

# Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial<sup>†</sup>

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## Aims

This multicentre, randomized trial compared three strategies of AF ablation: ablation of complex fractionated electrograms (CFE) alone, pulmonary vein isolation (PVI) alone, and combined PVI + CFE ablation, using standardized automated mapping software.

## Methods and results

Patients with drug-refractory, high-burden paroxysmal (episodes >6 h, >4 in 6 months) or persistent atrial fibrillation (AF) were enrolled at eight centres. Patients ( $n = 100$ ) were randomized to one of three arms. For CFE alone ( $n = 34$ ), spontaneous/induced AF was mapped using validated, automated CFE software and all sites <120 ms were ablated until AF termination/non-inducibility. For PVI ( $n = 32$ ), all four PV antra were isolated and confirmed using a circular catheter. For PVI + CFE ( $n = 34$ ), all four PV antra were isolated, followed by AF induction and ablation of all CFE sites until AF termination/non-inducibility. Patients were followed at 3, 6, and 12 months with a visit, ECG, 48 h Holter. Atrial fibrillation symptoms were confirmed by loop recording. Repeat procedures were allowed within the first 6 months. The primary endpoint was freedom from AF >30 s at 1 year. Patients (age  $57 \pm 10$  years, LA size  $42 \pm 6$  mm) were 35% persistent AF. In CFE, ablation terminated AF in 68%. Only 0.4 PVs per patient were isolated as a result of CFE. In PVI, 94% had all four PVs successfully isolated. In PVI + CFE, 94% had all four PVs isolated, 76% had inducible AF with additional CFE ablation, with 73% termination of AF. There were significantly more repeat procedures in the CFE arm (47%) vs. PVI (31%) or PVI + CFE (15%) ( $P = 0.01$ ). After one procedure, PVI + CFE had a significantly higher freedom from AF (74%) compared with PVI (48%) and CFE (29%) ( $P = 0.004$ ). After two procedures, PVI + CFE still had the highest success (88%) compared with PVI (68%) and CFE (38%) ( $P = 0.001$ ). Ninety-six percent of these patients were off anti-arrhythmics. Complications were two tamponades, no PV stenosis, and no mortality.

## Conclusion

In high-burden paroxysmal/persistent AF, PVI + CFE has the highest freedom from AF vs. PVI or CFE alone after one or two procedures. Complex fractionated electrogram alone has the lowest one and two procedure success rates with a higher incidence of repeat procedures.

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## Keywords

Atrial fibrillation • Ablation • Automated mapping • Fractionated electrograms • Multicentre • Randomized trial

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## Introduction

Elimination of the triggers of atrial fibrillation (AF) through electrical isolation of the pulmonary veins (PVs) has been the basis of most AF ablation approaches to date in both the paroxysmal and persistent AF populations.<sup>1</sup> Studies have correlated outcome of ablation directly with the degree of PV isolation in predominantly paroxysmal AF patients.<sup>2</sup> However, alternative approaches to AF ablation have been proposed, specifically focused on modifying the substrate responsible for AF perpetuation, as opposed to just eliminating the triggers for AF initiation.

Specifically, atrial electrograms (EGMs) demonstrating continuous fractionation and/or very short cycle length (CL) during AF may represent critical pivot points or rotors that are responsible for the maintenance of AF.<sup>3</sup> These so-called complex fractionated electrograms (CFE) may therefore serve as a potential target of ablation. Previous data have shown that targeting CFE may result in AF slowing, regularization, and termination.<sup>4</sup> These acute changes in AF may correlate with long-term freedom from AF recurrence, but the data are very limited and restricted to single-centre experiences.<sup>4–6</sup> Furthermore, these studies have targeted CFE by visual inspection alone, but identification of CFE can be very challenging and subjective, limiting the utility of CFE as an ablation endpoint. Automated mapping algorithms have been designed and validated to identify CFE regions, and have been shown to improve ablation outcomes.<sup>7,8</sup>

Whether trigger-based ablation strategies, such as pulmonary vein isolation (PVI), or substrate-based strategies, such as CFE, should be used alone or in combination is not well known. Comparative data are limited to single-centre reports,<sup>9–12</sup> and most of these used visual identification of CFE as opposed to a standardized, automated approach. Thus, the purpose of this prospective, randomized, multicentre study was to compare three strategies of AF ablation using a standardized, validated approach to substrate ablation: ablation of CFE alone, PVI alone, and combined PVI + CFE ablation.

## Methods

### Study design

We conducted a prospective, multicentre, randomized trial. The trial was registered with ClinicalTrials.gov on 22 August 2006 with the identifier number NCT00367757. Enrolment commenced in August 2006. Patients were randomized 1:1:1 to one of three AF ablation strategies: CFE alone, PVI alone, or combined PVI + CFE. Enrolment occurred at eight centres (four in Canada and four in Europe). All participating operators were experienced AF ablation specialists (>100 AF ablations per operator/year). Because of the nature of the procedures, operators were not blinded to the randomization, but patients were (single-blind design). Randomization was done by random allocation centrally at the clinical trial centre and was stratified by site. Allocation concealment was maintained at all sites by sequentially numbered, opaque, sealed envelopes. Data were collected, managed, and analysed by a central, independent monitoring group with a restricted access database. Written informed consent was obtained from each participant prior to study inclusion. The study protocol was approved by the institutional ethics review board at each institution.

### Patient population

Patients undergoing first-time ablation for symptomatic AF that was refractory to at least one anti-arrhythmic drug were enrolled. At least one episode of AF had to be documented by ECG or Holter within 12 months of randomization in the trial. All patients had to have high-burden paroxysmal AF or persistent AF. Definitions of paroxysmal and persistent AF follow those outlined in the ACC/AHA/ESC Guidelines for the Management of Patients with AF.<sup>13</sup> High-burden paroxysms were included in the study because of data suggesting that even paroxysmal AF patients with greater amounts of arrhythmia may have abnormal atrial substrate changes which may need to be targeted in addition to PV triggers.<sup>7,14</sup> Specifically, 'high-burden' paroxysmal AF was defined as >four self-terminating episodes within 6 months, two of which were at least 6 h in duration within the last year. Persistent AF was defined as episodes sustained for >7 days, but less than 12 months, requiring termination by pharmacological or electrical cardioversion. Detailed inclusion and exclusion criteria for patients are outlined in Table 1.

### Catheter ablation strategies

All patients underwent catheter ablation using radiofrequency (RF) energy. Patients were all anticoagulated with warfarin to maintain an international normalized ratio (INR) of 2–3 for at least 4 weeks prior to the procedure as outlined in the inclusion criteria. Patients

**Table 1** Study inclusion and exclusion criteria

Inclusion criteria	
Patients age 18 or greater	
Patients with a 'high burden' of paroxysmal atrial fibrillation or persistent atrial fibrillation. 'High burden' paroxysmal atrial fibrillation will be defined as more than four episodes within 6 months that are self-terminating, with at least two episodes >6 h by symptoms within the last year. Persistent atrial fibrillation will be defined as a sustained episode >7 days but <12 months in duration that was terminated by a non-ablative therapeutic intervention (cardioversion or drug)	
AF must be symptomatic and refractory to at least one anti-arrhythmic medication	
At least one episode of AF must have been documented by ECG or Holter within 12 months of randomization in the trial	
Patients must be on continuous anticoagulation with warfarin (INR 2–3) for >4 weeks prior to the ablation	
Patients must be able and willing to provide written informed consent to participate in the clinical trial	
Exclusion criteria	
Patients with permanent atrial fibrillation	
Patients with AF felt to be secondary to an obvious reversible cause	
Patients with inadequate anticoagulation as defined in the inclusion criteria	
Patients with left atrial thrombus on transesophageal echo prior to the procedure	
Patients with contraindications to systemic anticoagulation with heparin or coumadin	
Patients who have previously undergone atrial fibrillation ablation	
Patients with left atrial size >55 mm	
Patients who are or may potentially be pregnant	

AF, atrial fibrillation.

were not ablated, if transesophageal echocardiography (TEE) prior to the procedure demonstrated left atrial thrombus. All patients except those at one centre ( $n = 9$ ) underwent pre-procedural TEE. All procedures were performed in the fasting state under conscious sedation or general anaesthesia depending on each participating centre. Anti-arrhythmic medications were stopped at least five half-lives prior to the procedure, except amiodarone, which was stopped at least 8 weeks prior.

All procedures were performed via transseptal access to the left atrium (LA). After transseptal access, patients were anticoagulated with intravenous heparin to maintain an ACT of  $>300$  s. A multipolar catheter (minimum eight bipoles) was placed in the coronary sinus (CS). A decapolar, circular mapping catheter was utilized for both mapping and confirmation of PV isolation (according to the randomized ablation strategy). Ablation was performed using a 3.5 mm irrigated-tip ablation catheter (Therapy Cool Path, St Jude Medical, Minneapolis, MN, USA). Power was limited to 40 W (30 W on the posterior wall) with an irrigation flow rate of 30 mL/min. Prior to irrigated-tip catheter availability, the first 21 patients were ablated using an 8 mm non-irrigated-tip ablation catheter (Therapy Dual 8, St Jude Medical, Minneapolis, MN, USA) using a maximum power of 60 W (40 W on the posterior wall) and temperature of 50°C. These patients were evenly distributed across the three study arms. Continuous impedance monitoring was used and RF was discontinued if a  $>10 \Omega$  impedance rise was observed. All procedures were guided using an electroanatomical mapping system (Ensite NavX, St Jude Medical, Minneapolis, MN) to construct a three-dimensional shell of the PVs, LA, CS, and right atrium (RA) if required, using the circular mapping and/or ablation catheters. Post-ablation, all study maps and data were copied to DVD and sent to the central database for analysis/adjudication. The specifics of each of the three ablation strategies were as follows.

### Trigger-based strategy (pulmonary vein isolation)

Pulmonary vein isolation was performed using a standard wide circumferential PV antral isolation approach. Through transseptal accesses, the circular mapping and ablation catheters were advanced into the LA, followed by reconstruction of the LA, PV, and CS anatomy using the mapping system. The ostia and antra of the PVs were defined by examination of the 3D electroanatomical shell, impedance, and signal mapping as the catheter was pulled back from inside the vein, and when available, intracardiac echocardiography. The circular mapping catheter was then placed sequentially within each of the four PV antra to record PV potentials. Circumferential RF lesions were then placed at least 1–2 cm outside of the PV ostia to encircle and electrically isolate each of the PV antra while avoiding PV stenosis. Because of the narrow ridge of tissue between the anterior aspect of the left superior PV and the left atrial appendage, ablation was allowed within 1 cm of the ostium of the left superior PV to encircle and isolate this vein. As each antrum was encircled, the circular catheter was used to confirm electrical isolation. Radiofrequency isolation of the PV antrum was considered complete when all PV potentials within each antrum were abolished, as recorded by the circular mapping catheter during sinus rhythm or CS pacing. Ablation tags were only placed on the LA shell, if RF energy had been applied for more than 20 s at a given spot. Rechecking of all the antra was performed at the end of the ablation procedure to confirm the presence of block (minimum 30 min wait after last ablation lesion). The goal was to isolate all four PV antra for every patient. If the patient was in AF at the end of the procedure, they were electrically cardioverted back to sinus rhythm. Remapping of the PVs post-cardioversion was performed

to confirm PV isolation. Termination and/or non-inducibility of AF were not endpoints of this ablation strategy.

### Substrate-based strategy (complex fractionated electrograms)

The detailed technique for ablating CFE using the automated mapping software has been described and validated previously.<sup>7</sup> In brief, if the patient was not already in AF at the start of the procedure, AF was induced by rapid atrial pacing from the distal tip of the CS catheter. Pacing was performed at the shortest 1:1 atrial capture rate for up to 15 s at a time, up to five times in a row, with 30 s between attempts. If AF could not be sustained for longer than 1 min, an infusion of isoproterenol (causing an increase in baseline heart rate  $\geq 50\%$ , dose up to 10 mcg/min) was used to sustain AF. Induced AF needed to persist for  $>1$  min prior to mapping for CFE.

Once in AF, CFE mapping using an automated algorithm (Ensite NavX, St Jude Medical) was performed in the LA, CS, and RA. Bipolar EGMs were obtained during AF by mapping with the circular mapping catheter and/or the 3.5 mm tip ablation catheter. In areas where the circular mapping catheter could not obtain good atrial contact, mapping was supplemented using the 3.5 mm tip ablation catheter. Bipolar recordings were filtered at 30–500 Hz. The algorithm measures the time between multiple, discrete deflections ( $-dV/dT$ ) in a local AF EGM recording over a specified length of time (5 s) and then averages these inter-deflection time intervals to calculate a mean CL of the local EGM during AF. This mean CL is then projected onto the LA anatomical shell as a colour-coded display. The shorter the CL, the more rapid and fractionated the local EGM. Specifically for this study, regions with a mean CL of less than 120 ms were defined as 'CFE' based on previously published data.<sup>7,15</sup> Selectable peak-to-peak EGM amplitude, EGM width, and post-EGM refractory period were defined to assist in algorithm deflection detection and have been previously validated (Table 2).<sup>7</sup> At the start of the procedure, the baseline signal noise level was determined and the peak-to-peak detection limit was set just above the noise level (typically 0.03–0.05 mV) to avoid noise detection while allowing detection of CFEs that are typically of very low amplitude ( $<0.5$  mV).<sup>4</sup> Deflection width and refractory criteria were set at 15–20 ms and 35–45 ms, respectively, to avoid double-counting individual EGM deflections. To avoid including signals from bipoles that

**Table 2** Recommended settings for automated complex fractionated electrogram mapping algorithm

Peak-to-peak sensitivity (minimum detection threshold, avoids detecting noise)	0.03–0.05 mV
EGM refractory period (avoids double-counting a single EGM with multiple components)	35–45 ms
EGM width (avoids detection of broader, far-field EGMs)	15–20 ms
EGM segment length (total recording duration at each point, obtains a mean CL for that point)	5 s
Interpolation (maximum distance between points which will be used to assign average values for a vertex)	4–6 mm
Internal/external projection (avoids collection of EGMs from electrodes that are not in good contact with map shell)	4–6 mm

EGM, electrogram; CL, cycle length.

were internal in the LA, the internal interpolation of the algorithm was set at 4–6 mm to include only those signals obtained from bipoles with good atrial shell contact. Width, refractory, and interpolation criteria were set at 15 ms, 45 ms, and 4 mm respectively, as more validation data became available over the course of the study; however, the validation data showed little change in sensitivity or specificity over the narrow ranges specified above.<sup>7,15</sup>

Complex fractionated electrogram sites defined by the algorithm (CL < 120 ms) were targeted for ablation. Regions with the shortest CL were targeted first, followed by longer CL regions (up to 120 ms). Ablation at a CFE site was continued until local EGM elimination which typically required 30–60 s of RF application. During ablation of CFE sites, the mean atrial fibrillation cycle length (AFCL) and AF regularity were periodically measured from a selected CS recording. As per previous technique,<sup>7</sup> the CS recording with the shortest average CL was selected, and the same site was used for pre- and post-ablation comparisons. Atrial fibrillation cycle length was determined by counting the number of discrete atrial EGMs over a 15 s recording (x) and dividing 15 000 by x. The CS recording was also periodically examined to look for regularization to atrial flutter (AFL) or atrial tachycardia (AT) during CFE ablation. Termination rates of AF during CFE ablation were also recorded. No intravenous anti-arrhythmics were used during initial ablation to change AFCL or help regularize/terminate AF. The endpoint for CFE ablation was (i) elimination of all CFE sites in the LA, CS, and RA or termination of AF and (ii) non-inducibility of AF post-ablation. If AF terminated as a result of CFE ablation, an attempt was made to reinduce AF using the same standardized protocol detailed in the first paragraph of this section. If isoproterenol was used initially to maintain AF, then the same dose was used for post-ablation induction. If the patient remained inducible for AF (AF persisting > 1 min), then further CFE ablation was performed in the LA, CS, and RA until all CFE sites were eliminated or until AF became non-inducible. If AF did not terminate after eliminating all CFE sites, sinus rhythm was restored by electrical cardioversion. If AF regularized to an AFL/AT, which did not terminate after all CFE sites were ablated, the flutter/tachycardia was mapped and ablated or cardioverted electrically at the discretion of the investigator. At the very end of the CFE procedure, investigators were also asked to place the circular mapping catheter into each of the PVs to assess if any of them had been incidentally isolated as a result of CFE ablation.

### Combined strategy (pulmonary vein isolation + complex fractionated electrograms)

Patients randomized to this arm first underwent wide circumferential PVI as described in the 'trigger-based' strategy above. The endpoint was complete isolation of all four PVs documented by a circular mapping catheter. Following completion of the PVI procedure, if the patient was spontaneously in AF, mapping was performed in AF to identify regions of CFE using the automated algorithm as described in the 'substrate-based' strategy above. If the patient was not in AF at the end of the PVI, AF induction was performed according to the protocol described earlier with or without the use of isoproterenol. If the patient was non-inducible, then no further ablation was performed. If the patient was inducible (AF persisting > 1 min), CFE regions were mapped and ablated using the automated software to the same endpoint as described in Substrate-based strategy section. If AF did not terminate after mapping and ablation of all CFEs in the LA, RA, and CS, the AF was electrically cardioverted and the procedure terminated. If AF regularized to an AFL/AT, which did not terminate after all CFE sites were ablated, the flutter/tachycardia was mapped and ablated or cardioverted electrically at the discretion of the investigator.

### Repeat ablation procedures

Up to one additional ablation procedure was allowed by the protocol. In order to keep patients on the same follow-up schedule, it was recommended that a repeat ablation be done no sooner than 3 months, but less than 6 months after the initial procedure. The strategy used for the second ablation procedure had to be identical to the initial randomized strategy used in the first procedure.

### Follow-up

All patients were discharged home within 2 days following the procedure. Post-procedure, patients continued anticoagulation with warfarin to maintain an INR of 2–3 for a minimum of 3 months. In all patients, anti-arrhythmic medications were continued for 2 months post-ablation and were chosen from one of sotalol, propafenone, flecainide, or dofetilide. Anti-arrhythmic medications were discontinued in all patients after 2 months.

Patients were followed in the outpatient clinic of their respective institutions at 3, 6, and 12 months post-ablation ( $\pm 2$  weeks for each time point for follow-up). Monthly telephone interviews were also done. A 12-lead ECG and 48 h Holter recording was done routinely in all patients at each of the 3, 6, and 12 months follow-up visits. External loop recorders (minimum 2 weeks) and/or transtelephonic monitors were used to confirm rhythms for any patient-reported symptoms outside of the routine follow-ups. Interrogation of implanted devices was also used, when applicable, to confirm arrhythmia recurrence. Recurrences were based upon patient reporting, loop, Holter, device, and/or ECG detection. A 'recurrence' of atrial arrhythmia was considered any episode lasting > 30 s (symptomatic or asymptomatic). A blanking period of 3 months after the initial ablation was employed such that recurrences during this time were not counted.<sup>1</sup>

Patients also had a routine spiral computed tomography or magnetic resonance imaging of the chest within 6 months post-ablation to assess for PV stenosis. Pulmonary vein stenosis was graded as mild if there was <50% narrowing, moderate if there was 50–70% narrowing, and severe if there was >70% narrowing.

No patients were lost to follow-up and all underwent the required outpatient visits and monitoring.

Although the HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation had not yet been published at the time this protocol was designed, the follow-up was consistent with the requirements of this document.<sup>1</sup>

### Study endpoints

The primary endpoint of the study was freedom from AF recurrence from Months 3 to 12 post-ablation after one or two procedures on and off anti-arrhythmic medications (excludes the pre-specified blanking period from Months 0 to 3). Secondary endpoints included freedom from any atrial arrhythmia recurrence, namely AF, AT, or AFL after one and two procedures from Months 3 to 12 on and off anti-arrhythmic drugs. Other secondary endpoints included incidence of peri-procedural complications, procedural characteristics (fluoroscopy time, mapping time, etc.), and number of repeat procedures. All endpoints were pre-specified prior to unblinding the data.

### Sample size and statistical analysis

At the time that this protocol was designed, there was very little data available as to the success rates of each of the three strategies to determine a proper sample size calculation. The study was therefore conceived as an exploratory study. Most studies published at the time had sample sizes of 30–40 patients and that served as the basis for our sample size determination. The goal was to enrol a total of

30 patients per arm ( $n = 90$ ). The study enrolment period was extended to boost enrolment, and we ended up exceeding our projected sample size ( $n = 101$ ). Enrolment per centre was as follows: Southlake Regional Health Centre ( $n = 20$ ), Ospedale Regionale di Treviso ( $n = 18$ ), Montreal Heart Institute ( $n = 16$ ), Casa di Cura Santa Maria ( $n = 13$ ), Haukeland University Hospital ( $n = 12$ ), Hamilton Health Sciences ( $n = 12$ ), Royal Jubilee Hospital ( $n = 9$ ), and Hospital General Universitario Gregorio Marañón ( $n = 1$ ). Only patients who underwent ablation were included for analysis.

All data are reported as a mean  $\pm$  standard deviation for continuous variables and number of subjects (%) for categorical variables unless otherwise indicated. Continuous variables were compared using ANOVA. Categorical variables were compared using the Fisher's exact test. Changes in AFCL were compared using paired t-test analysis. Freedom from atrial arrhythmia was determined and compared using Kaplan–Meier analysis and the log-rank test. To compare the efficacy of each of the three procedures, the Tukey method was applied for multiple comparisons. For the single procedure success rate, all patients experiencing a recurrence from 3 to 12 months were considered to have failed. For the two procedure success rate, patients experiencing a recurrence after a second procedure on or before the 12-month visit or patients who had a recurrence but did not undergo repeat ablation were considered to have failed. A  $P$ -value of  $<0.05$  was considered significant for all statistical determinations. All tests of significance were two-sided. All analysis was performed using SAS software version 9.1.3 (SAS, Cary, NC, USA).

## Results

### Patient characteristics

A total of 101 patients were enrolled into the study (Figure 1). Patients were randomized to PVI ( $n = 33$ ), CFE ( $n = 34$ ), and PVI + CFE ( $n = 34$ ). One patient randomized to PVI did not end up undergoing ablation, so only 32 patients were available for analysis in this group ( $n = 100$  total).

Patients enrolled in the study were predominantly male ( $n = 74$ , 74%) with an age of  $57 \pm 10$  years. The duration of AF symptoms pre-ablation was  $7 \pm 7$  years (median 4.4 years, range 1–43). Atrial

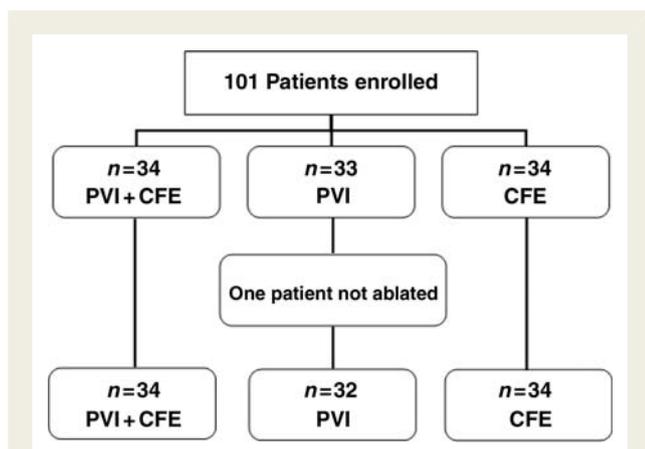
fibrillation was high-burden paroxysmal in 64 patients (64%) and persistent in 36 patients (36%). High-burden paroxysmal AF patients had a median of 11 episodes per month (interquartile range 3–54) with median episode duration of 10 h (interquartile range 2–17). Patients failed  $1.4 \pm 0.9$  anti-arrhythmics prior to ablation. Important co-morbidities included prior stroke/transient ischaemic attack (5%), coronary artery disease (7%), valvular heart disease (20%), heart failure (3%), and hypertension (45%). Mean ejection fraction was  $62 \pm 10\%$  and the left atrial size was  $42 \pm 6$  mm. Characteristics of each group are detailed in Table 3 and there were no significant differences between groups.

### Mapping and ablation details

In the CFE arm, AF was spontaneous in 14 patients (41%) and induced in 20 (59%). Pacing alone induced AF in 10 of 20 patients, while isoproterenol was used in addition to pacing in the other 10 of 20 patients. The mean dose of isoproterenol used was  $5 \pm 3$  mcg/min (range 1.5–10). Complex fractionated electrogram mapping was performed with the automated mapping algorithm with a mean of  $317 \pm 290$  points per map (range 112–949). Complex fractionated electrogram regions were most commonly located within the PV antra (24 patients, 70%), on the LA roof ( $n = 24$ , 70%), posterior LA wall ( $n = 23$ , 68%), at the base of the LA appendage ( $n = 23$ , 68%), on the high LA septum ( $n = 22$ , 65%), low LA septum ( $n = 19$ , 56%), CS ( $n = 17$ , 50%), and the mitral valve annulus ( $n = 14$ , 41%). Overall, CFE were less commonly seen in the RA vs. LA, specifically the right atrial septum ( $n = 11$ , 32%), crista terminalis ( $n = 7$ , 21%), superior vena cava ( $n = 7$ , 21%), and the cavotricuspid isthmus ( $n = 5$ , 15%). As a result of CFE ablation, AF cycle length increased from a baseline of  $180 \pm 119$  to  $219 \pm 46$  ms ( $P = 0.03$ ). Complex fractionated electrogram ablation terminated AF in 23 of 34 (68%) of patients. Specifically, AF terminated to sinus rhythm in 14 of 34 (41%) and to other regular atrial arrhythmias in 9 of 34 (26%), specifically typical right AFL ( $n = 6$ ) and left AFL/AT ( $n = 3$ ). In all six of the patients with right AFL, and two of the left AFL/AT patients, the regularized rhythm was successfully ablated with restoration of sinus rhythm. In the patients who did not terminate, sinus rhythm was restored by electrical cardioversion. At the end of the procedure, repeat induction was attempted in 25 of 34 (73%) patients; in the other nine patients, induction was not attempted because they had ongoing AF which did not terminate during CFE ablation. Despite further ablation in the re-induced patients, AF remained inducible in two patients; left AFL/AT remained inducible in six patients; and typical right AFL in one patient. Only  $0.4 \pm 1.0$  PVs (median 0, range 0–3) were isolated as a result of CFE ablation.

In the PVI arm, 10 of 32 (31%) of patients were spontaneously in AF at the start of the procedure. Isolation of all PV antra was achieved in 94% (30 of 32) of patients. In the remaining two patients, three of four PVs were successfully isolated. At the end of PVI ablation, six patients had ongoing AF which required cardioversion back to sinus rhythm.

In the PVI + CFE arm, isolation of all PV antra was achieved in 94% (32 of 34) of patients. In the remaining two patients, three of four PVs were successfully isolated. At the end of PV isolation, AF was ongoing in 14 (41%) patients and induced in another 12 (35%) patients with the use of pacing and isoproterenol



**Figure 1** Study patient randomization flowchart. A total of 101 patients were enrolled in the study. Only 100 underwent ablation, with one patient in the PVI arm not undergoing the ablation procedure.

**Table 3** Study patient characteristics

	CFE (n = 34)	PVI (n = 32)	PVI + CFE (n = 34)	P-value
Age (years)	57 ± 9	55 ± 11	59 ± 10	0.32
Male	25 (74%)	24 (75%)	25 (74%)	0.41
Paroxysmal	21 (62%)	21 (66%)	22 (65%)	0.75
Persistent	13 (38%)	11 (34%)	12 (35%)	0.70
AF duration (years)	6.4 ± 6.0	6.4 ± 6.6	7.6 ± 9.4	0.18
Number failed AAD	1.4 ± 0.8	1.4 ± 0.8	1.4 ± 0.9	0.52
Stroke/TIA	2 (6%)	1 (3%)	2 (6%)	0.44
Hypertension	15 (44%)	16 (50%)	14 (41%)	0.20
Body mass index (kg/m <sup>2</sup> )	31 ± 10	29 ± 9	29 ± 9	0.36
Coronary disease	3 (9%)	1 (3%)	3 (9%)	0.23
Valvular disease	6 (18%)	6 (19%)	8 (23%)	0.25
Heart failure	1 (3%)	2 (6%)	0 (0%)	0.15
Ejection fraction	64 ± 10%	62 ± 7%	59 ± 12%	0.38
Left atrial size (mm)	41 ± 6	43 ± 5	41 ± 6	0.21

AF, atrial fibrillation; AAD, anti-arrhythmic drugs; TIA, transient ischaemic attack.

**Table 4** Procedural characteristics (first procedure)

	CFE	PVI	PVI + CFE	P-value
Procedural duration (min)	224 ± 68	181 ± 74	225 ± 68	0.11
Mapping time (min)	39 ± 18	29 ± 21	41 ± 20	0.09
Fluoroscopy time (min)	56 ± 28	58 ± 27	60 ± 34	0.29
Radiofrequency time (min)	63 ± 33	64 ± 42	78 ± 50	0.07

(dose 7 ± 4 mcg/min). Thus, 26 patients (76%) received adjuvant CFE ablation after PVI. Automated CFE mapping was performed with a mean of 205 ± 261 points per map (range 103–1094). Complex fractionated electrogram regions were mostly located at the base of the LA appendage (18 patients, 69%), on the low LA septum (n = 18, 69%), high LA septum (n = 17, 65%), CS (n = 16, 61%), mitral valve annulus (n = 15, 58%), the LA roof (n = 11, 42%), and the posterior wall (n = 5, 19%). Right atrial sites were less common, specifically the right atrial septum (n = 8, 31%), crista terminalis (n = 6, 23%), and the cavotricuspid isthmus (n = 5, 19%). Adjuvant CFE ablation prolonged AF cycle length from a baseline of 215 ± 146 to 235 ± 135 ms (P = 0.04). Atrial fibrillation terminated in 19 of 26 (73%) of patients: 11 to sinus, 5 to right AFL, and 3 to left AFL/AT. In four of the patients with right AFL and one of the left AFL/AT patients, the regularized rhythm was successfully ablated with restoration of sinus rhythm. The others were cardioverted. Atrial fibrillation re-induction was attempted in the 15 of the 19 patients who terminated with ablation. Despite further ablation in the re-induced patients, AF remained inducible in four patients; left AFL/AT remained inducible in five patients; and typical right AFL in one patient.

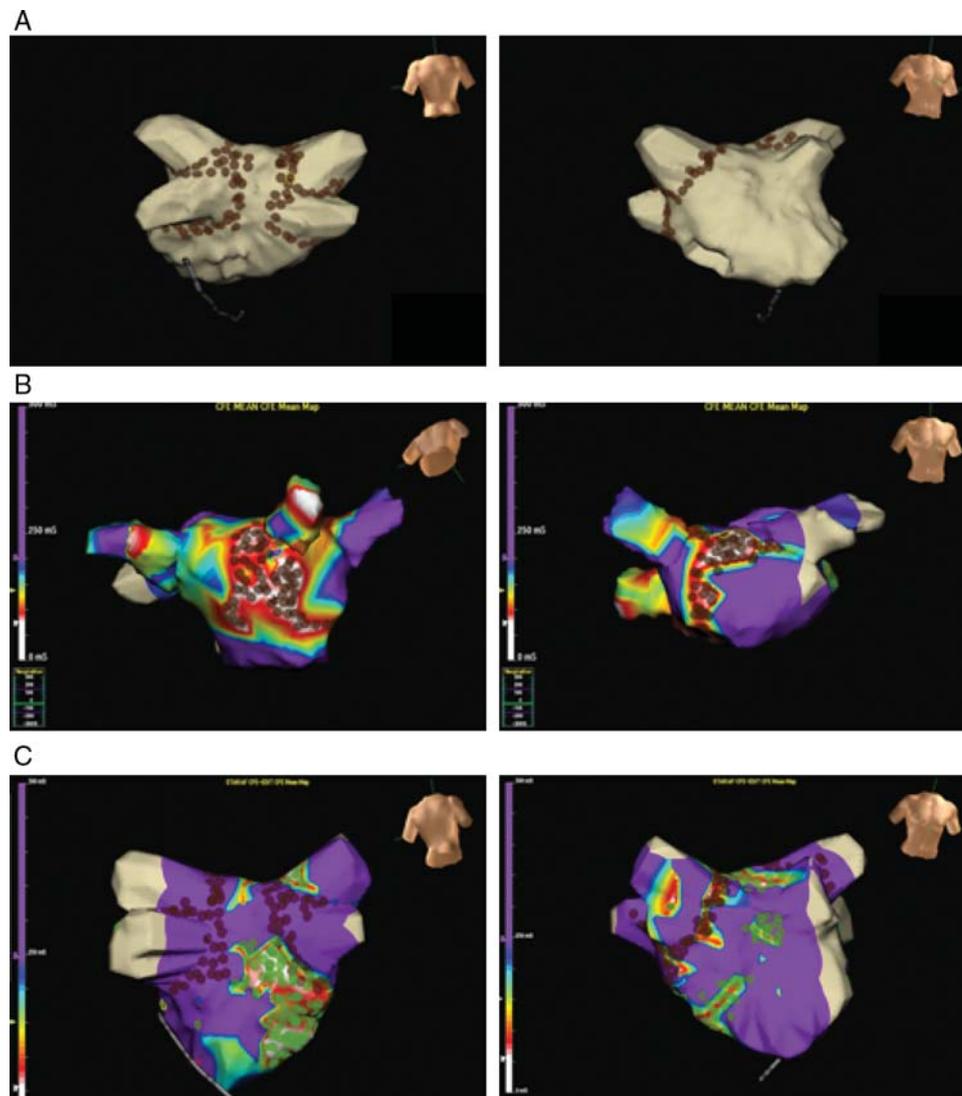
Mapping, procedural, fluoroscopy, and RF times for first procedures in each arm are presented in Table 4. In spite of the combination of two approaches in PVI + CFE, fluoroscopy times were

similar among the three groups. There was a trend towards shorter procedure time (P = 0.11) and less mapping time (P = 0.09) in the PVI arm compared with the other two arms. As expected, there was also a trend towards more RF time in the PVI + CFE group, but this did not reach statistical significance (P = 0.07). Representative maps of each of the three arms are presented in Figure 2A–C.

## Outcomes

At the 12-month follow-up, 94% of all enrolled patients were off anti-arrhythmic medications. Among patients considered to have a successful post-ablation outcome, 96% were off anti-arrhythmics. Patients with a successful post-ablation outcome who were still on anti-arrhythmics were evenly distributed across the three arms, specifically two patients (6%) in PVI + CFE, one patient (3%) in PVI, and one patient (3%) in CFE.

After one procedure, PVI + CFE had the highest freedom from AF (74%) compared with PVI (48%) and CFE (29%) (P = 0.004) (Figure 3A). The outcome for PVI + CFE was significantly better than either PVI (P = 0.03) or CFE (P < 0.001) alone. After two procedures, PVI + CFE still had the highest freedom from AF at 1 year (88%) compared with PVI (68%) and CFE (38%) (P = 0.001), with PVI + CFE still significantly better than either PVI (P = 0.04) or CFE (P < 0.001) alone (Figure 4A).

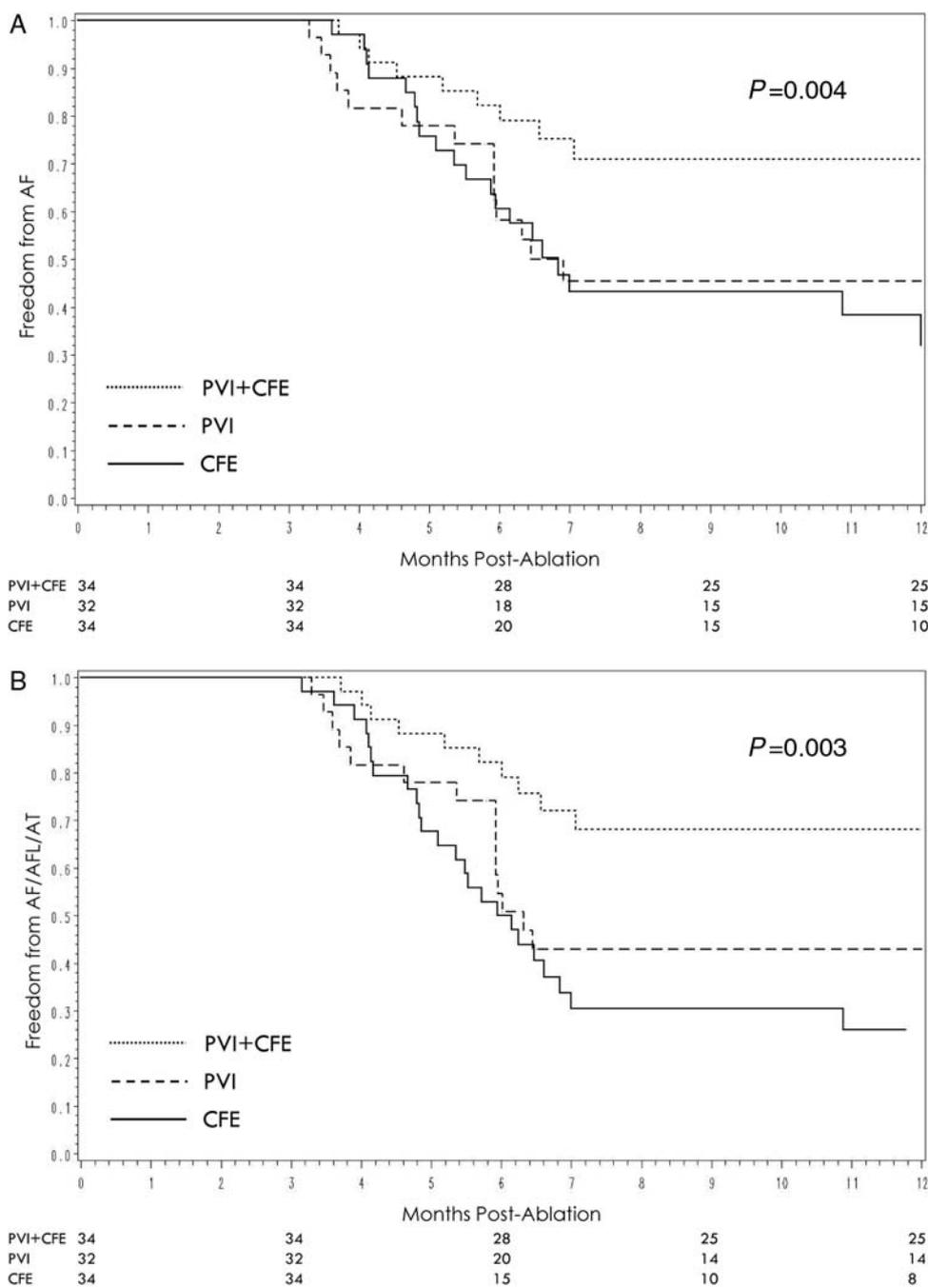


**Figure 2** (A–C) Representative left atrial (LA) electroanatomical maps illustrating the three ablation strategies used in the study. On the left side are panels showing posterior or modified posterior views of the LA and on the right side are panels showing the anterior view of the LA. (A) Pulmonary vein isolation (PVI) strategy. Brown points represent points of radiofrequency (RF) energy application around the four pulmonary venous (PV) antra with the endpoint of electrical isolation of all four PV antra. (B) Complex fractionated electrogram (CFE) strategy. The colour-coded map shows regions of highly fractionated atrial electrograms during AF (shown in red and white colours, equivalent to a local cycle length < 120 ms). The brown points represent applications of RF energy over CFE regions with the endpoint of AF termination/non-inducibility. (C) Combined procedure of PVI followed by CFE ablation. The brown points illustrate ablation points applied around all four PV antra with the endpoint of electrical isolation. The colour-coded map shows regions of highly fractionated electrograms (red and white) that were mapped during AF post-PVI. The green points represent RF energy applications to CFE regions after PVI with the endpoint of AF termination/non-inducibility.

When the combined endpoint of freedom from AF/AFL/AT was considered, PVI + CFE still had the highest success rate (74%) compared with PVI (45%) and CFE (24%) ( $P = 0.003$ ) after one procedure (Figure 3B). The outcome for PVI + CFE was significantly better than either PVI ( $P = 0.02$ ) or CFE ( $P < 0.001$ ) alone. After two procedures, PVI + CFE had a success rate of 88% compared with 68% for PVI and 32% for CFE ( $P = 0.001$ ). Again, the outcome for PVI + CFE was significantly better than

the outcome of PVI ( $P = 0.04$ ) or CFE ( $P < 0.001$ ) alone (Figure 4B).

When the high-burden paroxysmal and persistent subgroups were analysed separately, PVI + CFE had a significantly better outcome compared with CFE at 1 year after one procedure for both freedom from AF ( $P = 0.002$ ) and freedom from AF/AFL/AT ( $P = 0.001$ ) (Figure 5). PVI + CFE also had a significantly higher success rate compared with PVI in the persistent subgroup

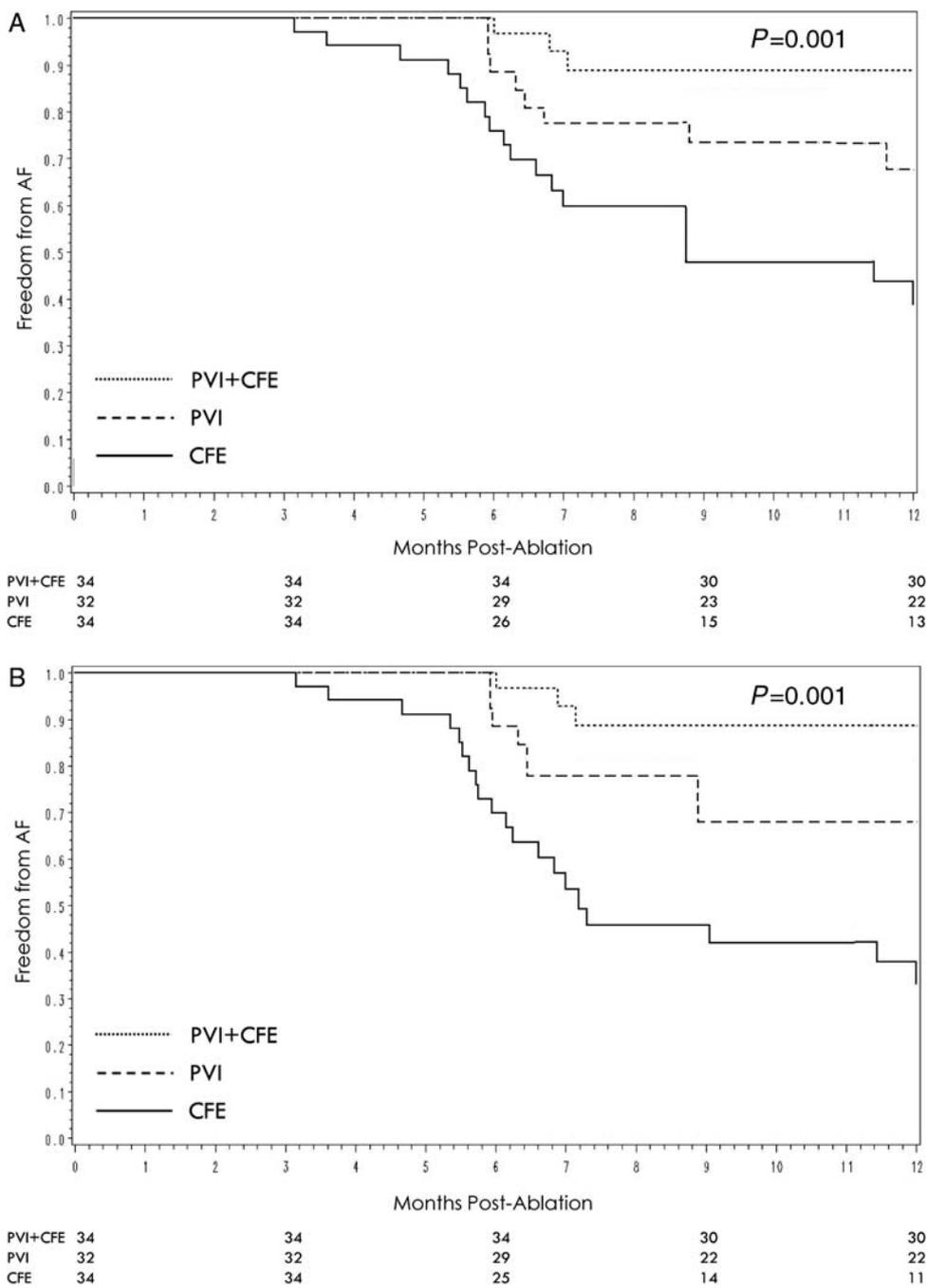


**Figure 3** (A and B) Kaplan–Meier curves depicting time to first atrial fibrillation (AF) recurrence (A) and time to first AF, atrial flutter (AFL), or atrial tachycardia (AT) recurrence (B) after one procedure in the pulmonary vein isolation (PVI) strategy, the complex fractionated electrogram (CFE) strategy, and the combined strategy of PVI followed by CFE ablation (PVI + CFE). PVI + CFE had a significantly higher freedom from AF after one procedure (74%) compared with either PVI (48%) or CFE (29%) alone (log-rank  $P = 0.004$ ). PVI + CFE also had a significantly higher freedom from AF/AFL/AT after one procedure (74%) compared with either PVI (45%) or CFE (24%) alone (log-rank  $P = 0.003$ ). *Post hoc* analysis comparing individual groups is detailed in text. Ninety-six percent of patients who were considered successful were off anti-arrhythmic medications and were evenly distributed among groups (also detailed in text). Numbers at risk for each group are indicated below the x-axis.

( $P = 0.03$ ). In the high-burden paroxysmal subgroup, there was no statistically significant benefit of PVI + CFE over PVI alone ( $P = 0.14$ ). However, the relative benefit of PVI + CFE over PVI alone was similar in both subgroups (interaction  $P = 0.87$ ).

### Repeat procedures

A mean of  $1.2 \pm 0.4$  procedures were done per patient. Repeat procedures were performed  $5 \pm 2$  months after the first procedure. PVI + CFE had the lowest incidence of repeat procedures.

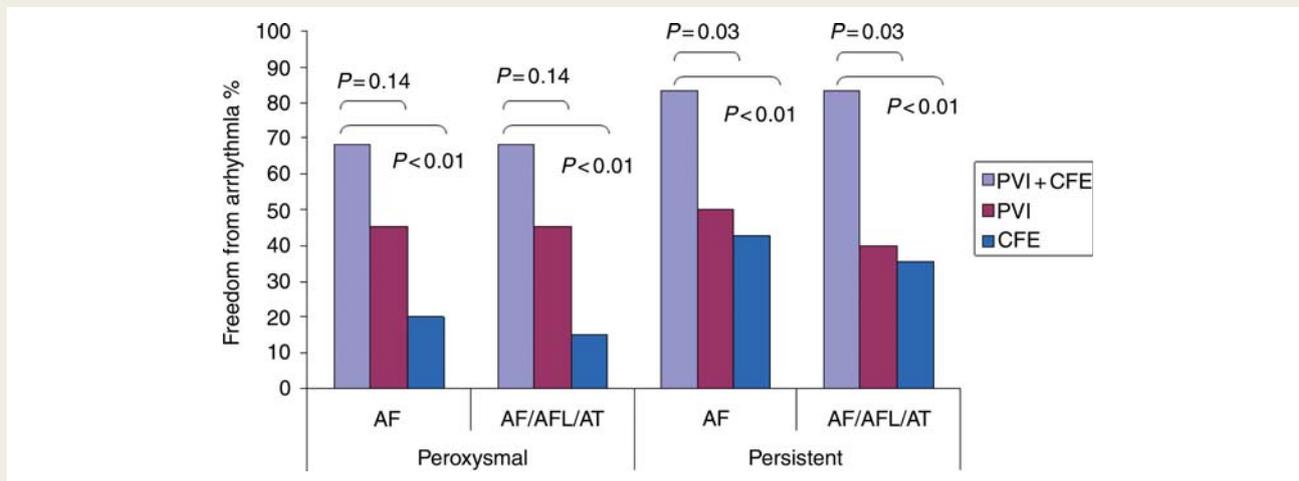


**Figure 4** (A and B) Kaplan–Meier curves depicting time to first atrial fibrillation (AF) recurrence (A) and time to first AF, atrial flutter (AFL), or atrial tachycardia (AT) recurrence (B) after two procedures in the pulmonary vein isolation (PVI) strategy, the complex fractionated electrogram (CFE) strategy, and the combined strategy of PVI followed by CFE ablation (PVI + CFE). For the endpoint of AF (A), the combined strategy of pulmonary vein isolation followed by complex fractionated electrogram ablation (PVI + CFE) had a significantly higher freedom from AF (88%) compared with either pulmonary vein isolation (PVI) (68%) or complex fractionated electrogram ablation (CFE) (38%) alone ( $P = 0.001$ ). For the endpoint of AF/AFL/AT, PVI + CFE still had the highest freedom from arrhythmia (88%) compared with PVI (68%) or CFE (32%) alone ( $P = 0.001$ ). *Post hoc* analysis comparing individual groups is detailed in text. Numbers at risk for each group are indicated below the x-axis.

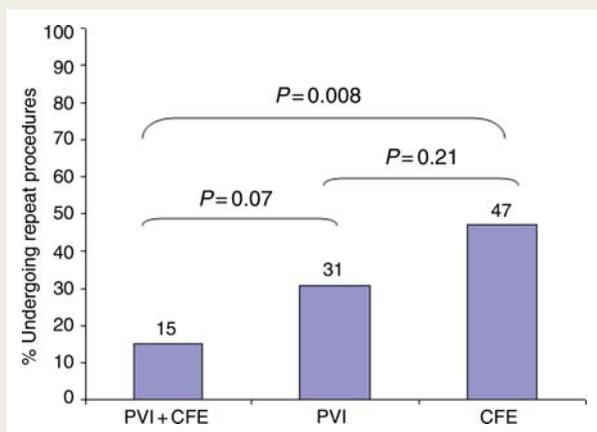
There were significantly more repeat procedures in the CFE arm (47%,  $n = 16$ ) vs. PVI (31%,  $n = 10$ ) or PVI + CFE (15%,  $n = 5$ ) ( $P = 0.01$ ). The percentage of patients undergoing repeat procedures and comparisons of each group are shown in Figure 6.

### Complications

Adverse events occurred in eight patients overall including both initial and repeat procedures. These are detailed in Table 5. Two cardiac perforations occurred, resulting in cardiac tamponade. Four patients had



**Figure 5** Percentage of patients free from either atrial fibrillation (AF) or AF, atrial flutter (AFL) or atrial tachycardia (AT) in the high-burden paroxysmal and persistent subgroups after one procedure. The freedom from arrhythmia was highest in the combined pulmonary vein isolation followed by complex fractionated electrogram ablation arm (PVI + CFE) in both the high-burden paroxysmal and persistent subgroups. However, the difference between PVI + CFE and pulmonary vein isolation alone (PVI) was not statistically significant in the high-burden paroxysmal subgroup ( $P = 0.14$ ), whereas it was statistically significant in the persistent subgroup ( $P = 0.03$ ). PVI + CFE had a significantly higher success rate compared with CFE in both subgroups for both endpoints.



**Figure 6** Percentage of patients undergoing repeat ablation procedures in each of the three arms of the study. The combined arm of pulmonary vein isolation followed by complex fractionated electrogram ablation (PVI + CFE) had the lowest percentage of patients undergoing repeat procedures (15%). This difference was statistically significant compared with the complex fractionated electrogram (CFE) arm alone ( $P = 0.008$ ) which had 47% of patients undergoing repeat ablation. There was only a trend towards significance compared with the pulmonary vein isolation (PVI) arm alone ( $P = 0.07$ ), which had 31% of patient undergoing repeat ablation. There was no statistical difference between the percentage of repeat procedures in the PVI and CFE arms alone ( $P = 0.21$ ).

minor bleeding related to the procedure (three femoral hematomas and one hematuria from urinary catheter insertion), none requiring transfusion or intervention. One patient had a vascular complication (pseudoaneurysm) that was managed with local injection, and one

**Table 5** Study adverse events

	CFE	PVI	PVI + CFE
Cardiac tamponade	1	1	0
Minor bleeding <sup>a</sup>	1	1	2
Major bleeding	0	0	0
Vascular complication <sup>b</sup>	0	1	0
Embolic complication	0	0	0
Mild PV stenosis (<50%)	0	1	0
Severe PV stenosis (>50%)	0	0	0
Death	0	0	0

<sup>a</sup>Three femoral hematomas, one hematuria.  
<sup>b</sup>One femoral pseudoaneurysm.

patient had minor (30%) PV stenosis of one vein (left inferior). There were no occurrences of significant PV stenosis, embolic complication, stroke, atrial-esophageal fistula, or death.

## Discussion

### Main findings

This prospective, randomized, multicentre study demonstrates that ablation of CFE alone in high-burden paroxysmal/persistent AF patients has a low success rate when compared with PVI or PVI + CFE after one or two procedures. In spite of using automated, validated CFE mapping software resulting in an acute termination rate of >60%, CFE resulted in a success rate less than 50% and also resulted in the highest number of repeat ablation procedures. In contrast, when CFE was added to PVI, the success rate was superior to either strategy alone after one or

two procedures. Furthermore, PVI + CFE reached higher success rates with fewer repeat ablation procedures compared with the other two strategies. Thus, CFE ablation guided by automated mapping software may have an additive benefit over PVI alone, but does not suffice as an ablation strategy in and of itself. This study is the first randomized, multicentre trial to compare these techniques using a consistent, validated approach to CFE ablation in a high-burden paroxysmal/persistent AF population. It is also unique since it utilized the same ablation strategy for the repeat procedure as was used for the initial ablation.

## Utility of complex fractionated electrograms ablation alone

A substantial amount of information suggests that CFE may be an important target for AF ablation. From early animal and human experiments, it was found that atrial regions exhibiting very rapid activation may represent critical rotors responsible for maintaining AF.<sup>16,17</sup> Furthermore, regions demonstrating very fragmented potentials, to the point of almost continuous baseline activity, may represent pivot points or regions of very slow conduction responsible for continued fibrillatory conduction.<sup>3</sup> Complex fractionated electrograms may also be generated by local changes in autonomic tone and may therefore represent sites of autonomic plexi in the atrium.<sup>18</sup> However, electrogram fractionation may also occur as a result of tissue anisotropy, wavefront collision, or wave break, which can be transient phenomena that change over time.<sup>16,19</sup> Signals that meet the specific definition of CFE may exhibit some transient activity, potentially affected by global AFCL. However, studies have shown that CFE are both spatially and temporally stable, particularly when observed/analysed over a short period of time (2–8 s) as is done with automated mapping algorithms.<sup>20,21</sup>

In the clinical setting, one investigator has been able to achieve very good success rates by exclusively targeting CFE for AF ablation,<sup>4,22</sup> but these results have not been replicated by others.<sup>5</sup> One potential limitation of the latter study is that CFE regions were identified by visual interpretation alone, and this can be challenging given that CFE regions are often low voltage and difficult to localize if not observed over a few seconds. Automated CFE mapping, as employed in the current study, offers more objective identification and ablation of CFE regions.<sup>7</sup> Yet, in spite of this, the success rate of CFE alone was still low even after two procedures. This is not surprising given the known importance of triggers for AF originating from predominantly PV sites.<sup>2</sup> Although CFE ablation may eliminate the substrate required for chronic AF maintenance, it does not eliminate the triggers that can initiate paroxysms of AF and AT/AFL. We had a very low rate of incidental PV isolation as a result of CFE ablation (0.4 PVs isolated per patient).

It is interesting that the low success rate occurred even though the rate of acute procedural AF termination was high (more than 65%), with a substantial prolongation of AFCL, both of which have been shown previously to correlate with long-term freedom from AF.<sup>6</sup> One possible explanation is that acute termination may not be predictive of post-ablation success.<sup>23</sup> Another may be that the changes in AFCL and acute termination may demonstrate

successful alteration of the AF substrate, but this may not be sufficient unless the triggers (PV and non-PV) have been concomitantly eliminated.

## Utility of complex fractionated electrograms as an adjuvant strategy

Previous data have suggested that when elimination of triggers for AF (PVI) is combined with ablation of the substrate required for AF maintenance, the outcome may be improved compared with either approach alone in a variety of AF patients.<sup>7,11,24,25</sup> However, the data on this have been mixed, with some reports suggesting no benefit of additional CFE ablation,<sup>9</sup> or variable benefit depending on the specific AF population targeted.<sup>10</sup> For example, persistent patients may benefit from such additional ablation, whereas paroxysms may not.<sup>24</sup> Again, part of the variability in outcomes may be due to the fact that most of these studies ablated CFE by visual identification alone, without the use of more objective, automated mapping methods. In two studies using automated CFE mapping, there was a promising benefit of adjuvant CFE ablation combined with PVI compared with PVI alone, but neither study was a randomized comparison.<sup>7,8</sup> Another potential explanation is that in this study, biatrial CFE ablation was performed, whereas only the LA was included in the previous data.<sup>9</sup> Furthermore, our study focused on a high-burden AF population, not just a lone paroxysmal population,<sup>10</sup> which may explain why our outcomes differed.

In the present study, the combination of PVI + CFE had the best outcome compared with either of the other two arms in a population of high-burden paroxysmal/persistent AF patients after either one or two procedures. Furthermore, PVI + CFE achieved this success with a smaller number of repeat procedures compared with either of the other two arms. Although there is data suggesting that even lone, paroxysmal AF patients have abnormal atrial substrate changes which may need to be targeted,<sup>14</sup> there was a trend but no statistically significant benefit of PVI + CFE over PVI alone in the high-burden paroxysmal AF subgroup. Pulmonary vein isolation alone may be considered a cornerstone of AF ablation,<sup>1</sup> but it may not be sufficient for higher-burden AF populations. In our study, the one and two procedural success rates for PVI alone were modest, consistent with other single-centre studies showing success rates of 50–75% with 25–50% of these patients typically requiring more than one procedure.<sup>6,9,26</sup> Thus, in spite of the fact that the same incidence of PV isolation was achieved in both the PVI and PVI + CFE arms (94%), the combined arm had a better outcome. In the PVI + CFE arm, the better outcome did seem to correlate with a high rate of procedural termination of AF (73%) and AFCL prolongation, in contrast to the CFE arm. This is likely because the combined arm not only successfully modified the substrate, but also eliminated the triggers for AF.

This study was unique in that all repeat ablation procedures were done using the same approach as the initial randomized strategy, in contrast to prior data where repeat procedures were performed according to the discretion of the operator.<sup>9</sup> Thus, the two procedural success rate of this study is a more accurate reflection of the efficacy of each strategy and also demonstrates how one

strategy may minimize the number of repeat procedures for a patient compared with other approaches.

Finally, any advantage of combined ablation in terms of outcome could be offset by the additional mapping and ablation time. Although the mapping and procedural times for the combined approach were somewhat longer than the PVI approach alone, the differences were not statistically significant, which is consistent with the previous data.<sup>7</sup> The fact that the times for PVI + CFE were very similar to CFE alone may also reflect a learning curve for operators who are more used to performing PVI. Also, the use of automated CFE mapping software may have prevented the additional time for CFE ablation from being excessive.

## Clinical implications

This study is the first multicentre, randomized trial to compare trigger and substrate-based ablation strategies in a high-burden paroxysmal/persistent AF population. The study is also unique in that both initial and repeat ablations involved the same randomized strategy and CFE ablation was guided by objective, validated, automated mapping methods. The results show that CFE ablation coupled with PVI may offer a better outcome with fewer repeat procedures compared with PVI or CFE alone. Furthermore, the benefit can be obtained without excessively prolonging mapping or ablation times. Pulmonary vein isolation alone is moderately effective in this population as a lone strategy, whereas CFE alone results in a poor long-term outcome with significantly more repeat procedures. These results not only build upon the knowledge gained from earlier, single-centre studies, but also serve as the basis for further, larger-scale trials. These results also show that consistent, successful results from AF ablation can be obtained across a spectrum of operators working in medium-volume centres that do not represent the usual high-volume, extensively published centres.

## Study limitations

The study is limited by the sample sizes of each arm, although clear, significant differences were seen between all arms, even after two procedures. To more accurately assess the difference between the PVI and PVI + CFE strategy, a much larger-scale study would have to be performed. Another potential limitation is that the study included a mixed AF population of both paroxysmals and persistents. Previous studies, including this one, have suggested that adjuvant CFE ablation may have a larger impact in persistent AF. However, at the time the protocol was conceived, it was unclear if PVI alone was sufficient for all paroxysmal AF. Data had shown that adjuvant ablation beyond PVI alone was effective in paroxysmal AF.<sup>6,7</sup> Data have also shown that even paroxysmal AF patients with greater amounts of arrhythmia have abnormal atrial substrate changes which may need to be targeted in addition to PV triggers.<sup>7,14</sup> The paroxysmal group in this study represented one with a high burden of disease and very prolonged AF episodes (median 10 h/episode). However, the difference between PVI + CFE and PVI was not statistically significant in the high-burden paroxysmal subgroup. This study also did not include long-standing persistent AF patients (more than 1 year), which limits the applicability of our results. The use of isoproterenol in a minority of patients (10 in CFE arm and 12 in PVI + CFE) may have affected

AFCL, although the baseline CL of 180 ms was not rapid compared with prior publications.<sup>6,7</sup> Furthermore, it is unlikely to have affected CFE given that the automated algorithm averages CFE analysis over several seconds, helping to identify stable, consistent CFE sites vs. transient regions.<sup>20</sup> Atrial fibrillation cycle length may also have been affected by CS ablation, however, CS ablation was done after all LA ablation was complete, and most of the change in AFCL was seen prior to CS ablation. Atrial fibrillation cycle length was also not an endpoint of this study. Finally, this study did not systematically evaluate the efficacy of linear lesions either alone or in combination with other strategies. Whether linear ablation would further improve outcomes or not is a question that requires further, randomized study.

## Conclusions

In high-burden paroxysmal/persistent AF, PVI + CFE has the highest freedom from AF vs. PVI or CFE alone after one or two procedures. Complex fractionated electrogram alone has the lowest one and two procedure success rates with a higher incidence of repeat procedures.

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