Ablation for atrial fibrillation

The impact of adjunctive complex fractionated atrial electrogram ablation and linear lesions on outcomes in persistent atrial fibrillation: a meta-analysis

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Aims
In persistent atrial fibrillation (PsAF), success rates for pulmonary vein isolation (PVI) alone are limited and additional substrate modification is often performed. The two most widely used substrate-based strategies are the ablation of complex fractionated atrial electrograms (CFAE) and left atrial linear ablation (LALA) at the roof and mitral isthmus. However, it is unclear whether adjunctive CFAE ablation or LALA add significant benefit to PVI alone. We performed a meta-analysis to better gauge the benefit of adjunctive CFAE ablation and LALA in PsAF.

Methods and results
Electronic databases were systematically searched. We included studies that examined the impact of CFAE ablation or LALA in addition to a PVI-based strategy on clinical outcomes in PsAF. We included both randomized and non-randomized studies. Totally 10 studies (n = 1821) were included: 6 evaluating CFAE ablation, 3 LALA, and 1 both approaches. In comparison with PVI alone, the addition of CFAE ablation [RR 0.86; 95% confidence intervals (CI) 0.64, 1.16; \( P = 0.32 \)] or LALA (RR 0.64; 95% CI 0.37, 1.09; \( P = 0.10 \)) offered no significant improvement in arrhythmia-free survival. However, adjunctive CFAE ablation was associated with significant increases (\( P < 0.05 \)) and LALA non-significant increases in procedure and fluoroscopy times.

Conclusion
In PsAF, the addition of CFAE ablation or LALA, in comparison with PVI alone, offers no significant improvement in arrhythmia-free survival. Furthermore, they are associated with increases in both procedural and fluoroscopy times. The optimal ablation strategy for PsAF is currently unclear and needs further refinement.

Keywords
Atrial fibrillation • Catheter ablation • Meta-analysis • Complex fractionated atrial electrograms • Pulmonary vein isolation

Introduction
Catheter ablation is a highly successful treatment for patients with symptomatic paroxysmal atrial fibrillation (PAF). In these patients, the cornerstone of ablation is elimination of the atrial fibrillation (AF) triggers by pulmonary veins isolation (PVI), and the degree of success directly correlates with the longevity of vein isolation. However, success rates of catheter ablation in patients with persistent AF (PsAF) are significantly lower. Furthermore, it has been suggested that in PsAF, the pulmonary veins are less important in the pathophysiology and a more complex ‘substrate’-based ablation is necessary in addition to PVI.

The two substrate-based strategies that have achieved most widespread use are the ablation of complex fractionated atrial electrograms (CFAE) and left atrial linear ablation (LALA) at the roof and mitral isthmus (MI). A number of small studies have evaluated the benefit of these substrate-based strategies in addition to PVI. Meta-analyses of these studies have concluded that in PsAF, adjunctive substrate-based ablation improves success rates and their use has been endorsed by a consensus statement. However, a recent large
randomized trial has provided conflicting results and questioned the value of both substrate-based ablation strategies in PsAF. We performed this meta-analysis to incorporate the new data.

**Methods**

**Search strategies**

The electronic databases PUBMED and EMBASE were searched (until May 2015) to find primary references and reviews, together with published bibliographies and the Cochrane library. The following search terms were used: ‘atrial fibrillation’ and ‘catheter ablation’ or ‘complex fractionated atrial electrograms’ or ‘substrate ablation’ or ‘linear ablation’ or ‘mitral isthmus’ or ‘roof line’.

**Study selection and outcomes**

We selected studies that examined the impact of CFAE ablation or LALA, in addition to PVI, on clinical outcomes. For the purposes of the study, LALA was considered as a roof line (joining contralateral superior pulmonary veins) and/or a mitral line (joining the mitral annulus with either the left inferior pulmonary vein or left superior pulmonary vein/roof line).

Studies comparing PVI with CFAE ablation or LALA alone were excluded. If studies included more than two arms, we excluded one of the study arms if it was not relevant to the aims of our analysis.

We selected only studies that included patients with PsAF. Studies that enrolled patients with both PAF and PsAF were included if PsAF data were presented separately and could be extracted.

We included randomized controlled trials (RCTs), prospective non-randomized studies, and retrospective case–control studies.

The following outcomes were evaluated:

- Recurrent AF/atrial tachycardia (AT) off antiarrhythmic drugs (AADs) after a single procedure
- Procedure time
- Fluoroscopy time
- The incidence of major complications

For each study, irrespective of its stated primary endpoint, we aimed to use data for the endpoint of recurrent AF/AT, off AADs, after a single procedure. However, if this was not available, results for success on or off AADs were used.

In view of the potential pro-arrhythmic effect of adjunctive substrate-based ablation, we also evaluated the occurrence of post-procedural atrial flutter/tachycardia after a single procedure.

Studies in the abstract form without a published manuscript were excluded. Studies where the results were reported so that a 2×2 table of results could not be constructed were also excluded.

**Data extraction**

Studies were assessed for eligibility and demographic and clinical outcomes extracted by two independent investigators (P.A.S. and J.S.). Each reviewer extracted the data to construct a 2×2 table for each study. When there were differences between observers, they reviewed the papers together to reach joint conclusions.

**Methodological quality**

For the RCTs, as well as the non-randomized prospective studies, quality assessment was performed using the Cochrane Collaboration’s risk of bias tool.5

**Statistics**

Results were analysed using Review Manager 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Summary estimates of the univariate relative risk (RR) were calculated using the random effects model based on DerSimonian and Laird’s meta-analytic statistical method.6 The random effects model was chosen in view of the significant methodological heterogeneity seen between studies. For all meta-analyses, Cochran’s χ² test and the I² statistic were quantified.7,8

To assess for sources of heterogeneity, we performed sensitivity analysis based on study size (larger vs. smaller), study design (RCT vs. non-RCT), and for CFAE ablation, the approach to CFAE identification (visual vs. automated).

In all analyses, a P-value of < 0.05 was considered significant. Publication bias was assessed graphically by generating a funnel plot of the logarithm of effect size against the standard error for each trial.

**Results**

**Search results**

The search strategy yielded 7557 citations (Figure 1). Of these, 7542 were excluded by title/abstract and 15 retrieved for detailed evaluation: 9 evaluating CFAE ablation, 5 LALA, and 1 study both.

**CFAE ablation**

Of the nine studies, three were excluded. In one study, data for PsAF were not presented separately.9 One study compared electroanatomic mapping system-guided circumferential PVI with CFAE ablation, with electrogram-guided PVI without CFAE ablation.10 As such, it was impossible to differentiate the impact of CFAE ablation from the different approaches to PVI. Lastly, one study compared CFAE ablation alone with CFAE ablation and PVI.11

**Linear lesions**

Of the five studies, two were excluded. In one study, the primary outcome was AT, and data for AF recurrence after ablation in PsAF were not provided.12 Another was excluded as it compared segmental PVI vs. circumferential PVI plus LALA.13 As such, it was
impossible to differentiate the impact of LALA from the different approaches to PVI.

One study evaluated both adjunctive CFAE ablation and LALA and was included in both analyses.4

Overall, 10 studies were included in the analysis, 6 evaluating CFAE ablation, 3 evaluating LALA, and 1 study evaluating both approaches.4,14–22

Study quality
Overall study quality was variable (Table 1). The two non-randomized studies were at high risk of bias, especially the retrospective case–control study by Verma et al.16,19 In the majority of the RCTs, the randomization process was not well described, and therefore, it was difficult to draw definitive conclusions concerning the risk of bias.

Study characteristics
CFAE ablation
The 7 studies enrolled 1368 patients. Of these, 771 were included in our analysis due to the exclusion of one of the randomization arms from 4 of the RCTs (see below) and patients with PAF. There was significant methodological heterogeneity in terms of patient characteristics, study design, and ablation strategy (Table 2).

There were five RCTs, one prospective cohort study,16 and one retrospective case–control study.19

Of the five RCTs, one study randomized patients to PVI alone vs. PVI plus CFAE ablation.17 However, patients were only randomized to CFAE ablation vs. no CFAE ablation if their AF did not terminate after PVI. The other four RCTs had three study arms, and in each, we included only the two arms that helped best achieve the stated aim of our analysis.

In the study by Elayi et al., we excluded the anatomic pulmonary vein (PV) ablation group as PVI was not an endpoint.15 In the study by Dixit et al., we excluded the empiric non-PV ablation group due to its potential overlap with CFAE ablation.18 In STAR AF, we excluded patients who received CFAE ablation alone.18 In STAR AF 2, we excluded the LALA group.4

There was significant variation in the approach to CFAE ablation, including CFAE identification, as well as the areas where CFAEs were targeted.

The endpoint included in our analysis varied. All studies included a blanking period and presented data for recurrent AF/AT after a single procedure. However, while six studies gave data for success off AADs, STAR AF only gave data for success on or off AADs, though few patients (4% with a successful outcome) were actually taking AADs at 12 months.18

Linear lesions
The 4 studies included 1042 patients (Table 2). Of these, 507 patients were included in our analysis due to exclusion of patients with PAF and the CFAE treatment arm in STAR AF 2.4

There was significant methodological heterogeneity in terms of patient characteristics and ablation strategy.

All studies were randomized. With the exception of STAR AF 2, all studies had only 2 randomization arms.4 In three of the studies, the LALA included both roof and mitral lines,4,20,21 while in the fourth study, only a mitral line was performed.22 Acute block across the MI (31–76%) and roof line (44–93%) was achieved variably.

The endpoint included in our analysis varied. All studies included a blanking period and presented data for recurrent AF/AT after a single procedure. Three studies presented data for outcomes off AADs, while one study, by Fassini et al., only presented data for success on or off AADs. However, in this study, the number of patients on AADs at the end of the study was similar in patients with PVI only compared with those receiving adjunctive LALA (56 vs. 50%, respectively).22

Data synthesis
CFAE ablation
During a mean follow-up of 12–36 months, 428 of 771 (56%) patients had recurrent AF/AT after a single ablation procedure.

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**Table 1** Risk of bias in individual studies assessed using Cochrane Collaboration’s bias assessment tool5

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elayi15</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>U</td>
<td>L</td>
</tr>
<tr>
<td>Lin16</td>
<td>H</td>
<td>H</td>
<td>L</td>
<td>L</td>
<td>U</td>
<td>L</td>
</tr>
<tr>
<td>Oral17</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>U</td>
<td>L</td>
</tr>
<tr>
<td>Verma (2010)18</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Dixit14</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Verma (2015)4</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Fassini22</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>U</td>
<td>L</td>
</tr>
<tr>
<td>Willems21</td>
<td>L</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<tr>
<td>Gaita20</td>
<td>L</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>U</td>
<td>L</td>
</tr>
</tbody>
</table>

Only the RCTs and prospective non-randomized studies are included.

H, high risk; L, low risk; U, unclear risk.
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patient no.</th>
<th>Mean/median follow-up time (months)</th>
<th>Design</th>
<th>Persistent AF (%)</th>
<th>Ablation strategies Group 1 (n)</th>
<th>Group 2 (n)</th>
<th>Group 3 (n)</th>
<th>Ablation endpoint and for LALA acute success of block across line</th>
<th>CFAE ID or acute LALA block</th>
<th>CFAE/linear ablation sites</th>
<th>Endpoint used in meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verma16 (2007)</td>
<td>200</td>
<td>12</td>
<td>CCS SC</td>
<td>40</td>
<td>PVI (100)</td>
<td>PVI + CFAE (100)</td>
<td>–</td>
<td>PVI: all signals around PVs abolished CFAE: elimination of all CFAEs at ablation sites</td>
<td>Visual LA septum/ anterior wall</td>
<td>AF/AT beyond 2 months Off AADs Single procedure</td>
<td></td>
</tr>
<tr>
<td>Elayi15 (2008)</td>
<td>144</td>
<td>16</td>
<td>RCT MC</td>
<td>100</td>
<td>PVI (48)</td>
<td>PVI + CFAE (49)</td>
<td>CPVA (47)</td>
<td>PVI: entry block CFAE: elimination of all fractionated areas</td>
<td>Visual LA/RA/CS</td>
<td>AF/AT &gt; 1 min beyond 2 months Off AADs Single procedure</td>
<td></td>
</tr>
<tr>
<td>Lin16 (2009)</td>
<td>60</td>
<td>19</td>
<td>PCS SC</td>
<td>100</td>
<td>PVI + RL + ML (30)</td>
<td>PVI + RL + ML + CFAE (30)</td>
<td>–</td>
<td>PVI: entry block or dissociated potentials CFAE: abolition of local potentials</td>
<td>Auto LA/CS</td>
<td>AF &gt; 1 min beyond 2 months Off AADs Single procedure</td>
<td></td>
</tr>
<tr>
<td>Oral17 (2010)</td>
<td>119</td>
<td>10</td>
<td>RCT SC</td>
<td>100</td>
<td>PVI (50)</td>
<td>PVI + CFAE (50)</td>
<td>–</td>
<td>PVI: entry block or dissociated potentials CFAE: AF termination or 2 h of additional ablation</td>
<td>Visual LA/CS</td>
<td>AF/AT ≥ 30 s beyond 12 weeks Off AADs Single procedure</td>
<td></td>
</tr>
<tr>
<td>Verma18 (2010)</td>
<td>100</td>
<td>12</td>
<td>RCT MC</td>
<td>35</td>
<td>PVI (32)</td>
<td>PVI + CFAE (34)</td>
<td>CFAE (34)</td>
<td>PVI: all signals around PV antrum abolished CFAE: elimination of all CFAE sites or AF termination and AF non-inducibility</td>
<td>Auto LA/RA/CS</td>
<td>AF/AT &gt; 30 s beyond 3 months On or off AADs Single procedure</td>
<td></td>
</tr>
<tr>
<td>Dixit14 (2012)</td>
<td>156</td>
<td>12</td>
<td>RCT SC</td>
<td>100</td>
<td>PVI + ablation of non-PV triggers (55)</td>
<td>PVI + ablation of non-PV triggers + CFAE (51)</td>
<td>PVI + empiric ablation at sites of common non-PV triggers (50)</td>
<td>PVI: entry and exit block CFAE: abolition of local potentials</td>
<td>Auto LA</td>
<td>AF/AT &gt; 30 s beyond 6 weeks Off AADs Single procedure</td>
<td></td>
</tr>
<tr>
<td>Verma4 (2015)</td>
<td>589</td>
<td>18</td>
<td>RCT MC</td>
<td>100</td>
<td>PVI (67)</td>
<td>PVI + CFAE (263)</td>
<td>PVI + RL + ML (259)</td>
<td>PVI: entrance and exit block CFAE: abolition of local potentials</td>
<td>Auto ML 75% RL 93% LA/RA/CS ML + RL</td>
<td>AF/AT &gt; 30 s beyond 3 months Off AADs Single procedure</td>
<td></td>
</tr>
</tbody>
</table>

PVI vs. PVI plus LALA
Overall, there was no difference in the risk of recurrence with adjunctive CFAE ablation in comparison with PVI alone (RR 0.86; 95% confidence intervals [CI] 0.64, 1.16; P = 0.32) with moderate heterogeneity (P = 0.003, I² = 70%) (Figure 2).

The study heterogeneity appeared sensitive to study size (Table 3). When the largest three studies were grouped together, there was a non-significant increase in arrhythmia recurrence with adjunctive CFAE ablation (RR 1.16; 95% CI 0.99, 1.36; P = 0.06) with no heterogeneity (P = 0.39, I² = 0%). In contrast, grouping the four smaller studies together, there was significant benefit from CFAE ablation (RR 0.57; 95% CI 0.42, 0.78; P = 0.0005) with no heterogeneity (P = 0.60, I² = 0%).

When only the five RCTs were included, there was again no benefit from adjunctive CFAE ablation (RR 0.97; 95% CI 0.72, 1.31; P = 0.87). In contrast, the risk of recurrent AF/AT was significantly lower with adjunctive CFAE ablation in the two non-randomized studies (RR 0.54; 95% CI 0.33, 0.90; P = 0.02).

When only the four studies using an automated approach to CFAE identification were included, there was no benefit from CFAE ablation (RR 0.88; 95% CI 0.55, 1.40; P = 0.58).

Only three studies clearly documented the occurrence of atrial flutter/tachycardia following a single procedure. In total, there were 49 cases. The incidence of post-procedural atrial flutter/tachycardia was not significantly different with adjunctive CFAE ablation compared with PVI alone (RR 1.24; 95% CI 0.66, 2.31; P = 0.51) without heterogeneity (P = 0.43, I² = 0%).

Six studies published analysable data on procedure time and five on fluoroscopy time. Adjuvant CFAE ablation was associated with significant increases in both procedure time (mean increase 48 min; 95% CI 30, 65 min; P < 0.00001) and fluoroscopy time (mean increase 16 min; 95% CI 8, 24 min; P = 0.0002).

Only four studies documented analysable complications by treatment group. Overall, there were 24 complications with no significant difference with adjunctive CFAE ablation compared with PVI alone (RR 1.04; 95% CI 0.43, 2.48; P = 0.94).

There was asymmetry within the funnel plot, with smaller studies demonstrating a greater benefit from CFAE ablation than larger studies (Figure 3A).

### Linear lesions

During a mean follow-up of 12–36 months, 322 of 507 (64%) patients had recurrent AF/AT after a single procedure. Overall, there was no difference in the risk of recurrence with adjunctive LALA in comparison with PVI alone (RR 0.64; 95% CI 0.37, 1.09; P = 0.10) with marked heterogeneity (P < 0.0001, I² = 88%) (Table 3 and Figure 4).

The study heterogeneity in part appeared sensitive to study size (Table 3). When the two smaller studies were grouped together, there was significant benefit from LALA (RR 0.39; 95% CI 0.25, 0.59; P < 0.00001) without heterogeneity (P = 0.96, I² = 0%). In contrast, when the largest two studies were combined, there was no difference in recurrence (RR 0.94; 95% CI 0.57, 1.56; P = 0.81), though the heterogeneity remained (P = 0.006, I² = 87%).

Only two studies clearly documented the occurrence of atrial flutter/tachycardia following a single procedure. In total, there were 44 cases. The incidence of post-procedural atrial flutter/
Tachycardia was not significantly different following adjunctive LALA in comparison with PVI alone (RR 1.27; 95% CI 0.61, 2.62; \( P = 0.52 \)) without heterogeneity (\( \chi^2 = 0.10; \, df = 6 \, (P = 0.003); \, I^2 = 70\% \)).

One study presented analysable data on procedure time and three on fluoroscopy time.\(^4\)\(^,\)\(^22\) Adjunctive LALA ablation was associated with a non-significant increase in fluoroscopy time (mean increase 6 min; 95% CI 1.13 min; \( P = 0.08 \)). Only STAR AF 2 provided analysable data on procedure time, with LALA associated with a significant increase compared with PVI alone (mean increase 56 min; 95% CI 39, 73 min; \( P < 0.00001 \)).

Two studies documented complications by treatment group.\(^4\)\(^,\)\(^22\) Overall, there were 25 complications with no significant difference with adjunctive LALA ablation compared with PVI alone (RR 1.41; 95% CI 0.53, 3.77; \( P = 0.50 \)).

There was asymmetry within the funnel plot, with smaller studies demonstrating a greater benefit from LALA ablation than larger studies (Figure 3B).

**Discussion**

This meta-analysis, including data on over 1200 patients, has demonstrated that in PAF, additional substrate modification, using CFAE ablation or LALA, offers no significant improvement in arrhythmia-free survival in comparison with PVI alone. Furthermore, both substrate-based approaches are associated with increases in procedural and fluoroscopy times.

The results of our analysis differ significantly from prior meta-analyses, which have consistently found that additional substrate ablation improves outcomes in comparison with PVI alone.\(^2\) The differences in our results predominantly relate to the addition of new data from STAR AF 2.\(^4\) However, it is noteworthy that for both substrate modification techniques early smaller studies demonstrated a significant benefit from adjunctive ablation that subsequent larger studies failed to confirm. Furthermore, although the number of studies is small, making interpretation difficult, both

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**Table 3** Summary estimates of RRs of recurrent AF/AT after a single procedure for adjunctive CFAE ablation or LALA in comparison with PVI alone

<table>
<thead>
<tr>
<th>Summary estimates</th>
<th>RR (95% CI)</th>
<th>Patient number</th>
<th>Events</th>
<th>No. of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFAE ablation—recurrent AF/AT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>0.86 (0.64, 1.16)</td>
<td>771</td>
<td>428</td>
<td>7</td>
</tr>
<tr>
<td>Only randomized studies</td>
<td>0.97 (0.72, 1.31)</td>
<td>631</td>
<td>383</td>
<td>5</td>
</tr>
<tr>
<td>Only non-randomized studies</td>
<td>0.54 (0.33, 0.90)</td>
<td>140</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>Larger studies</td>
<td>1.16 (0.99, 1.36)</td>
<td>511</td>
<td>326</td>
<td>3</td>
</tr>
<tr>
<td>Smaller studies</td>
<td>0.57 (0.42, 0.78)</td>
<td>260</td>
<td>102</td>
<td>4</td>
</tr>
<tr>
<td>Automated CFAE identification</td>
<td>0.88 (0.55, 1.40)</td>
<td>494</td>
<td>299</td>
<td>4</td>
</tr>
<tr>
<td>Manual CFAE identification</td>
<td>0.80 (0.55, 1.17)</td>
<td>277</td>
<td>129</td>
<td>3</td>
</tr>
<tr>
<td>Linear lesions—recurrent AF/AT</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>0.64 (0.37, 1.09)</td>
<td>507</td>
<td>322</td>
<td>4</td>
</tr>
<tr>
<td>Larger studies</td>
<td>0.94 (0.57, 1.56)</td>
<td>384</td>
<td>261</td>
<td>2</td>
</tr>
<tr>
<td>Smaller studies</td>
<td>0.39 (0.25, 0.59)</td>
<td>123</td>
<td>61</td>
<td>2</td>
</tr>
</tbody>
</table>
funnel plots were asymmetrical, with smaller studies tending to demonstrate more positive results in favour of CFAE ablation or LALA. While there are a number of potential causes for such asymmetry, it is possible that publication bias contributed to this finding.

In our analysis, neither CFAE ablation nor LALA was associated with an increase in major complications. However, it was not powered to detect significant differences in safety. Furthermore, since both ablation approaches increase procedure and fluoroscopy times, adjunctive substrate ablation has the potential to increase risk. Furthermore, a longer procedure time is likely to increase cost, though this is more difficult to quantify.

One of the contentious issues in substrate-based ablation is the optimal procedural endpoint. While the endpoint of PVI is relatively objective and reproducible, endpoints for substrate-based ablation strategies are much more subjective and the optimal endpoint for CFAE ablation is less clear-cut. A number of observational studies have suggested that AF termination to sinus rhythm during ablation is associated with improved outcomes, and as a consequence, AF termination has been proposed as an important endpoint for any PsAF ablation strategy. The CFAE RCTs included in our analysis largely used the broad endpoint of AF termination to sinus rhythm or abolition of all identified CFAE signals. However, the endpoint of elimination of all CFAE electrograms is relatively subjective and open to interpretation by the operator. It is possible that a greater emphasis on the endpoint of AF termination in the CFAE studies may have resulted in more extensive ablation and led to improved outcomes.

Another difficult issue in CFAE ablation is identifying optimal target sites. While early studies used a visual approach, recent studies used automated software to improve objectivity and reproducibility. However, in our analysis, the approach to CFAE identification had no significant impact on results.

Despite the widespread use of CFAE ablation, their exact pathophysiology is unclear. When they were initially proposed as a therapeutic target, it was suggested that CFAE activity might represent the continuous re-entry of fibrillation waves. However, subsequent evidence has suggested that the mechanisms underlying CFAEs are diverse, and in some cases, they may be caused by remote activity at the recording site, rather than pure local effects.

In contrast, the importance of atrial fibrosis in AF is well established. The degree of left atrial fibrosis is strongly associated with AF progression, and an increase in fibrosis is independently associated with arrhythmia recurrence after ablation. However, CFAE sites are more likely to be found in areas of healthy atrial tissue, rather than dense scar.

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**Figure 3** Funnel plot of the logarithm of effect size plotted against the standard error for each trial assessing the benefit of adjunctive CFAE ablation (A) and LALA (B) compared with PVI alone.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight</th>
<th>Risk ratio M-H, random, 95% Cl</th>
<th>Year</th>
<th>Risk ratio M-H, random, 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fassini</td>
<td>20.7%</td>
<td>0.38 [0.20, 0.74]</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Willems</td>
<td>23.0%</td>
<td>0.39 [0.23, 0.67]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Gaita</td>
<td>27.6%</td>
<td>0.72 [0.54, 0.97]</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>Verma 2015</td>
<td>28.6%</td>
<td>1.20 [0.96, 1.50]</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.64 [0.37, 1.09]</td>
<td></td>
<td></td>
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<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\tau^2 = 0.25$; $\chi^2 = 24.23$, df = 3 ($P &lt; 0.0001$); $I^2 = 88%$</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.66$ ($P = 0.10$)</td>
<td></td>
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</tbody>
</table>

**Figure 4** Summary of the RR of recurrent AF/AT after a single procedure with adjunctive LALA compared with PVI alone.
Taken together, these findings question the importance of CFAEs in the pathophysiology of PsAF and in turn the relevance of empiric CFAE ablation in improving outcomes.

The utilization of LALA to treat PsAF is based on the hypothesis that multiple re-entrant wavelets are responsible for AF perpetuation, and that reducing their number by atrial compartmentalization will terminate AF. However, the use of LALA in AF ablation has well-recognized disadvantages, including an inability to achieve block across ablation lines and recovery across previously blocked lines. Both factors may be arrhythmogenic, which may explain why LALA does not appear to improve outcomes following percutaneous AF ablation.25 In our study, the incidence of post-ablation atrial flutter/tachycardia was not significantly increased following PVI with adjunctive LALA compared with PVI alone, though the analysis was significantly underpowered to address this question.

In the studies included in our analysis, acute block across the MI and roof line was achieved variably. Although this variation in successful block did not appear to underlie the difference in outcome between the studies, it is possible that improving the rate of block may improve outcomes. In addition, to try to reduce methodological heterogeneity, we limited LALA to linear lesions at the roof and MI. However, other linear lesions are sometimes performed, and it is possible that these additional lines may improve outcomes.

In PsAF ablation, repeat procedures are often performed, and published success rates after multiple procedures are typically significantly higher than after a single procedure. In our analysis, we used the endpoint of recurrent AF/AT, off AADs, after a single procedure. We chose this as it is a uniformly reported endpoint, it is more easily comparable between study arms as often the proportion of patients with redo procedures is different between groups, and in repeat procedures, the operator does not necessarily follow the original ablation strategy.

It is possible that adjunctive substrate ablation with CFAE or LALA has greater benefit when used as part of a multiple procedure strategy, rather than after a single procedure. Due to the limited data available, it was not possible to address this question in our analysis. However, STAR AF 2 did provide comprehensive multiple procedure results, with operators mandated to adhere to the original ablation strategy during repeat procedures.7 Repeat ablation was performed in 21% of the PVI group, 26% of the CFAE group, and 33% of the LALA group. In each group, success rates improved with multiple procedures, with freedom from AF/AT with or without AADs seen in 61, 50, and 48% of patients, respectively. However, no benefit from adjunctive substrate ablation was seen.

The optimal ablation strategy for PsAF is therefore unclear. Although in unselected patients success rates for PVI alone have been limited, the benefit of the two most widely endorsed substrate-based ablation strategies—CFAE ablation and LALA—is uncertain.1 More recently, alternative more patient-specific approaches to substrate modification have been proposed.27,28 These include the identification and ablation of focal sources and rotors and the targeting of low-voltage left atrial areas. Although these have shown encouraging early results, they require further detailed evaluation.

In addition, it is possible that in certain PsAF patients, potentially identified using clinical factors or imaging, PVI alone may be adequate.25 Of interest here are the results of the SARA study, a randomized study comparing ablation with AADs in 146 PsAF patients.29 In this study, which excluded patients with longstanding PsAF, a severe cardiomyopathy and advanced atrial remodelling, the majority of the 98 patients randomized to an ablation strategy had PVI alone. At 12 months, success in the ablation group was over 70%.

Limitations

Although meta-analysis is a well-recognized technique, it has limitations. Key amongst these is the difficulty in combining studies with differing methodology. The studies we included demonstrated significant methodological heterogeneity, most importantly concerning differences in ablation strategy, the approach to CFAE ablation, the type of LALA performed, and the study endpoints. Although we used a random effects model in our analysis to take account of this heterogeneity, these factors are important and need to be considered when interpreting our findings.

Though most studies gave data for our stated endpoint of recurrent AF/AT off AADs after a single procedure, in two studies, results were only given for patients on or off AADs. However, in STAR AF, at the end of the study, only 4% of patients with a successful procedure were actually on AADs, and in the study by Fassini et al., the proportion of patients taking AADs was very similar in the two study groups, suggesting that AAD use is unlikely to have had a major impact on our results.18,22

Only two studies included patients with purely longstanding PsAF. It is possible that patients with a more advanced AF substrate, as may be found in longstanding PsAF, may benefit more from empiric substrate modification. In addition, it is possible that a substrate-based approach combining CFAE ablation and LALA may be superior to using each technique individually. However, from the data included in our analysis, it was not possible to answer either question.

Although our analysis included a significantly larger number of patients than previous studies, the number of studies and patients is still relatively small. Furthermore, follow-up in many studies was short.

Conclusion

In PsAF, the addition of CFAE ablation or LALA, in comparison with PVI alone, offers no significant improvement in arrhythmia-free survival. The optimal ablation strategy for PsAF is currently unclear and needs further refinement.

Conflict of interest: None declared.

References

Adjunctive complex fractionated atrial electrogram ablation and linear lesions


