Patent Foramen Ovale Closure in the Setting of Cryptogenic Stroke: A Meta-Analysis of Five Randomized Trials

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Background: The clinical benefit of patent foramen ovale (PFO) closure after cryptogenic stroke has been a topic of debate for decades. Recently, 3 randomized controlled trials of PFO closure in patients with cryptogenic stroke demonstrated a significantly reduced risk of recurrent stroke compared with standard medical therapy alone. This meta-analysis was performed to clarify the efficacy of PFO closure for future stroke prevention in this population. *Methods:* A systematic literature search was undertaken. Published pooled data from 5 large randomized clinical trials (CLOSE, RESPECT, Gore REDUCE, CLOSURE I, and PC) were combined and then subsequently analyzed. Enrolled patients with cryptogenic stroke were assigned to receive standard medical care or to undergo endovascular PFO closure, with a primary outcome of reduction in stroke recurrence rate. Secondary outcomes included rates of transient ischemic attack (TIA), composite outcome of stroke, TIA, and death from all causes, and rates of atrial fibrillation events. *Results:* We analyzed data for 3412 patients. Transcatheter PFO closure resulted in a statistically significant reduced rate of recurrent stroke, compared with medication alone. Patients undergoing closure were 58% less likely to have another stroke. The number needed to treat with PFO closure to reduce recurrent stroke for 1 patient was 40. *Conclusions:* Endovascular PFO closure was associated with a reduced risk of recurrent stroke in patients with a prior cryptogenic cerebral infarct. Although the absolute stroke reduction was small, these findings are clinically significant, given the young age of this patient population and the patients' lifetime risk of recurrent stroke. **Key Words:** PFO—cryptogenic stroke—PFO closure—recurrent stroke—meta-analysis.

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Introduction

Approximately one third of all ischemic strokes do not have a clearly defined cause despite sufficient diagnostic evaluation. These strokes are classified as cryptogenic and account for approximately 200,000 strokes annually in the United States.[1] In the younger population with ischemic stroke, nearly half of all strokes are identified as cryptogenic.[1] Defining the etiology of a cryptogenic stroke has profound implications for subsequent treatment, and is of paramount importance, particularly in regard to reducing recurrent stroke risk in the young.

A commonly debated question over the preceding few decades has been the role that the presence of a patent

foramen ovale (PFO) plays in cryptogenic stroke and whether closure should be pursued. It should be noted that an estimated 25% of the population has a PFO, and the presence of a PFO in itself is not known to increase the risk of ischemic stroke[2] However, PFO is estimated to be present in 40%-50% within the subset of patients with cryptogenic stroke.[3,4] PFO has been postulated to be a potential cause of cerebral infarct within the younger population with cryptogenic stroke, potentially via paradoxical embolism. The initial body of evidence supporting endovascular PFO closure for the prevention of additional cerebrovascular events consisted of greater than 50 observational studies that cumulatively showed substantial and unequivocal benefits with the intervention.[5] However, in 2012, the first true clinical experiment on transcatheter PFO closure and future stroke prevention was published, with 2 more trials publicized the following year.[6-8] The CLOSURE I trial investigating the STARFlex device did not show any statistically significant benefit of mechanical closure over medical therapy. The STARFlex device has since been removed from the market, and this trial was critiqued for including patients with lacunar stroke. The PC trial and RESPECT studied the AMPLATZER PFO occluder, and both showed excellent safety-related results, as well as a high rate of closure of the PFO. However, neither of these studies individually showed the superiority of closure over medical therapy alone. Despite the consistently null overall outcome of these trials, on closer inspection, the results of the RESPECT and the PC trial published simultaneously appeared highly suggestive of benefit for mechanical closure over medical therapy.[9]

Recently, 3 additional randomized controlled trials (RCTs) of PFO closure in patients with cryptogenic stroke demonstrated a significant reduced risk of recurrent stroke compared with standard medical therapy alone.[10-12] Saver et al reported extended follow-up data from the RESPECT trial, concluding that PFO closure with the AMPLATZER device was associated with a lower rate of recurrent ischemic strokes than medical therapy alone.[10] The Gore REDUCE trial[11] (which evaluated the GORE HELEX and the CARDIOFORM septal occluders) and the CLOSE trial[12] (in which various occluder devices were utilized) also showed reduced recurrent stroke rates after transcatheter PFO closure compared with standard medical therapy in young patients with cryptogenic stroke. The aim of this meta-analysis was to provide a summative analysis of the landmark studies to determine the efficacy of device closure in comparison with medical therapy in preventing recurrent ischemic strokes.

Methods

Search Strategy

The study was conducted in accordance with principles established for meta-analyses of RCTs (PRISMA guidelines).[13] A systematic literature search of PubMed, Embase, and Google Scholar databases was conducted from January 2008 to September 2017 for articles of interest. Search terms included varying combinations of the following: "cryptogenic stroke," "PFO," "closure," "ischemic stroke," "percutaneous closure," "atrial septal defect (ASD)," "endovascular," "catheter-based closure," and "recurrent stroke." Bibliographies of relevant publications were hand-searched to attempt complete inclusion of all possible studies of interest. RCTs were eligible and were included in the meta-analyses. Individual case reports, case series, editorials, review articles, retrospective studies, case-control studies, and meeting abstracts were excluded.

Inclusion and Exclusion Criteria

The PRISMA statement of reporting systematic reviews and meta-analysis was applied (see Supplementary Table S1).

The following inclusion criteria were used:

1. studies with adult (age ≥18 years) patients and
2. studies comparing percutaneous PFO closure versus medical therapy in patients with cryptogenic stroke and PFO or ASD.

The following exclusion criteria were applied:

1. studies with nonhuman participants,
2. studies that did not have a direct comparison between closure device and medical therapy, and
3. studies that did not report rates of recurrent strokes or transient ischemic attacks (TIAs).

Study End Points

The primary outcome of interest was the rate of recurrent ischemic stroke. Secondary outcomes included rate of TIA and composite outcomes of stroke or TIA and all-cause death. We also studied various complication rates, including atrial fibrillation, vascular complications, and others. All events that occurred during follow-up were analyzed using an intention-to-treat principle.

Study Selection and Data Extraction

Two reviewers (L.G. and A.H.) screened all studies that appeared relevant on the basis of "title" and "abstract" for full article review. The studies included were required to be RCTs that directly compared percutaneous closure of PFO with experimental or commercially available devices with the medical therapy and had an average follow-up of at least 1 month.

Statistical Analysis

Analysis was performed on an intention-to-treat basis. Data were summarized across treatment arms using the Mantel–Haenszel odds ratio (OR). We evaluated the