Efficacy of adjunctive ablation of complex fractionated atrial electrograms and pulmonary vein isolation for the treatment of atrial fibrillation: a meta-analysis of randomized controlled trials
Kong MH, Piccini JP, Bahnson TD

CRD summary
The review found that pulmonary vein isolation plus complex fractionated atrial electrogram ablation increased freedom from atrial fibrillation after a single procedure compared with pulmonary vein isolation alone. However, procedure times were significantly longer. These conclusions require cautious interpretation due to limitations in the review, including marked variation between the included trials and lack of assessment of trial quality.

Authors' objectives
To assess the effectiveness of pulmonary vein isolation plus complex fractionated atrial electrogram ablation for treating drug-refractory atrial fibrillation.

Searching
MEDLINE, the Cochrane Library, the US Food and Drug Administration, and ClinicalTrials.gov were searched. Search terms were reported. Reference lists of studies retrieved and expert consensus documents were checked. The search was limited to full-length peer-reviewed publications in English.

Study selection
Randomised controlled trials (RCTs) of stand-alone pulmonary vein isolation versus pulmonary vein isolation plus complex fractionated atrial electrogram ablation (adjunctive complex fractionated atrial electrogram ablation) in adults (over 18 years old) with atrial fibrillation were eligible for inclusion. Trials had to include at least three months' follow-up.

The primary outcome of interest was freedom from atrial fibrillation or atrial tachycardia after a single ablation, with or without the use of anti-arrhythmic drugs. Secondary outcomes of interest were repeat ablation, post-procedural atrial tachycardia, procedural times, complications and post-ablation use of anti-arrhythmic drugs.

The mean age of participants in the included trials was 58 years; most were male (76%). The mean duration of atrial fibrillation was six years (where reported). The mean left atrial diameter was 44.4mm and mean left ventricular ejection fraction was 55.7%. Participants had longstanding persistent atrial fibrillation and/or paroxysmal atrial fibrillation, described as drug-refractory in most trials.

Most included trials administered either antral or circumferential pulmonary vein isolation followed (in the intervention group) by complex fractionated atrial electrogram ablation; most used a similar definition of complex fractionated atrial electrograms, which was based on published criteria (Nadamee 2004). Maximum energy outputs, target temperatures during radio-frequency energy delivery and use of anticoagulant and anti-arrhythmic drugs varied widely across trials. Trial definitions of freedom from atrial fibrillation or atrial tachycardia were varied. Additional review outcomes included atrial fibrillation organisation into atrial fibrillation during ablation and subsequent conversion to sinus rhythm.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Odds ratios (ORs) with 95% confidence intervals (CIs) were extracted or calculated for dichotomous outcomes. Means, with standard deviations for continuous outcomes, were compared using the student's t-test. Groups receiving
pulmonary vein isolation with complex fractionated atrial electrogram ablation were compared with groups receiving any type of pulmonary vein isolation alone. Study groups receiving complex fractionated atrial electrogram ablation alone were excluded from analysis. Data were analysed by intention-to-treat.

Two reviewers independently extracted the data, with disagreements resolved by a third reviewer.

**Methods of synthesis**
Dichotomous data were combined to calculate pooled odds ratios and 95% confidence intervals using the DerSimonian Laird random-effects model. Methods used to combine continuous data were not reported. Heterogeneity was assessed using $I^2$. A subgroup analysis was conducted by type of atrial fibrillation (persistent or paroxysmal) and the effect of excluding each study in turn was examined.

**Results of the review**
Six RCTs were included (n=538 participants, range 60 to 144). The prognostic characteristics of participants did not differ significantly at baseline. The mean duration of follow-up ranged from three to 17 months for the primary outcome of freedom from atrial fibrillation or atrial tachycardia after a single ablation.

At three or more months’ follow-up, adjunctive complex fractionated atrial electrogram ablation was associated with significantly higher rates of freedom from atrial fibrillation or atrial tachycardia than pulmonary vein isolation alone (OR 2.0, 95% CI 1.04 to 3.8; six RCTs), with moderate heterogeneity ($I^2=63\%$).

Rates of repeat ablation did not differ significantly between the groups. Adjunctive complex fractionated atrial electrogram ablation was associated with significantly longer mean total procedural time, fluoroscopy time and radiofrequency energy application time than pulmonary vein isolation alone (all p<0.001). Rates of post-procedural atrial tachycardia were poorly reported in the included trials. Data on procedural complications were also poorly reported and did not permit comparison of the groups (total 18 events reported in five RCTs).

In subgroup analysis by type of atrial fibrillation, the findings were no longer statistically significant for either paroxysmal atrial fibrillation (OR 1.4, 95% CI 0.74 to 2.7; three RCTs; $I^2=6\%$), or persistent atrial fibrillation (OR 2.1, 95% CI 0.42 to 10.3; two RCTs; $I^2=88\%$).

Other outcomes were reported in the review.

**Authors’ conclusions**
Pulmonary vein isolation with adjunctive complex fractionated atrial electrogram ablation increased the likelihood of freedom from atrial fibrillation after a single procedure. However, procedural times were significantly increased.

**CRD commentary**
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies. The search restriction by language and publication status meant that some studies might have been missed. It did not appear that publication bias was formally assessed. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently extract the data, but the process used for study selection was not described.

It did not appear that study quality was systematically assessed. Adequate detail was provided on the clinical characteristics of individual trials. Appropriate statistical methods were used to pool the dichotomous data, assess for statistical heterogeneity and investigate differences between the studies. As the authors noted, the included trials had small samples, differed widely in participant characteristics and study protocols, and had relatively short duration of follow-up.

The authors’ conclusions require cautious interpretation due to limitations in the review, including marked heterogeneity between the trials and failure to assess trial quality.

**Implications of the review for practice and research**
Practice: The authors stated that the benefits of pulmonary vein isolation with adjunctive complex fractionated atrial electrogram ablation for atrial fibrillation need to be weighed against possible added risks associated with increased procedural, fluoroscopy and radio-frequency energy application times.

Research: The authors stated that more studies are needed to evaluate risks and benefits associated with adjunctive complex fractionated atrial electrogram ablation, including its efficacy in the absence of anti-arrhythmic drugs and in specific groups (such as those with persistent atrial fibrillation). Studies with longer-term follow-up are needed.

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