
6. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol*. 2004;43:2044–2053. doi: 10.1016/j.jacc.2003.12.054.
7. Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, Torrecilla EG, Khaykin Y. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. *Eur Heart J*. 2010;31:1344–1356. doi: 10.1093/eurheartj/ehq041.
8. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372:1812–1822. doi: 10.1056/NEJMoa1408288.
9. Menzies D. Systematic reviews and meta-analyses. *Int J Tuberc Lung Dis*. 2011;15:582–593. doi: 10.5588/ijtld.10.0719.
10. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol*. 1998;51:1235–1241.
11. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed January 18, 2015.
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–9, W64.
13. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Accessed January 18, 2015.
14. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive–trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol*. 2009;38:287–298. doi: 10.1093/ije/dyn188.
15. Verma A, Patel D, Famy T, Martin DO, Burkhardt JD, Elayi SC, Lakkireddy D, Wazni O, Cummings J, Schweikert RA, Saliba W, Tchou PJ, Natale A. Efficacy of adjuvant anterior left atrial ablation during intracardiac echocardiography-guided pulmonary vein antrum isolation for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2007;18:151–156. doi: 10.1111/j.1540-8167.2006.00673.x.
16. Verma A, Novak P, Macle L, Whaley B, Beardsall M, Wulffhart Z, Khaykin Y. A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: acute effects on AF and efficacy as an adjuvant strategy. *Heart Rhythm*. 2008;5:198–205. doi: 10.1016/j.hrthm.2007.09.027.
17. Di Biase L, Elayi CS, Fahmy TS, Martin DO, Ching CK, Barrett C, Bai R, Patel D, Khaykin Y, Hongo R, Hao S, Beheiry S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Wang P, Al-Ahmad A, Arruda M, Themistoclakis S, Bonso A, Rossillo A, Raviele A, Schweikert RA, Burkhardt DJ, Natale A. Atrial fibrillation ablation strategies for paroxysmal patients: randomized comparison between different techniques. *Circ Arrhythm Electrophysiol*. 2009;2:113–119. doi: 10.1161/CIRCEP.108.798447.
18. Lin YJ, Tai CT, Chang SL, Lo LW, Tuan TC, Wongcharoen W, Udyavar AR, Hu YF, Chang CJ, Tsai WC, Kao T, Higa S, Chen SA. Efficacy of additional ablation of complex fractionated atrial electrograms for catheter ablation of nonparoxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2009;20:607–615.
19. Oral H, Chugh A, Yoshida K, Sarrazin JF, Kuhne M, Crawford T, Chalfoun N, Wells D, Boonyapisit W, Veerareddy S, Billakanty S, Wong WS, Good E, Jongnarangsin K, Pelosi F Jr, Bogun F, Morady F. 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;53:782–789. doi: 10.1016/j.jacc.2008.10.054.
20. Chen M, Yang B, Chen H, Ju W, Zhang F, Tse HF, Cao K. Randomized comparison between pulmonary vein antral isolation versus complex fractionated electrogram ablation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2011;22:973–981. doi: 10.1111/j.1540-8167.2011.02051.x.
21. Nührich JM, Steven D, Berner I, Rostock T, Hoffmann B, Servatius H, Sultan A, Lüker J, Treszl A, Wegscheider K, Willems S. Impact of biatrial defragmentation in patients with paroxysmal atrial fibrillation: results from a randomized prospective study. *Heart Rhythm*. 2014;11:1536–1542. doi: 10.1016/j.hrthm.2014.06.002.
22. Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, Hongo R, Hao S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Arruda M, Schweikert RA, Natale A. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. *Heart Rhythm*. 2008;5:1658–1664. doi: 10.1016/j.hrthm.2008.09.016.
23. Deisenhofer I, Estner H, Reents T, Fichtner S, Bauer A, Wu J, Kolb C, Zrenner B, Schmitt C, Hessling G. 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;20:514–521. doi: 10.1111/j.1540-8167.2008.01379.x.
24. Dixit S, Marchlinski FE, Lin D, Callans DJ, Bala R, Riley MP, Garcia FC, Hutchinson MD, Ratcliffe SJ, Cooper JM, Verdino RJ, Patel VV, Zado ES, Cash NR, Killian T, Tomson TT, Gerstenfeld EP. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. *Circ Arrhythm Electrophysiol*. 2012;5:287–294. doi: 10.1161/CIRCEP.111.966226.
25. Nam GB, Jin ES, Choi H, Song HG, Kim SH, Kim KH, Hwang ES, Park KM, Kim J, Rhee KS, Choi KJ, Kim YH. Effect of substrate modification in catheter ablation of paroxysmal atrial fibrillation: pulmonary vein isolation alone or with complex fractionated electrogram ablation. *Tex Heart Inst J*. 2012;39:372–379.
26. Jourda F, Providencia R, Marijon E, Bouzeman A, Hireche H, Khoueiry Z, Cardin C, Combes N, Combes S, Boveda S, Albenque JP. Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. *Europace*. 2015;17:225–231. doi: 10.1093/europace/euu215.
27. Mont L, Bisbal F, Hernández-Madrid A, Pérez-Castellano N, Viñolas X, Arenal A, Arribas F, Fernández-Lozano I, Bodegas A, Cobos A, Matía R, Pérez-Villacastín J, Guerra JM, Ávila P, López-Gil M, Castro V, Arana JI, Brugada J; SARA investigators. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J*. 2014;35:501–507. doi: 10.1093/eurheartj/eht457.
28. Garrey W. The nature of fibrillary contraction of the heart: its relation to tissue mass and form. *Am J Physiol*. 1914;33:397–414.
29. Scherr D, Dalal D, Cheema A, Cheng A, Henrikson CA, Spragg D, Marine JE, Berger RD, Calkins H, Dong J. Automated detection and characterization of complex fractionated atrial electrograms in human left atrium during atrial fibrillation. *Heart Rhythm*. 2007;4:1013–1020. doi: 10.1016/j.hrthm.2007.04.021.

30. Hunter RJ, Diab I, Tayebjee M, Richmond L, Sporton S, Earley MJ, Schilling RJ. Characterization of fractionated atrial electrograms critical for maintenance of atrial fibrillation: a randomized, controlled trial of ablation strategies (the CFAE AF trial). *Circ Arrhythm Electrophysiol*. 2011;4:622–629. doi: 10.1161/CIRCEP.111.962928.
31. Habel N, Znojkiewicz P, Thompson N, Müller JG, Mason B, Calame J, Calame S, Sharma S, Mirchandani G, Janks D, Bates J, Noori A, Karnbach A, Lustgarten DL, Sobel BE, Spector P. The temporal variability of dominant frequency and complex fractionated atrial electrograms constrains the validity of sequential mapping in human atrial fibrillation. *Heart Rhythm*. 2010;7:586–593. doi: 10.1016/j.hrthm.2010.01.010.
32. Nakagawa H, Scherlag BJ, Patterson E, Ikeda A, Lockwood D, Jackman WM. Pathophysiologic basis of autonomic ganglionated plexus ablation in patients with atrial fibrillation. *Heart Rhythm*. 2009;6(12 Suppl):S26–S34. doi: 10.1016/j.hrthm.2009.07.029.
33. Verma A, Sanders P, Champagne J, Macle L, Nair GM, Calkins H, Wilber DJ. Selective complex fractionated atrial electrograms targeting for atrial fibrillation study (SELECT AF): a multicenter, randomized trial. *Circ Arrhythm Electrophysiol*. 2014;7:55–62. doi: 10.1161/CIRCEP.113.000890.
34. Scherr D, Khairy P, Miyazaki S, Aurillac-Lavignolle V, Pascale P, Wilton SB, Ramoul K, Komatsu Y, Roten L, Jadidi A, Linton N, Pedersen M, Daly M, O'Neill M, Knecht S, Weerasooriya R, Rostock T, Manninger M, Cochet H, Shah AJ, Yeim S, Denis A, Derval N, Hocini M, Sacher F, Haissaguerre M, Jais P. 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. doi: 10.1161/CIRCEP.114.001943.
35. Squara F, Latcu DG, Massaad Y, Mahjoub M, Bun SS, Saoudi N. Contact force and force-time integral in atrial radiofrequency ablation predict transmurality of lesions. *Europace*. 2014;16:660–667. doi: 10.1093/europace/euu068.
36. Marijon E, Fazaa S, Narayanan K, Guy-Moyat B, Bouzeman A, Providencia R, Treguer F, Combes N, Bortone A, Boveda S, Combes S, Albenque JP. Real-time contact force sensing for pulmonary vein isolation in the setting of paroxysmal atrial fibrillation: procedural and 1-year results. *J Cardiovasc Electrophysiol*. 2014;25:130–137. doi: 10.1111/jce.12303.
37. Haïssaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clémenty J, Jaïs P. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *J Cardiovasc Electrophysiol*. 2005;16:1138–1147. doi: 10.1111/j.1540-8167.2005.00308.x.
38. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463. doi: 10.1016/j.echo.2005.10.005.
39. Pokushalov E, Romanov A, Artyomenko S, Turov A, Shugayev P, Shirokova N, Katritsis DG. Ganglionated plexi ablation for longstanding persistent atrial fibrillation. *Europace*. 2010;12:342–346. doi: 10.1093/europace/euq014.
40. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol*. 2012;60:628–636. doi: 10.1016/j.jacc.2012.05.022.
41. Lin YJ, Tsao HM, Chang SL, Lo LW, Hu YF, Chang CJ, Tsai WC, Suenari K, Huang SY, Chang HY, Wu TJ, Chen SA. Role of high dominant frequency sites in nonparoxysmal atrial fibrillation patients: insights from high-density frequency and fractionation mapping. *Heart Rhythm*. 2010;7:1255–1262. doi: 10.1016/j.hrthm.2010.06.019.
42. Lin YJ, Suenari K, Lo MT, Lin C, Hsieh WH, Chang SL, Lo LW, Hu YF, Cheng CC, Kihara Y, Chao TF, Hartono B, Wu TJ, Lin WS, Hsu KH, Kibos AS, Huang NE, Chen SA. Novel assessment of temporal variation in fractionated electrograms using histogram analysis of local fractionation interval in patients with persistent atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2012;5:949–956. doi: 10.1161/CIRCEP.111.967612.
43. Koskinas KC, Fragakis N, Katritsis D, Skeberis V, Vassilikos V. Ranolazine enhances the efficacy of amiodarone for conversion of recent-onset atrial fibrillation. *Europace*. 2014;16:973–979. doi: 10.1093/europace/eut407.
44. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64:2222–2231. doi: 10.1016/j.jacc.2014.09.028.

Circulation
Arrhythmia and Electrophysiology

Is There Still a Role for Complex Fractionated Atrial Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and Persistent Atrial Fibrillation?: Meta-Analysis of 1415 Patients

Rui Providência, Pier D. Lambiase, Neil Srinivasan, Girish Ganesh Babu, Konstantinos Bronis, Syed Ahsan, Fakhar Z. Khan, Anthony W. Chow, Edward Rowland, Martin Lowe and Oliver R. Segal

Circ Arrhythm Electrophysiol. 2015;8:1017-1029; originally published online June 16, 2015;
doi: 10.1161/CIRCEP.115.003019
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3149. Online ISSN: 1941-3084

Supplemental Material

S-Table 1 - Assessment of studies according to Delphi or Newcastle-Ottawa scale criteria included in the meta-analysis

Author, Ref	Study Classification	
	Delphi criteria	Newcastle–Ottawa Scale
Verma et al. 2007 [1]		7
Elayi et al. 2008 [2]	4	
Verma et al. 2008 [3]		7
Deisenhofer et al. 2009 [4]	4	
Di Biasi et al. 2009 [5]	5	
Lin et al. 2009 [6]		8
Oral et al. 2009 [7]	4	
Verma et al. 2010 [8]	6	
Chen et al. 2011 [9]	4	
Dixit et al. 2012 [10]	4	
Nam et al. 2012 [11]		8
Nürich et al. 2014 [12]	4	
Verma et al. 2014 [13]	7	

S-Table 2 - Data on automated complex fractionated atrial electrogram (CFAE) mapping systems and CFAE ablation protocol and parameters

Author, Ref	Automated CFAE mapping systems		CFAE ablation protocol
	Filters/Settings	CFAE Criteria	
Verma et al. 2007 [1]	-	-	8mm 70W 50℃ EGM elimination (<0.2mV)
Elayi et al. 2008 [2]	-	-	3.5mm irrigated 50W 41℃ CFAE ablation guided by visual inspection
Verma et al. 2008 [3]	Filter 30-500Hz Noise level ≈ 0.03-0.05mV Deflection width and refractory criteria 20-30ms	Bipolar recordings -dV/dT over 5-s CFAE : mean CL <120ms	3.5mm irrigated 25-35W Ablation until local EGM elimination ≈ 30-60s CFAE ablation performed before PVI
Deisenhofer et al. 2009 [4]	-	-	4mm irrigated 35W, 43℃ Local CFAE ablation endpoint not specified
Di Biasi et al. 2009 [5]	-	-	3.5mm irrigated 35-45W, <41℃ Complete elimination of CFAE potentials <20s
Lin et al. 2009 [6]	Bipolar electrogram peak >2x maximal noise amplitude P-P sensitivity 0.05-0.1mV Refractory period 30ms Duration 10ms	Bipolar recordings Continuous CFAEs (>8-s): Average fractionated interval <50ms over 5-s CFAE map done before and after PVI	4mm irrigated 25-30W, 35-40℃ 4mm non-irrigated 45-50W, 45-50℃ (posterior) Ablation until local signal were abolished (≤0.05mV bipolar) or FI ↑ to >120ms CFAE ablation after PVI and lines
Oral et al. 2009 [7]	-	-	3.5mm irrigated 20-35W, 45℃ Voltage abatement or 40-s
Verma et al. 2010 [8]	Filter 30-500Hz Noise level ≈ 0.03-0.05mV Deflection width 15-20ms Refractory criteria 35-45ms Internal interpolation set at 4-6mm	Bipolar recordings -dV/dT over 5-s CFAE : mean CL <120ms	3.5mm irrigated 30-40W first patients 8mm non-irrigated 40-60W Ablation until local EGM elimination ≈ 30-60s CFAE mapping and ablation performed after PVI
Chen et al. 2011 [9]	Filter 30-500Hz P-P sensitivity 0.1mV Refractory criteria 40ms Duration 10ms	Bipolar recordings Recording duration 6s CFAE : mean CL <120ms	4mm irrigated 35W, 45℃ Ablation until local EGM elimination CFAE ablation performed either before or after PVI
Dixit et al. 2012 [10]	NavX: Refractory period 50ms Width 10ms Sensitivity 0.5-1.0mV CARTO: Threshold 0.05-0.5mV	Mean fractionation interval <120ms NavX: 5-s recordings CARTO: 2.5 seconds records	8mm non-irrigated 50-70W, <50℃ 3.5mm irrigated 20-40W, <42℃ 3-5 lesions per region for >20-s to achieve 5-10Ω impedance decrease and CFAE abolishment CFAE mapping and ablation performed after PVI
Nam et al. 2012 [11]	-	-	4mm irrigated 30-40W 43℃ -
Nürich et al. 2014 [12]	-	-	3.5m irrigated 30-35W, 42℃ EGM-guided ablation performed
Verma et al. 2014 [13]	Filter 30-300Hz P-P sensitivity 0.03-0.05mV Deflection width 15-20ms Refractory criteria 35-45ms Internal interpolation 6-8mm	Bipolar recordings -dV/dT over 5 seconds CFAE : mean CL <120ms	4mm irrigated 25-30-40W CFAE mapping and ablation after PVI Ablation until local EGM elimination ≈ 20-60s First target regions with shortest CL

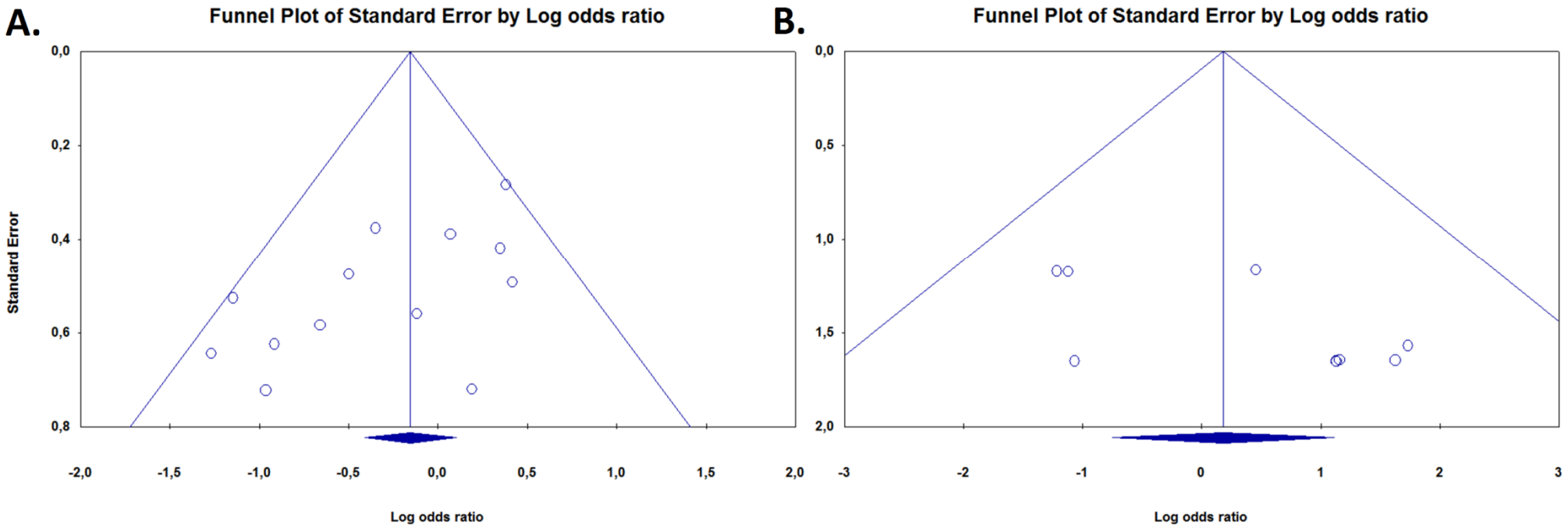
Legend: CARTO - CARTO® mapping system (Biosense-Webster, Diamond Bar, CA, USA), CFAE – complex fractionated atrial electrograms, CL – cycle length, EGM – electrogram, FI – fractionated interval, NavX –EnSite™ NavX™ Navigation & Visualization Technology (St Jude Medical, Austin, Texas, USA), PVI – pulmonary vein isolation. Note: power and temperatures specified above represent the maximal values mentioned in the manuscript.

S-Table 3 – Meta-regression data

Variable	r	P
% of pts with persistent AF	0	0.146
Age	-0.09	0.150
% of female pts	0.01	0.542
AF duration (years)	0.38	0.008
LA size (mm)	-0.02	0.566
LV ejection fraction	-0.01	0.783
% of pts with structural heart disease	0	0.818
Follow-up duration (months)	-0.02	0.398
Average number of ablation procedures per pt	-0.61	0.490
% of isolated PVs	-0.14	0.124

Legend: AF – atrial fibrillation, LA – left atrium, LV – left ventricle, PVI– pulmonary vein.

S-Figure 1 - Funnel-plots: A. Freedom from atrial tachycardia (AT)/atrial fibrillation (AF); B. Complications



Note: The inverted and symmetrical funnel aspect can be observed for the assessed endpoints, with 95% of the studies lying within the confidence limit lines. This suggests that publication bias is not present among the selected studies for the meta-analysis.

Supplemental Material - References

1. Verma A, Patel D, Famy T, Martin DO, Burkhardt JD, Elayi SC, Lakkireddy D, Wazni O, Cummings J, Schweikert RA, Saliba W, Tchou PJ, Natale A. Efficacy of adjuvant anterior left atrial ablation during intracardiac echocardiography-guided pulmonary vein antrum isolation for atrial fibrillation. J Cardiovasc Electrophysiol. 2007;18:151-6.

2. Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, Hongo R, Hao S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Arruda M, Schweikert RA, Natale A. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. Heart Rhythm 2008;5:1658–1664

3. Verma A, Novak P, Macle L, Whaley B, Beardsall M, Wulffhart Z, Khaykin Y. A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: acute effects on AF and efficacy as an adjuvant strategy. Heart Rhythm. 2008;5:198-205.

4. Deisenhofer I, Estner H, Reents T, Fichtner S, Bauer A, Wu J, Kolb C, Zrenner B, Schmitt C, Hessling G. 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;20:514–521.

5. Di Biase L, Elayi CS, Fahmy TS, Martin DO, Ching CK, Barrett C, Bai R, Patel D, Khaykin Y, Hongo R, Hao S, Beheiry S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Wang P, Al-Ahmad A, Arruda M, Themistoclakis S, Bonso A, Rossillo A, Raviele A, Schweikert RA, Burkhardt DJ, Natale A. Atrial fibrillation ablation strategies for paroxysmal patients: randomized comparison between different techniques. Circ Arrhythm Electrophysiol. 2009;2:113-9.

6. Lin YJ, Tai CT, Chang SL, Lo LW, Tuan TC, Wongcharoen W, Udyavar AR, Hu YF, Chang CJ, Tsai WC, Kao T, Higa S, Chen SA. Efficacy of additional ablation of complex fractionated atrial electrograms for catheter ablation of nonparoxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2009;20:607-15.

7. Oral H, Chugh A, Yoshida K, Sarrazin JF, Kuhne M, Crawford T, Chalfoun N, Wells D, Boonyapisit W, Veerareddy S, Billakanty S, Wong WS, Good E, Jongnarangsin K, Pelosi F Jr, Bogun F, Morady F. 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;53:782–789.

8. Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, Torrecilla EG, Khaykin Y. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. Eur Heart J. 2010;31:1344-56.

9. Chen M, Yang B, Chen H, Ju W, Zhang F, Tse HF, Cao K. Randomized comparison between pulmonary vein antral isolation versus complex fractionated electrogram ablation for paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2011;22:973-81.

10. Dixit S, Marchlinski FE, Lin D, Callans DJ, Bala R, Riley MP, Garcia FC, Hutchinson MD, Ratcliffe SJ, Cooper JM, Verdino RJ, Patel VV, Zado ES, Cash NR, Killian T, Tomson TT, Gerstenfeld EP. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. Circ Arrhythm Electrophysiol. 2012;5:287-94.

11. Nam GB, Jin ES, Choi H, Song HG, Kim SH, Kim KH, Hwang ES, Park KM, Kim J, Rhee KS, Choi KJ, Kim YH. Effect of substrate modification in catheter ablation of paroxysmal atrial fibrillation: pulmonary vein isolation alone or with complex fractionated electrogram ablation. Tex Heart Inst J. 2012;39:372-9.

12. Nührich JM, Steven D, Berner I, Rostock T, Hoffmann B, Servatius H, Sultan A, Lüker J, Treszl A, Wegscheider K, Willems S. Impact of biatrial defragmentation in patients with paroxysmal atrial fibrillation: results from a randomized prospective study. Heart Rhythm. 2014;11:1536-42.

13. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372:1812-22.