Meta-analysis of transcatheter closure versus medical therapy for patent foramen ovale in prevention of recurrent neurological events after presumed paradoxical embolism

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CRD summary
This review included observational studies of patients with a heart defect (patent foramen ovale) who had a stroke of unknown cause or transient ischaemic attack. The authors concluded that repair of the defect reduced risk of a further neurological event compared with medical therapy. Potential for biases and uncertain quality of the evidence base limit the reliability of this conclusion.

Authors' objectives
To compare the rate of recurrent neurological events between transcatheter closure and medical management of patients with cryptogenic stroke/transient ischaemic attack and concomitant patent foramen ovale (congenital heart defect).

Searching
The Cochrane Library, EMBASE and MEDLINE were searched. Search terms were reported.

Study selection
Observational studies of transcatheter closure or those that compared transcatheter closure with medical therapy (with at least 100 patients) were eligible for inclusion. Studies had to report the primary outcome of recurrent stroke or transient ischaemic attack. Secondary outcomes included procedural failure, device-related complications, and residual shunting post-procedure. Studies that reported composite outcomes for atrial septal defects along with patent foramen ovale were excluded.

The included studies used a variety of devices for patent foramen ovale closure including Cardia, Helex, CardiSEAL, Angelwings, and Occlutech. The mean age of patients ranged from 38 to 53 years. The rate of atrial septal aneurysm ranged from 4.5 to 62% and the rate of hypertension ranged from 6 to 51.6% (where reported). The rates of hyperlipidaemia, smoking and diabetes varied across studies. Studies used various antiplatelet and anticoagulant therapies.

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

Assessment of study quality
Quality assessment was not undertaken using a standard tool, although quality items such as selection characteristics, ascertainment of outcome and loss to follow-up were discussed.

The authors did not state how many reviewers undertook quality assessment.

Data extraction
Data were extracted on the incidence of recurrent stroke, transient ischaemic attack and secondary outcomes, and used to calculate risk differences (RDs), odds ratios (ORs), relative risks (RRs) and incidences, with 95% confidence intervals (CIs).

The authors did not state how many reviewers extracted the data.

Methods of synthesis
Fixed-effect meta-analysis was used to calculate pooled incidence, odds ratios, risk differences and relative risks, with 95% confidence intervals. \( I^2 \) was used to assess statistical heterogeneity; random-effects meta-analysis was used when there was substantial heterogeneity (\( I^2 > 50\% \)).

Subgroup analysis by type of device was conducted. Meta-regression was used to assess the effect of various patient characteristics on outcome.
Publication bias was assessed using funnel plots and Egger's test. The Duval and Tweedie trim-and-fill method was used when there was significant publication bias.

**Results of the review**

Forty-eight studies were included in the review (10,327 patients): ten comparative studies, and 38 non-comparative studies. The study sample size ranged from 16 to 1,055 patients. The length of follow-up ranged from 0.1 to 6.7 years. The loss to follow-up ranged from 0 to 19.2%, where reported.

Transcatheter closure was associated with statistically significantly reduced risk of recurrent neurological events compared with medical therapy (RR 0.25, 95% CI 0.11 to 0.58; I²=66%; 10 studies). The pooled incidence of recurrent neurological events was 0.76 per 100 patient years (95% CI 0.48 to 1.05) for transcatheter closure and 4.39 per 100 patient years (95% CI 3.20 to 5.59) for medical therapy.

Subgroup analysis indicated that the risk of neurological events was lower with anticoagulants compared with antiplatelets (RR 0.58, 95% CI 0.41 to 0.82; 12 studies; I²=0%). The risk of recurrent neurological events was significantly lower with no residual shunt than shunt patients (OR 0.33, 95% CI 0.21 to 0.53; 17 studies).

Other results were presented in the review.

There was no evidence of publication bias with transcatheter closure studies, but there was evidence of bias with medical therapy studies.

**Authors' conclusions**

Accepting the limitations of the review, surgical transcatheter closure was associated with a reduction in neurological events compared with medical therapy.

**CRD commentary**

Inclusion criteria for the review were broadly defined. Three relevant databases were searched, but the search dates and language restrictions were not reported. Publication bias was assessed and was detected in one of the analyses. The authors did not state if any attempts were made to reduce reviewer error and bias during the review.

Quality assessment of the included studies was not undertaken using a standard checklist, which made it difficult to assess the reliability of the evidence base. Data were combined using meta-analysis, although there was evidence of substantial statistical heterogeneity in some of the analyses. The authors noted that the choice of medical therapy versus transcatheter closure was often down to patient choice, which may have introduced selection bias. The authors acknowledged that many of the studies had short follow-up periods, which may not be sufficient to detect recurrent ischaemic events.

The potential for biases, notably selection bias, and the uncertain quality of the evidence base limit the reliability of the pooled results. The authors' call for further research appears warranted.

**Implications of the review for practice and research**

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

**Research:** The authors stated that further randomised controlled trials were needed to determine the benefit of transcatheter closure versus medical management. Ongoing randomised controlled trials may help clarify the issue.

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**Bibliographic details**

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