Closure Versus Medical Therapy for Preventing Recurrent Stroke in Patients With Patent Foramen Ovale and a History of Cryptogenic Stroke or Transient Ischemic Attack

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The optimal therapy for preventing recurrent stroke in people with cryptogenic stroke and patent foramen ovale (PFO) has not been defined. The choice between medical therapy (antithrombotic treatment with antiplatelet agents or anticoagulants) and transcatheter device closure has been the subject of intense debate during the past several years. Despite the lack of scientific evidence, a substantial number of people undergo transcatheter device closure (TDC) for secondary stroke prevention.

Objectives
To compare the safety and efficacy of TDC with best medical therapy alone for preventing recurrent stroke (fatal or nonfatal) or transient ischemic attacks (TIAs) in people with PFO and a history of cryptogenic stroke or TIA and to identify specific subgroups of people most likely to benefit from closure for secondary prevention.

Search Methods
We searched the Cochrane Stroke Group Trials Register (July 2014), the Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library Issue 2, 2014), MEDLINE (1950 to July 2014), and EMBASE (1980 to July 2014). In an effort to identify unpublished and ongoing trials, we searched 7 trial registers and checked reference lists.

Selection Criteria
We included randomized controlled trials, irrespective of blinding, publication status, and language, comparing the safety and efficacy of device closure with medical therapy for preventing recurrent stroke or TIA in patients with PFO and a history of cryptogenic stroke or TIA.

Data Collection and Analysis
Two review authors independently selected trials for inclusion, assessed quality, and extracted data. The primary outcome measures of this analysis were the composite end point of ischemic stroke or TIA events as well as recurrent fatal or nonfatal ischemic stroke. Secondary end points included all-cause mortality, serious adverse events (atrial fibrillation, myocardial infarction, bleeding), and procedural success and effective closure. We used the Mantel–Haenszel method to obtain pooled risk ratios using the random-effects model regardless of the level of heterogeneity. We pooled data for the primary outcome measure with the generic inverse variance method using the random-effects model, yielding risk estimates as pooled hazard ratio, which accounts for time-to-event outcomes.

Main Results
We included 3 randomized controlled trials involving a total of 2303 participants: 1150 participants were randomized to receive TDC and 1153 participants were randomized to receive medical therapy. Overall, the risk of bias was regarded as high. The mean follow-up period of all 3 included trials was less than 5 years. Baseline characteristics (age, sex, and vascular risk factors) were similar across trials. Intention-to-treat analyses did not show a statistically significant risk reduction in the composite end point of recurrent stroke or TIA in the TDC group when compared with medical therapy (risk ratio: 0.73; 95% confidence interval [CI], 0.45–1.17; Figure). A time-to-event analysis combining the results of 2 randomized controlled trials also failed to show a significant risk reduction with TDC (hazard ratio: 0.69; 95% CI, 0.43–1.13). When assessing stroke prevention alone, TDC still did not show a statistically significant benefit (risk ratio: 0.61; 95% CI, 0.29–1.27; hazard ratio: 0.55; 95% CI 0.26–1.18). In a sensitivity analysis including the 2 studies using the Amplatzer PFO Oceluder, TDC showed a possible protective effect on recurrent stroke compared with medical therapy (hazard ratio: 0.38; 95% CI, 0.14–1.02); however, it did not reach statistical significance. Safety analysis found that the overall risks for all-cause mortality and adverse events were similar in both the TDC and medical therapy groups. However, TDC increased the risk of new-onset stroke in patients with PFO and a history of cryptogenic stroke or TIA.

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atrial fibrillation (risk ratio: 3.50; 95% CI, 1.47–8.35) and may be associated with the type of device used.

**Conclusions**

The combined data from recent randomized controlled trials have shown no statistically significant differences between TDC and medical therapy in the prevention of recurrent ischemic stroke. The Amplatzer device closure showed a trend of protective effect in recurrent stroke compared with medical therapy, but this was associated with a significantly increased risk of atrial fibrillation. TDC closure was associated an increased risk of atrial fibrillation but not serious adverse events. Ongoing PFO closure trials and registries may provide further insight into the controversial issue of PFO closure in people with cryptogenic stroke or TIA and guide clinicians to the proper selection of closure device and people who may benefit.

This article is based on a Cochrane Review published in The Cochrane Library 2015, Issue 9 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.¹

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**Disclosures**

None.

**References**


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**Key Words:** atrial fibrillation ■ confidence interval ■ myocardial infarction ■ risk factors ■ secondary prevention
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