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Patent Foramen Ovale Closure for Recurrent Stroke Prevention: A Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Patent foramen ovale (PFO) has been shown to be associated with recurrent strokes. Randomized controlled trials (RCTs) evaluating the benefit of transcatheter closure of PFO over medical therapy in patients with cryptogenic stroke showed inconsistent results.

Objectives: We aimed by performing network meta-analysis to evaluate three different treatment strategies for stroke prevention, namely, PFO closure, antiplatelet therapy and oral anticoagulation.

Methods: We searched PUBMED and Cochrane database for RCTs comparing PFO closure to medical therapy in patients with PFO and cryptogenic stroke. Three different strategies were evaluated; PFO closure, antiplatelet therapy alone and oral anticoagulation. A Bayesian network meta-analysis was performed to calculate odds ratios (OR) and 95% credible intervals (CrI). The outcome of this study was recurrent stroke events at the longest follow up period reported.

Results: We included 4 RCTs with a total of 2821 patients. There was significant reduction of recurrent strokes with PFO closure when compared to antiplatelet therapy alone (OR 0.29, CrI 0.07-0.84). On the other hand, there were no statistically significant differences between PFO closure and oral anticoagulation (OR 0.52, CrI 0.1-1.92) or between anticoagulation and antiplatelet therapy (OR 0.55, CrI 0.13-2.14).

Conclusion: In patients with PFO and cryptogenic stroke, transcatheter PFO closure is associated with significant reduction in recurrent strokes when compared to antiplatelet therapy alone. This benefit was not statistically significant when PFO closure was compared with the use of oral anticoagulation.

Key Words

Patent foramen ovale • Stroke • Network meta-analysis

Introduction

The presence of patent foramen ovale (PFO) has been shown to be associated with increased incidence of stroke. [1–3] Therefore, PFO closure has the potential of prevention of recurrent stroke events in patients with PFO and cryptogenic stroke. Randomized controlled trials (RCTs) that evaluated the benefit of transcatheter PFO closure in recurrent stroke prevention showed inconsistent results. [4–9]. One of the differences between those trials is that oral anticoagulation was permitted in the medical therapy arm in some of the trials, [4, 6, 9] which could have contributed to the discrepancy in the results. Hence, in the current study we aimed by performing network meta-analysis to compare three different strategies for recurrent stroke prevention, namely, PFO closure, antiplatelet therapy alone and oral anticoagulation.

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Methods

We searched PubMed and Cochrane Central Register of Controlled Trials for trials comparing PFO closure to medical therapy from inception through October, 2017. Only studies in the English language or studies with an English translation were included. Citations were screened at the title/abstract level and relevant citations were retrieved as full reports. References from the included studies were also manually searched for relevant studies.

Studies were eligible for inclusion if they were randomized controlled trials that compared PFO closure to medical therapy in patients with cryptogenic stroke and PFO. If the medical therapy arm in any study included patients on antiplatelets and/or oral anticoagulation, the study was included only if recurrent stroke was reported separately for each group of patients. Studies were excluded if they were non randomized trials or if outcomes of patients on antiplatelets and patients on oral anticoagulation were not reported separately. Moreover, patients who received PFO closure plus anticoagulation and patients who did not receive any antithrombotic therapy in any of the included studies were excluded from the final analysis.

The outcome of the present study was recurrent strokes at the longest follow up period reported in each study. In the CLOSURE I trial, [6] the outcome included was recurrent strokes or transient ischemic attacks. Data were independently extracted from the included trials by the first and second authors (G.M. and D.S.) on a pre-specified data sheet. Any discrepancy was discussed until there was complete agreement on all the results in the final data sheet.

Network meta-analysis was performed using a Bayesian Markov chain Monte-Carlo model. [10] Dichotomous outcome variables were compared with odds ratios (OR) and 95% credible intervals (CrI). The more conservative random effect model was adopted for final interpretation of the results. Vague (non-informative) priors for between-study heterogeneity were applied to the random effects analyses. Analyses using the fixed effect model was also performed and was only shown in the forest plot diagram. Three chains with different starting variables were used. To achieve convergence, a burn-in phase of 10,000 simulations was performed then 20,000 simulations were performed for the final analyses. Convergence was confirmed by assessing whether the Monte Carlo error is less than 5% of the standard deviation of the effect estimates or between study variance and by visual inspection of Gelman Rubin graphs. [11, 12] The heterogeneity between trials was determined from the median between-trial variance $\tau 2$. A $\tau 2$ estimate of 0.40 was interpreted as a high degree of heterogeneity. [13] Consistency between direct and indirect evidence was assessed by plotting the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model. Consistency was suggested when each data point had a posterior

Table 1. Characteristics of included trials.

				Medical therapy		
Trial name	Mean age (years)	Female (%)	PFO closure device	Antiplatelets	Oral Anticoagulation	Follow up duration
CLOSE [5]	44	42	All available devices	aspirin, clopidogrel or aspirin/dipyridamole	Coumadin or direct oral anticoagulants	5.4 years
CLOSURE I [6]	46	48	STARFlex Septal Closure System	Aspirin	Coumadin	2 years
REDUCE [7]	45	40	HELEX and Cardioform Septal Occluders	aspirin, clopidogrel or aspirin/dipyridamole	N/A	3.2 years
RESPECT [8]	46	45	Amplatzer PFO Occluder	aspirin, clopidogrel or aspirin/dipyridamole	Coumadin	5.9 years

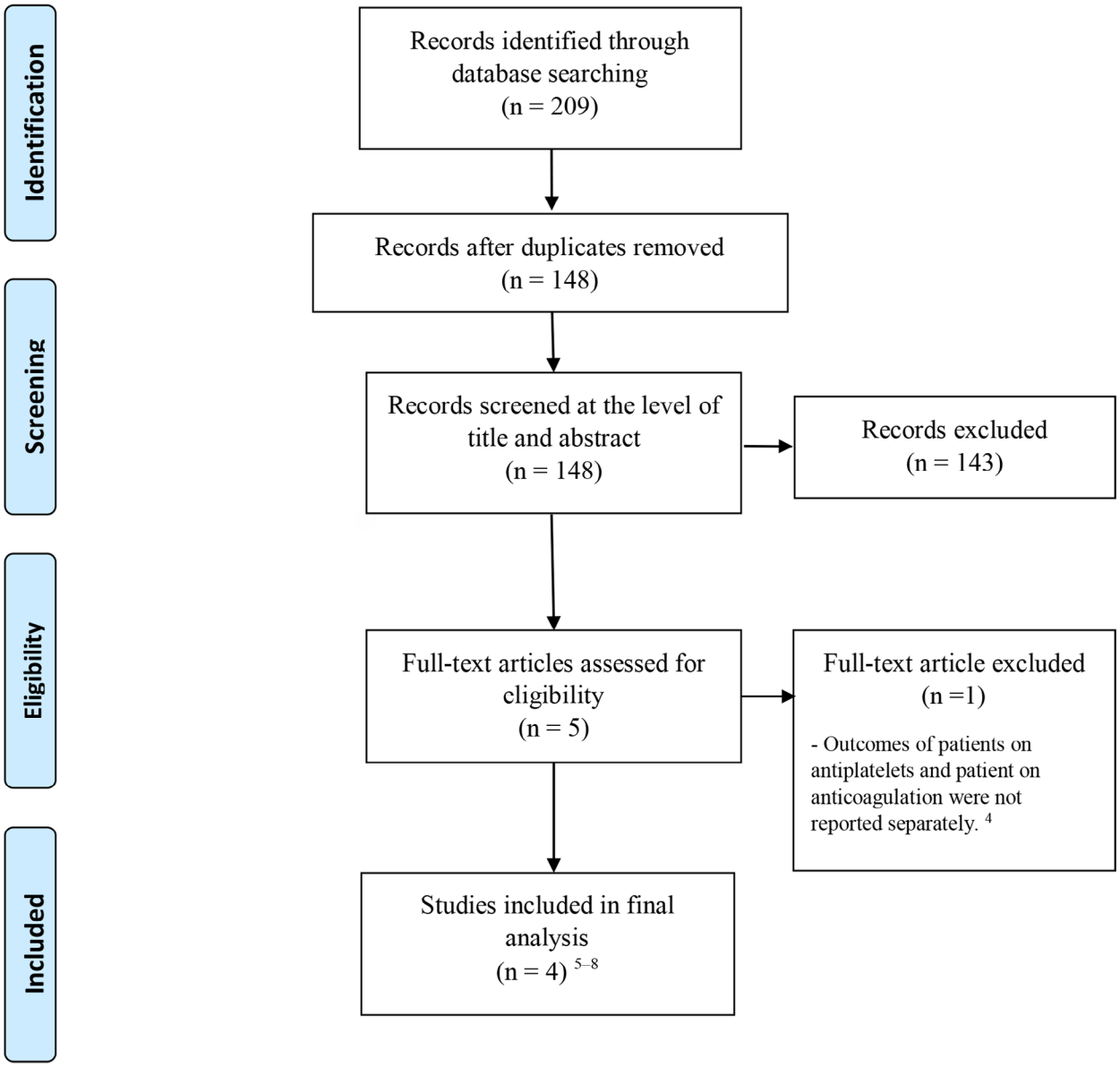

Figure 1. Flow diagram of study selection process according to PRISMA.

mean deviance contribution close to one. [12, 14] All statistical analyses were performed using WinBUGS 1.4 (MRC Biostatistics Unit, Cambridge, UK) [15] and the Microsoft Excel-based tool (NetMetaXL). [12]

Results

The process of citation screening and publication selection according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart is demonstrated in Figure 1. Initial screening was performed on 148 articles. Five trials were then fully retrieved for review and four trials were included in the final analyses. Two trials compared PFO closure to antiplatelet therapy and/or oral anticoagulation [6, 8], One trial compared PFO closure to antiplatelet therapy alone, [7] and one trial compared antiplatelet therapy one time to PFO closure and a second time to oral anticoagulation. [5] Characteristics of trials included in our study are shown in Table 1.

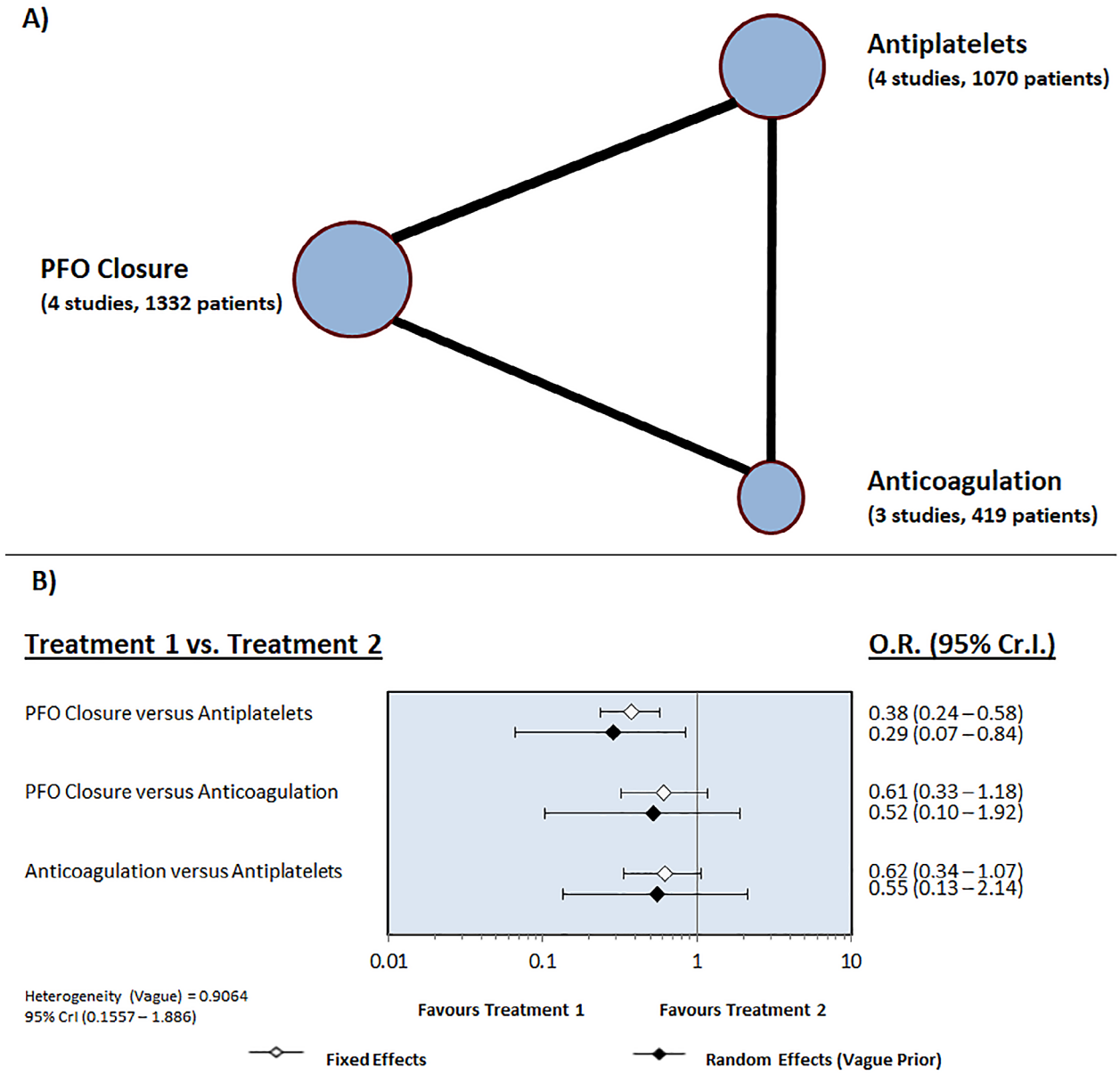

Figure 2. *Panel A.* Diagram of different treatment arms for recurrent stroke prevention. *Panel B.* Forest plot of mixed treatment comparisons showing statistically significant reduction of recurrent strokes with PFO closure only when compared to antiplatelet therapy. Both fixed and random effect models are shown.

The network included a total of 2821 patients. PFO closure was performed in 1332 patients, 1070 patients received antiplatelet therapy alone and 419 patients received oral anticoagulation alone (Figure 2A). There was significant reduction of recurrent strokes with PFO closure when compared to antiplatelet therapy alone (OR 0.29, CrI 0.07-0.84). On the other hand, the reduction in recurrent stroke when PFO closure was compared to oral anticoagulation was not statistically significant (OR 0.52, CrI 0.1-1.92). Moreover, the difference between oral anticoagulation and antiplatelet therapy in recurrent stroke reduction was also non statistically significant (OR 0.55, CrI 0.13-2.14). Heterogeneity assessment by τ2 was 0.9. Network com-

parisons of different treatment modalities are shown in Figure 2B. Plotting the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model suggested reasonable consistency between direct and indirect evidence.

Discussion

The present study is a network meta-analysis comparing three different strategies for recurrent stroke prevention in patients with PFO and cryptogenic stroke, namely, PFO closure, antiplatelet therapy and oral anticoagulation. The main finding of our study is that PFO closure is associated with significant reduction in recurrent strokes when compared to antiplatelet therapy alone.

Trans catheter PFO closure has been compared to medical therapy in randomized trials to evaluate the benefit in recurrent stroke prevention in patients with cryptogenic strokes. In the CLOSURE I [6] and the PC [4] trials as well as the early results of the RESPECT trial, [9] there was no significant benefit of PFO closure over medical therapy. However, when PFO closure was compared to antiplatelet therapy alone in the REDUCE [7] and CLOSE [5] trials, there was significant reduction in recurrent stroke events in patients who underwent PFO closure. Hence, the inclusion of patients on anticoagulation in the medical therapy arm might have contributed to the absence of difference between PFO closure and medical therapy.

A recent updated meta-analysis comparing PFO closure to medical therapy, whether antiplatelets or oral anticoagulation, PFO closure was associated with significant reduction in recurrent strokes. [16] In our study, however, we aimed to evaluate the benefit of PFO closure compared to antiplatelet therapy and oral anticoagulation separately. Based on the results of our study, there is clear benefit of PFO closure over antiplatelet therapy alone. On the other hand, when compared to oral anticoagulation, the benefit of PFO closure is less evident and needs further investigation.

There are limitations to our study that should be considered. There was marked heterogeneity between the results of the trials. However, we used the more conservative random effect model for interpretation of the results. Another limitation is the exclusion of the PC trial as outcomes were not reported separately for patients on antiplatelets and patients on anticoagulation in that trial. A third limitation is that we were unable to perform subgroup analysis based on factors like age, atrial septal aneurysm and shunt size that might have an impact on recurrent strokes. A fourth limitation is that the only outcome evaluated was recurrent strokes because there were no sufficient data on other outcomes that was stratified based on medical therapy used. Finally, the number of patients in the oral anticoagulation arm is small. Therefore, the results pertaining the use of anticoagulation should be taken with caution and more trials are needed to validate our findings.

In conclusion, when compared to antiplatelet therapy alone, PFO closure is an effective treatment strategy for recurrent stroke prevention in patients with PFO who had a cryptogenic stroke. This benefit was not statistically significant when PFO closure was compared with the use of oral anticoagulation.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

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