Review

Is Transcatheter Closure Better than Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale? A Meta-analysis of Randomised Trials

Vinayak Nagaraja, MBBS [a], Jwalant Raval, MBBS [b,*], Guy D. Eslick, MMedSc (Clin Epi), MMedStat [c], David Burgess, BMed, PhD [b,d] and A. Robert Denniss, MD, MSc [b,d]

[a] *Prince of Wales Hospital, Sydney, Australia*
[b] *Blacktown Hospital, Sydney, Australia*
[c] *The Whiteley-Martin Research Centre, Discipline of Surgery, The University of Sydney, Nepean Hospital, Sydney, Australia*
[d] *University of Western Sydney, Australia*

Introduction: **The prevalence of patent foramen ovale among patients with cryptogenic stroke is higher than that in the general population. Closure with a percutaneous device is often recommended in such patients, but it is not known whether this intervention reduces the risk of recurrent stroke.**

Methods: **A systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane library, Google Scholar, Science Direct, and Web of Science. Original data were abstracted from each study and used to calculate a pooled event rate (ER), odd ratio (OR) and 95% confidence interval (95% CI).**

Results: **Only three randomised trials comprising 2303 patients met full criteria for analysis. Procedural success (ER: 94.20%, 95% CI: 87.6–97.4%) and effective closure (ER: 92.70%, 95% CI: 85.9–96.4%) of closure therapy were good.**

The odds ratio for stroke (OR: 0.654, 95% CI: 0.358–1.193) and transient ischaemic attack (OR: 0.768, 95% CI: 0.413–1.429) did not confer a benefit of PFO closure over medical therapy. Age {<45 years (OR: 0.449, 95% CI: 0.117–1.722), >45 years (OR: 0.707, 95% CI: 0.27–1.856)}, gender {males (OR: 0.498, 95% CI: 0.247–1.004), females (OR: 1.16, 95% CI: 0.597–2.255)}, substantial shunt size (OR: 0.354, 95% CI: 0.089–1.406) and the presence of atrial septal aneurysm (OR: 0.7, 95% CI: 0.21–2.33) did not influence the treatment effect of PFO closure. However, the adverse events like major vascular complication (OR: 10.905, 95% CI: 1.997–59.562) and atrial fibrillation (OR: 3.297, 95% CI: 0.874–12.432) were significantly higher in the closure group.

Conclusions: **In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device does not confer an advantage over medical therapy and is associated with adverse events like major vascular complication and atrial fibrillation.**

(Heart, Lung and Circulation 2013;22:903–909)

Keywords. Patent foramen ovale; Cryptogenic stroke; Transcatheter closure; Randomised trials; Medical therapy

Introduction

Epidemiological studies have found a prevalence of 44–66% of patent foramen ovale (PFO) in patients with cryptogenic stroke as compared with 27% in autopsy series of all-cause deaths [1]. The higher prevalence of PFO in patients with cryptogenic stroke suggests that at least in some patients with cryptogenic stroke, the cause of stroke might be paradoxical thromboembolism. The optimal management strategy for treating patients with cryptogenic stroke (CS) who are discovered to have a patent foramen ovale (PFO) remains to be defined. The advent of percutaneously implantable devices has offered a widely applicable closure approach not requiring open heart surgery. Catheter-based closure of patent foramen ovale was introduced in 1992 [2]. Percutaneous closure has been available for over 20 years with very little hard evidence to guide patient and device selection. Investigators

Received 18 April 2013; received in revised form 8 July 2013; accepted 24 July 2013; available online 10 September 2013

* Corresponding author at: Department of Cardiology, Blacktown Hospital, Australia. Tel.: +61 029881800.
E-mail address: jwalant_21@yahoo.com (J. Raval).

1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2013.07.022

have used their own clinical judgement to decide when and how to percutaneously close PFO.

Observational long-term data suggest that closure of patent foramen ovale in patients with a history of ischaemic stroke may reduce the risk of recurrent stroke as compared with medical therapy alone [3,4]. CLOSURE 1 trial [5] failed to demonstrate any significant difference in recurrent neurological events with PFO closure compared with medical management with antiplatelet or anticoagulation therapy.

Recently three randomised trials have reviewed the benefit of closure over optimal medical therapy. We synthesised the available evidence from the randomised trials on secondary stroke prevention in patients with patent foramen ovale and cryptogenic stroke and primarily focus on the comparison of the two strategies.

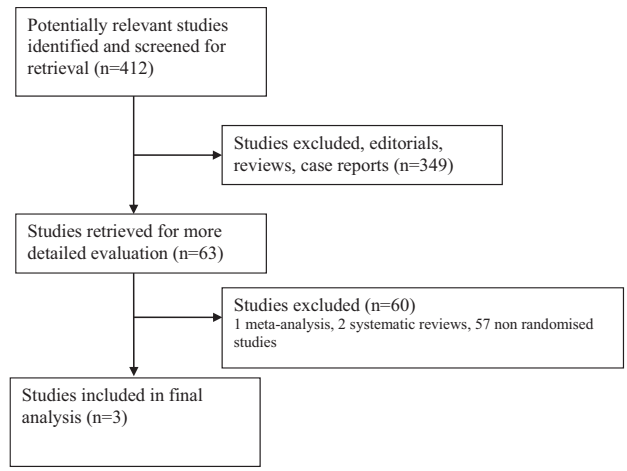

Figure 1. *Flow of Included Studies.*

Methods

Study Protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-analyses PRISMA guidelines where possible in performing our systematic review [6]. We performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct, and Web of Science to May 2013. The search terms included "patent foramen ovale," "PFO," "atrial septal aneurysm," "ASA transcatheter closure," "heart septal defects (atrial)," "interatrial shunt," "recurrent thromboembolism," "recurrent stroke," and "recurrent TIA." which were searched as text word and as exploded medical subject headings where possible. No language restrictions were used in either the search or study selection. The reference lists of relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

Study Selection

We included studies that met the following inclusion criteria:

- Studies identifying the population of patients with patent foramen ovale with cryptogenic stroke.
- Randomised controlled trials comparing transcatheter closure and medical therapy.

Data Extraction

We performed the data extraction using a standardised data extraction form, collecting information on the publication year, study design, number of cases, total sample size, population type, country, continent, mean age and clinical data. The event rate and confidence intervals were calculated.

Statistical Analysis

Pooled odds ratio, event rate and 95% confidence intervals used a random effects model [7]. We tested heterogeneity with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25, 50 and 75% corresponded to low, moderate and high degrees of heterogeneity respectively [8]. The quantified publication bias used the Egger's regression model [9], with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $P < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n + 10$, with n being the number of studies included in the meta-analysis [10]. All analyses were performed with Comprehensive Meta-analysis (version 2.0).

Results

The original search strategy retrieved 412 studies (Fig. 1). The excluded studies included one meta-analysis [11], two systematic reviews [1,12], 57 non-randomised studies, 349 studies (editorials, reviews, case reports). The abstracts were reviewed and after applying the inclusion and exclusion criteria, articles were selected for full-text evaluation. Of the articles selected, only three studies (2303 patients) met full criteria for analysis and are summarised in Tables 1A and 1B. The years of publication ranged from 2012 to 2013 (Fig. 2).

Procedural Success and Effective Closure

Procedural success (ER: 0.942, 95% CI: 0.876–0.974) and effective closure (ER: 0.927, 95% CI: 0.859–0.964) of closure therapy was good.

Odds Ratios

The odds ratio for stroke (OR: 0.654, 95% CI: 0.358–1.193) and transient ischaemic attack (OR: 0.768, 95% CI: 0.413–1.429) do not confer an advantage of PFO closure over medical therapy. Age {<45 years (OR: 0.449, 95% CI: 0.117–1.722), >45 years (OR: 0.707, 95% CI: 0.27–1.856)},