Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials

Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM

CRD summary
This review found pulmonary vein isolation in patients with atrial fibrillation was associated with increased odds of freedom from atrial fibrillation and fewer cardiac hospitalisations at 12 months follow-up. The unknown quality of the included trials and potential flaws in the analysis mean that the reliability of the authors' conclusions is not clear.

Authors' objectives
To evaluate the efficacy and safety of pulmonary vein isolation compared with medical therapy for patients with atrial fibrillation.

Searching
MEDLINE (January 1993 to December 2008), the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched for relevant published studies in English in peer reviewed publications. Search terms were reported. References of the included studies and of two expert consensus statements were searched for additional studies.

Study selection
Randomised controlled trials (RCTs) in which adults aged 19 years or over with atrial fibrillation received either pulmonary vein isolation or control/anti-arrhythmic therapy for the maintenance of sinus rhythm were eligible for inclusion. Trials were excluded when: patients in a previously reported study were included in the analysis; catheter ablation was used in two treatment arms; follow-up was less than 12 months; the control arm had less than 10 patients; surgical ablation was included; and when only patients with atrial flutter were included in a trial.

The majority of the included trials compared pulmonary vein isolation with anti-arrhythmic drug therapy and used the catheter ablation technique of circumferential pulmonary vein isolation; the remaining trial used segmental pulmonary vein isolation. There was substantial variation in pulmonary vein isolation methods, ablation end points, and methods of monitoring for recurrent atrial fibrillation at follow-up. The included patients comprised those with either persistent or paroxysmal atrial fibrillation. The mean age of the patients was 55 years, and men comprised 73% of the patients (where reported). The mean left ventricular ejection fraction of the patients was 60±4%. The primary outcome was freedom from atrial fibrillation at 12 months follow-up. Other outcomes evaluated were incidence of repeat pulmonary vein isolation, crossover to ablation therapy, hospitalisation for cardiac reasons, thromboembolic events, pulmonary vein stenosis, oesophageal injury, and all-cause mortality.

Two reviewers independently reviewed the citations to select studies.

Assessment of study quality
Quality items were summarised in terms of a priori sample size calculations.

The authors did not state how they assessed methodological quality.

Data extraction
Two reviewers independently extracted data to calculate odds ratios (OR), with corresponding 95% confidence intervals (CI), for the outcomes of interest, and complications of the procedure, using standardised forms. All outcomes were assessed using intention-to-treat analyses.

Methods of synthesis
The pooled odds ratios and 95% confidence intervals were calculated using a DerSimonian and Laird random-effects
model. The treatment effects for cardiovascular hospitalisations were reported with rate ratios using hospitalisations per patient years of exposure. Statistical heterogeneity was assessed using the Cochran Q statistic and the I² test.

To evaluate publication bias, the authors plotted trial precision (log/standard error) against the log odds ratio for the treatment effect, and evaluated funnel plots.

**Results of the review**

Six RCTs were included in the review (n=693 patients). Three trials did not report power calculations; the remaining three trials enrolled sufficient patients to fulfil sample size calculations. In trials where crossovers were permitted, 51% of patients assigned to receive non-catheter ablation crossed over and received pulmonary vein isolation. Across four trials that evaluated repeat performance of pulmonary vein isolation, 17% of patients required a repeat procedure. Follow-up was 12 months in all the trials.

There were statistically significant benefits observed with the use of pulmonary vein isolation for maintaining sinus rhythm (OR 9.74, 95% CI 3.98 to 23.87; six trials). There was significant statistical heterogeneity (Cochran Q statistic p<0.001). After the exclusion of one trial that enrolled only patients with persistent atrial fibrillation, higher odds of atrial fibrillation-free survival were found for patients for whom the majority presented with paroxysmal atrial fibrillation (OR 15.78, 95% CI 10.07 to 24.73).

In two trials that reported freedom from atrial fibrillation and anti-arrhythmic medication, 86% of patients randomly assigned to receive pulmonary vein isolation were free from atrial fibrillation and requiring anti-arrhythmic medication at 12 months follow-up.

Pulmonary vein isolation was associated with significantly decreased hospitalisation for cardiac causes (rate ratio 0.15, 95% CI 0.10 to 0.23; three trials).

The rate of major complications with pulmonary vein isolation was 2.6% and included tamponade, symptomatic pulmonary vein stenosis, pericardial effusion, phrenic nerve paralysis, and thromboembolic events. The rate of major complications for the patients who received antiarrhythmic medication was 8%, including pro-arrhythmia with flecainide, thyroid dysfunction secondary to amiodarone, sexual impairment, gastroenterological impairment, corneal micro-deposits, abnormal liver function tests, and sinus node dysfunction caused by amiodarone.

There was no evidence of publication bias from the analysis of the funnel plot.

**Authors’ conclusions**

The use of pulmonary vein isolation was associated with significant freedom from atrial fibrillation at one year of follow-up compared with treatment strategies that did not include pulmonary vein isolation ablation. The risk of major complications was comparable to other invasive interventional procedures in this population.

**CRD commentary**

The review addressed a clear question and criteria pertaining to inclusion were specified. The authors searched appropriate databases, but as the review was restricted to only full-length published trials written in English, there were risks of publication and language bias. Steps were taken to minimise errors and bias for study selection and data extraction, but were not reported for the assessment of methodological quality.

The authors did not appear to have formally assessed the methodological quality of the included trials, and the limited information provided made it difficult to make a judgement about the reliability of the results. Although the reviewers stated statistical heterogeneity was assessed, they only published the test for heterogeneity for the primary outcome, which was statistically significant. This meant that it was difficult to make a judgement about the appropriateness of pooling of trial results, given the clinical heterogeneity across the trials, which the authors correctly acknowledged.

The authors’ conclusions appeared to reflect the evidence presented. Some methodological limitations, including the risk of language and publication biases, the lack of formal quality assessment and the potential flaws arising in analysis, mean that it is difficult to make a judgement about the reliability of the authors’ conclusions.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that long-term randomised trials are required to ascertain safety and efficacy of pulmonary vein isolation for the maintenance of sinus rhythm, particularly in older patients, patients with multiple comorbidities (such as congestive heart failure caused by systolic or diastolic dysfunction), and patients with significant left atrial enlargement. Further trials of catheter ablation for atrial fibrillation should also incorporate cost-effectiveness analyses.

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