Device Closure of Patent Foramen Ovale
Versus Medical Therapy in Cryptogenic Stroke
A Systematic Review and Meta-Analysis

Abdur R. Khan, MD,* Aref A. Bin Abdulhak, MD,† Mujeeb A. Sheikh, MD,*
Sobia Khan, MBBS,* Patricia J. Erwin, MLS,‡ Imad Tleyjeh, MD,§ Sadik Khuder, PhD,#
Ehab A. Eltahawy, MD*

Toledo, Ohio; Kansas City, Missouri; Rochester, Minnesota; and Riyadh, Kingdom of Saudi Arabia

Objectives This study sought to perform a meta-analysis of randomized controlled trials comparing
closure device with medical therapy in the prevention of recurrent neurological events in patients with
cryptogenic stroke and patent foramen ovale.

Background The optimal strategy for secondary prevention of cryptogenic stroke with a patent
foramen ovale is unclear.

Methods Several databases were searched from their inception to March 2013, which yielded 3
eligible studies. The results were pooled as per the different patient populations defined in the
studies:—intention-to-treat, per-protocol, and as-treated cohorts. A generic inverse method was used
based on time-to-event outcomes in a fixed-effect model. A supplementary analysis pooled the results
from only 2 trials (RESPECT [Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to
Established Current Standard of Care Treatment] and PC Trial [Randomized Clinical Trial Comparing the
Efficacy of Percutaneous Closure of Patent Foramen Ovale (PFO) With Medical Treatment in Patients
With Cryptogenic Embolism]) as a similar device was used in them.

Results Our meta-analysis yielded effect-estimate hazard ratios of 0.67 (95% confidence interval [CI]:
0.44 to 1.00, $I^2 = 0\%$) in the intention-to-treat cohort, 0.62 (95% CI: 0.40 to 0.95, $I^2 = 0\%$) in the per-
protocol cohort, and 0.61 (95% CI: 0.40 to 0.95, $I^2 = 38\%$) in the as-treated cohort, showing beneficial
effects of device closure. The results became more robust with pooled results from RESPECT and the
PC Trial: The effect-estimate hazard ratios being 0.54 (95% CI: 0.29 to 1.01, $I^2 = 0\%$), 0.48 (95% CI: 0.24
to 0.94, $I^2 = 26\%$), and 0.42 (95% CI: 0.21 to 0.84, $I^2 = 26\%$) in the intention-to-treat, per-protocol, and
as-treated populations, respectively.

Conclusions Our meta-analysis suggests that PFO closure is beneficial as compared to medical
therapy in the prevention of recurrent neurological events. This meta-analysis helps to further
strengthen the role of device closure in cryptogenic stroke. (J Am Coll Cardiol Intv 2013;6:1316–23)
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Stroke is among the leading causes of mortality and serious long-term disability (1), with an estimated cost in terms of healthcare services, medication, and missed days of work being $38.6 billion each year in the United States alone (2). Approximately 795,000 strokes occur annually in the United States, with around 185,000 being recurrent attacks (3). Around one-third of the patients hospitalized with stroke are under the age of 65 years (4). Around 25% of all strokes are cryptogenic, and this reaches approximately 50% in the younger age group (5). Epidemiologic data reveal significant association between patent foramen ovale (PFO) and cryptogenic stroke both in the younger and older patient populations (6,7). Despite medical therapy, the rate of stroke recurrence in patients with PFO is estimated to be 25% within a 4-year period (8,9).

Therefore, there has been significant interest in percutaneous closure of PFO as a potential therapeutic option in this group of patients. Observational data and meta-analyses of observational studies suggest that percutaneous transcatheter closure of PFO is safe and has a low recurrence rate of stroke as compared to medical therapy (10–12). However, so far, published randomized controlled studies have not shown superiority of PFO closure over medical therapy (13–15).

The first trial presented on this issue—CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale)—failed to show any benefit of device closure (16). The CLOSURE I trial had several limitations that challenge the applicability of its outcome, namely: sluggish recruitment; off-label closure; inclusion of transient ischemic attack (TIA) causing heterogeneity in the patient population; and use of a device associated with a higher rate of periprocedural complications than that of current-generation devices (16). Specifically, the STARFlex device (NMT Medical Inc., Las Vegas, Nevada) used in the trial had a lower success rate and an increased incidence of periprocedural atrial fibrillation (17), which may have contributed to a higher-than–expected event rate in the device group. Two other randomized controlled trials have recently been published (14,15). These were the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial and the PC Trial (Percutaneous Closure of PFO Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism), which was a clinical trial. Both these trials trended toward a beneficial effect of device closure as compared to medical therapy, but the magnitude of effect estimate was low. It has been thought that the main limitation of these studies was modest statistical power (18).

Thus, the optimal strategy for secondary prevention in patients with cryptogenic stroke with a PFO remains unclear. Given this ongoing controversy, we performed a systematic review and meta-analysis that addressed the role of device closure versus medical therapy in cryptogenic stroke with PFO.

Methods

Data sources and search strategy. The systematic review was carried out in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (19). The search strategy and subsequent literature searches were performed by an experienced medical reference librarian (P.J.E.). The search strategies were developed in Ovid Medline, and translated to match the subject headings and key words for Ovid Embase, Cochrane Central, ISI Web of Science, and Scopus from database inception through March 21, 2013. The following MeSH, Emtree, and search word terms were used in combination: “patent foramen ovale”; “PFO”; “right to left shunt”; “atrial septal aneurysm”; “interatrial shunt”; “ASA” and “stroke”; “ischemic stroke”; “cryptogenic stroke”; “CVA”; “recurrent stroke”; “transient ischemic attack”; “TIA”; “brain infarction” and “medical therapy”; “platelet aggregation”; “anticoagulants”; “percutaneous closure”; “transcatheter closure”; “cardiac catheterization”; “septal occluder device” and “controlled trials”; “intervention study”; “randomized controlled trial.” There was no restriction of language.

To identify further articles, we searched for meeting abstracts in Embase and hand-searched references and related citations in review articles and commentaries. All results were downloaded into EndNote (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania), a bibliographic database manager, and duplicate citations were identified and removed.

Study selection. Two authors (A.R.K. and S.K.) independently assessed the eligibility of identified studies. The results that were further evaluated were limited to randomized controlled trials that focused on comparison of medical therapy versus percutaneous closure of PFO in patients with cryptogenic stroke.

Data extraction. Two reviewers (A.R.K. and A.B.) independently extracted data on a pre-defined data-collection form. Extracted data included the following: population under study; subject characteristics; type of medical therapy or device used; and data on efficacy and safety. The outcome was accepted as defined in individual trials and related to the recurrence of stroke, TIA, or all-cause mortality. Data on safety included adverse events reported due to the device or medical therapy.
Quality assessment. Two reviewers (S.K. and A.B.) independently assessed the methodological quality of selected studies using the Jadad scale. This scale is used to explore adequate randomization, blinding, and description of withdrawal or dropout (20).

Data synthesis and statistical analysis. Our intention was to investigate whether percutaneous closure of PFO is superior to medical therapy in patients with cryptogenic stroke. Data on efficacy and safety were analyzed and pooled separately.

Efficacy. All the included studies reported time-to-event outcomes using Cox proportional hazard ratios (HRs). CLOSURE I reported its results as time-to-event outcomes in intention-to-treat, modified intention-to-treat, and per-protocol populations. The modified intention-to-treat population was described as having received the study treatment regardless of the follow-up, whereas the per-protocol population had at least 22 months of follow-up after the randomly assigned treatment. RESPECT presented its analysis as raw count analysis in an intention-to-treat population. They also performed a survival analysis with time-to-event outcome because of unequal dropout rates between the 2 groups in order to provide an exposure-stratified comparison. They also reported results in 2 prespecified populations—per-protocol and as-treated cohorts. The per-protocol population received the randomly assigned treatment, whereas the as-treated population was classified according to the treatment actually received regardless of the randomization. The PC Trial also reported time-to-event outcomes as per intention-to-treat and per-protocol populations. The per-protocol population defined here received the randomly assigned treatment.

The meta-analysis was done using a fixed-effect model. A generic inverse variance method was used based on time-to-event outcomes reported. The results were pooled according to the different populations specified in the reported trials—as intention-to-treat, per-protocol, and as-treated populations. CLOSURE I and the PC Trial did not report results as as-treated, so the as-treated analysis was performed using intention-to-treat outcomes in the cohort.

We performed a supplementary analysis pooling the results from RESPECT and the PC Trial only, as a similar device was used in both trials.

Safety. Data on safety was analyzed as the total number of adverse events, atrial fibrillation, and bleeding outcomes. For atrial fibrillation, a sensitivity analysis was done after exclusion of data from CLOSURE I as the STARFlex device used appeared to cause a significant proportion of peri-procedural atrial fibrillation and has since been discontinued. A fixed-effects model was used with the Mantel-Haenszel method with nonfixed zero-cell correction to pool data. This method is recommended whenever sparse data is pooled (21). There was some heterogeneity found in the atrial fibrillation and bleeding outcomes; hence, a random-effects model and the Mantel-Haenszel method with continuity correction were used to account for it.

Cochran’s $Q$ test was used to assess heterogeneity among studies and was complemented by the $I^2$ statistic. The $I^2$ statistic describes the proportion of variation in treatment estimate that is not related to sampling error (22). All analyses were conducted using the statistical software RevMan (Version 5.2. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Results

Identification of studies. The literature search identified 504 publications, out of which 3 were eligible for inclusion in the analysis (Fig. 1) (13–15). All the included studies scored 3 on the Jadad scale. There was excellent agreement for the inclusion of the studies, data abstraction, and quality assessment between the reviewers (kappa statistics being 1.0, 0.92, and 1.0, respectively).

Study characteristics. Table 1 summarizes the characteristics of the included studies. The studies were conducted in the United States, Canada, United Kingdom, Europe, Brazil, and Australia. Thus, 3 studies comprising 2,303 participants included in the analysis. The relevant outcomes of interest in
all studies were the development of fatal or nonfatal ischemic stroke and all-cause mortality. CLOSURE I and the PC Trial also had TIA as a primary endpoint, which differs from stroke and all-cause mortality. CLOSURE I and the PC Trial were the development of fatal or nonfatal ischemic stroke or TIA within the previous 6 months; evidence of a PFO, as documented by TEE with a bubble study.

**Exclusion criteria**
- Identifiable cause of ischemic stroke/TIA; another source of R-L shunt, an acute or recent MI/unstable angina; LV aneurysm/akinesis; intracardiac thrombus or tumor
- Cerebral/cardiovascular, and systemic conditions that suggest other mechanisms for stroke; contraindication to medical/device therapy; limited life expectancy, inability to attend follow-up

**Device closure**
- STARFlex septal closure system (NMT Medical Inc., Boston, MA)

**Medical therapy**
- Warfarin (INR: 2 to 3); aspirin 325 mg/d or both

**Follow-up**
- 2 yrs

**Primary endpoint**
- Composite of stroke or TIA, death from any cause (30 days), death from neurologic causes (31 days to 2 yrs)

**Secondary endpoint**
- Major bleeding: death from any cause; stroke, TIA, and transient neurologic events of uncertain cause

*Aspirin with clopidogrel was removed from the protocol in 2006 based on changes to the American Heart Association/American Stroke Association treatment guidelines.

**Discussion**

**Findings.** The findings from our systematic review and meta-analysis suggest that device closure may have a beneficial effect in preventing recurrent neurological events in patients with cryptogenic stroke and PFO. The effect estimate reveals a 33% to 39% reduction in the hazard for a recurrent neurological event depending on the population.
analyzed. If we include RESPECT and the PC Trial, using only the Amplatzer device, the benefit becomes more apparent, with a reduction of approximately 46% to 58%. The safety of the device was comparable to medical therapy, with a low incidence of adverse events.

Not only did all the analyses have effect estimates in favor of device closure, the pooled results also confirmed a more significant beneficial effect. As mentioned, the trials most likely did not meet their expected outcome because of low numbers of enrolled patients, lower-than-expected event rates, and relatively short follow-up. All the reported studies had difficulty in enrollment. The trials were also performed in an environment of significant off-label closure (23). In addition to the total number of subjects enrolled, this likely led to a selection bias in which the enrolled population may not be representative of the groups most likely to benefit from PFO closure. This also may have diluted the actual beneficial effect of device closure in randomized patients.

Moreover, follow-up of study patients was likely too short to assess a significant difference in efficacy between the 2 groups. Observational data has demonstrated that event rates in medical therapy versus device closure appeared to separate after 2 years of follow-up (10). Recently, a propensity-matched comparison cohort showed that mortality or stroke benefit becomes more apparent in long-term follow-up (11). Data from RESPECT showed the same trend, with the curves continuing to diverge more after 2 years and continuing to diverge even at 5 years. The Kaplan-Meier curves in individual trials continued to diverge, suggesting that the postulated benefit may need more time to become significant.

Strengths of our analysis. To the best of our knowledge, this is the first systematic review and meta-analysis of randomized controlled trials to compare the efficacy and safety of device closure with medical therapy in cryptogenic stroke with PFO. Our results are consistent with a previous
observational data (24–27) and meta-analysis (12,28) in terms of safety and efficacy. Agarwal et al. (12) also reported a beneficial effect of transcatheter closure of PFO as compared to medical therapy in reduction of recurrent neurological events. Their analysis was based on non-randomized evidence derived from observational studies. Another analysis by Kitsios et al. (29) compared observational evidence with the only available randomized trial (CLOSURE I) presented at that time. They found a difference in the number of events between randomized and observational evidence. The device group in CLOSURE I had a higher incidence of events as compared to the observational data. First, this can be explained by the use of the STARFlex device, which had a higher incidence of peri-procedural atrial fibrillation and complications. Second, observational study design may have led to inclusion bias. Our analysis included only randomized controlled trials. We also performed a separate analysis excluding the CLOSURE I trial.

Limitations of our analysis. The results of our meta-analysis are weakened by limitations inherent to meta-analyses and to the included studies. The low number of included studies leads to low statistical power, especially for safety data analysis. The analysis of rare events is associated with its own limitations, where even a small change in the number of events can produce a dramatic change in the results (30). There was a lack of individual patient data, which may have affected the results of our analysis. Medical therapy was not uniform across the trials and even within trials, which may have had an effect on neurological events. Our pooled effect estimate has included trials that differ in the baseline risks of patients, devices used, and clinical endpoints measured that can be considered as a weakness of our analysis. However, it can be argued that it extends the generalizability of our findings to a wider range of population.

Future directions. There remain several unanswered questions in the field of cryptogenic stroke. It has been shown that not all ischemic strokes with a PFO will benefit from closure. High-risk subgroups that may benefit from device closure need to be defined further. One approach of identifying such high-risk subgroups is risk modeling. The RoPE (Risk of Paradoxical Embolism) study is currently being performed to develop models to identify PFO-related cryptogenic strokes and the risk of their recurrence (31). Another approach would be to pool patient-level data, which might help in identification of high-risk subgroups. Individual data meta-analysis is especially helpful when the effect of individual patient characteristics on the treatment is
being investigated (32). It would help to assess variation in treatment effect in patients with variation in individual characteristics. Should future randomized trials be contemplated, then efforts should be undertaken to ensure that enrolled patients are truly representative of the cryptogenic stroke population to avoid exclusion of the high-risk group—those particular population most likely to benefit from device therapy.

With the evidence available thus far, it may be more appropriate that individual patient characteristics, their clinical presentation, and structural assessment of the shunt be the subjects of a thorough discussion between the treating physicians and their patients concerning the risks, benefits, and alternatives of device closure. This will allow for identification of the most appropriate clinical scenarios for percutaneous closure of PFO.

**Conclusions**

Our meta-analysis suggests that percutaneous device closure for PFO is beneficial as compared to medical therapy in the prevention of recurrent cryptogenic stroke. This meta-analysis helps to further strengthen the role of device closure in cryptogenic stroke. The precise patient population likely to benefit most from device therapy is yet to be defined.

Reprint requests and correspondence: Dr. Ehab A. Eltahawy, Division of Cardiovascular Medicine, Department of Medicine, University of Toledo Medical Center, 3000 Arlington Avenue, Toledo, Ohio 43614. E-mail: ehab.eltahawy2@utoledo.edu.

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Role of PFO Closure in Cryptogenic Stroke

Key Words: cryptogenic stroke • device closure • patent foramen ovale • recurrent stroke • transcatheter closure.