



Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with Cryptogenic Stroke and Patent Foramen Ovale

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3 Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with
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6 Cryptogenic Stroke and Patent Foramen Ovale
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3 Abstract

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5 Background: Three randomized control trials (RCTs) comparing patient foramen
6 ovale (PFO) closure to medical therapy have been published – none showed PFO
7 closure to be statistically superior to medical therapy but each reported trends
8 favoring PFO closure.
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15 Objectives: To provide a comprehensive comparison of PFO closure versus medical
16 therapy in patients with cryptogenic stroke or transient ischemic attack (TIA) and
17 demonstrated PFO.
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27 Design: Systematic review with complete case meta-analysis and sensitivity
28 analyses
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35 Data sources: Medline, Embase 1980 up to May 2013
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40 Eligibility criteria: All randomized controlled trials (RCTs) comparing treatment
41 with percutaneous catheter-based closure of PFO to medical therapy (anticoagulant
42 or antiplatelet therapy) in patients with cryptogenic stroke or TIA and
43 echocardiographically confirmed PFO or atrial septal defect (ASD) were eligible.
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51 Methods: The primary outcome of interest was recurrence of ischemic stroke. We
52 utilized data from complete cases only for the primary endpoint and combined data
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3 from trials to estimate the pooled risk ratio (RR) and associated 95% confidence
4 intervals (CI) calculated using random effects models.
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10 Results: We identified 284 potentially eligible articles of which 3 RCTs including
11 2303 patients proved eligible and 1967 patients had complete data. Of the 1026
12 patients randomized to PFO closure and followed to study conclusion 22
13 experienced non-fatal ischemic strokes, as did 34 of 941 patients randomized to
14 medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: $p = 0.34$, $I^2 =$
15 8%, confidence in estimates low due to risk of bias and imprecision). Analyses for
16 ischemic stroke restricted to “per-protocol” patients or patients with concomitant
17 atrial septal aneurysm did not substantially change the observed risk ratios.
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Complication rates associated with either PFO closure or medical therapy were low.

Conclusions: Pooled data from 3 RCTs provides little support for PFO closure over
medical therapy for secondary prevention of cryptogenic stroke in patients with
PFO.

Abstract word count: 299

Study strengths

- Estimation of absolute benefits and risks of treatment strategies
- Careful assessment of risk of bias of individual studies using Cochrane criteria
- Evaluation of overall confidence in pooled outcome(s) estimates using GRADE

Limitations

- Primary analysis was restricted to patients with available data (complete case analysis). If event rates differed in those with missing data in intervention and control groups - of particular concern would be higher rates of events in those lost to follow-up in the PFO closure arm than the medical therapy arm - the complete case results may be misleading
- Individual patient-level data not available

Introduction

Observational studies suggest that younger patients with cryptogenic stroke are more likely to have a patent foramen ovale (PFO) than the general population.^{1,2} A proposed mechanism for stroke in these patients is passage of thrombi from the venous circulation to the arterial circulation through the PFO. Although what proportion of cryptogenic strokes are due to paradoxical embolism remains unknown, percutaneous closure of PFO using devices approved for hemodynamically significant secundum atrial septal defect (ASD) has increased greatly in the last 2 decades. A systematic review of observational studies suggests PFO closure may be superior to medical therapy (antiplatelet or anticoagulant agents) for secondary prevention of stroke in patients with patent foramen ovale and cryptogenic stroke.³

In the last two years 3 three randomized control trials (RCTs) comparing PFO closure to medical therapy have been published – none showed PFO closure to be statistically superior to medical therapy for the primary composite outcome but each reported trends favoring PFO closure.⁴⁻⁶ In one study, PFO closure was superior to medical therapy for the prevention of recurrent neurologic events in prespecified per-protocol and as-treated analyses.⁵

One systematic review and meta-analysis that included the 3 RCTs, and a second meta-analysis, have addressed this issue. Both were limited, however, by failure to

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3 fully consider risk of bias issues, failure to use the GRADE approach to determine
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5 overall confidence in estimates of intervention effect, and failure to consider the
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7 limitations of composite endpoints.
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12 We therefore undertook a systematic review of all RCTs comparing percutaneous
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14 PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFO
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16 or ASD. As composite endpoints varied between trials, we focused on individual
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18 endpoints of recurrent non-fatal stroke, recurrent TIA, death, major bleeding, and
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20 atrial fibrillation. We also examined per protocol rates of recurrent stroke in
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22 patients undergoing PFO closure compared to the medical therapy arm. Outcomes
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24 were defined as in each study.
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30 31 32 Methods

33 34 Eligibility criteria

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36 We included all RCTs comparing treatment with percutaneous catheter-based
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38 closure of PFO to medical therapy (anticoagulant or antiplatelet therapy) in patients
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40 with cryptogenic stroke or TIA and echocardiographically confirmed PFO or ASD.
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42 We excluded trials including participants with other indications for PFO/ASD
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44 closure (e.g. hemodynamic significance) or other indications for anticoagulant
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46 therapy (e.g. atrial fibrillation).
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53 Included articles met two prespecified criteria: 1) RCTs that compared PFO closure
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55 to medical therapy (antiplatelet or anticoagulant agents); 2) Greater than 90% of
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3 patients had prior unexplained stroke, TIA, or other arterial embolism, or this
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5 subset was reported separately. When more than one study reported data from a
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7 population, we used the most complete and updated results.
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10 11 12 13 Data sources and search strategy

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15 We searched Medline and Embase from 1980 to May 2013. We restricted the search
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17 to human subjects. Keywords included patent foramen ovale *or* atrial septal defect.
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19 Results were then limited to randomize controlled trial *or* controlled clinical trial *or*
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21 phase 3 clinical trial *or* phase 4 clinical trial. For every eligible study we identified,
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23 and for studies such as review articles that included citations to potentially eligible
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25 studies, one reviewer examined the reference list.
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32 33 Study selection

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35 Teams of two investigators independently screened each title and abstract from this
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37 search. If either of the two screeners identified a citation as potentially relevant, we
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39 obtained the full text article for detailed review. Teams of two reviewers
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41 independently determined the eligibility of all studies that underwent full text
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43 evaluation. Disagreements were resolved through discussion between the two
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45 reviewers.
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52 53 Data abstraction

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55 Using a custom made data collection form two of three reviewers (FAS, LCL, SAK)
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57 abstracted the following information from each identified study: mean follow-up
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3 time, total patient years follow-up (overall and per cohort), number of patients
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5 withdrawn or lost to follow-up, number of patients crossing over from medical
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7 therapy to PFO closure, number of patients undergoing PFO closure attempt,
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9 number of patients in whom PFO closure was technically successful, procedural
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11 complications (other than major bleeding) from PFO closure, and outcome event
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13 rates.
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19 Disagreements regarding data abstraction results were resolved through discussion
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21 between the two reviewers. The primary author abstracted additional information
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23 on study funding, eligibility criteria, patient demographics, and treatment
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25 characteristics.
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29 30 31 Risk of Bias and Confidence in Effect Assessment 32

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34 Two reviewers (FAS, LL) independently assessed, using the Cochrane risk for bias
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36 tool, seven domains: adequacy of sequence generation, allocation sequence
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38 concealment, blinding of participants and caregivers, blinding for outcome
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40 assessment, incomplete outcome data, selective outcome reporting, and the
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42 presence of other potential sources of bias not accounted for in the other 6
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44 domains.⁷
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50 We used GRADE methodology to rate confidence in estimates of effect for each
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52 outcome as high, moderate, low or very low.⁸ We used detailed GRADE guidance to
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3 assess overall risk of bias⁹, imprecision¹⁰, inconsistency¹¹, indirectness¹² and
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5 publication bias¹³, and summarized results in an evidence profile.
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10 For decisions regarding eligibility, risk of bias assessment, and data abstraction,
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12 reviewers resolved disagreement through discussion.
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14 15 16 17 18 Data Synthesis and Statistical Analysis

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20 We report descriptive statistics as proportions for categorical variables, and
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22 mean/median for continuous variables. Our primary analyses for non-fatal ischemic
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24 stroke, TIAs, and mortality included only patients with complete follow-up. We
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26 excluded patients for whom complete data was unavailable: those lost to follow-up,
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28 those who withdrew consent, or those who were found to not have PFO/ASD or
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30 history of TIA/stroke after randomization. For outcomes of bleeding and atrial
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32 fibrillation we used data as reported by the investigators from the intention to treat
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34 analyses.
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42 Rates of non-fatal ischemic stroke in patients treated as “per-protocol” from two of
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44 the three studies were also abstracted and pooled. The definition of per-protocol
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46 varied from study to study (CLOSURE 1: all randomized patients who received the
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48 treatment to which they were randomized, who had no major inclusion/exclusion
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50 criteria violations, and who had a follow-up of at least 22 months; RESPECT:
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52 patients who received the randomly assigned treatment, adhered to the protocol-
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54 mandated medical treatment, and did not have a major inclusion or exclusion
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3 violation). Event rates for non-fatal ischemic stroke in the “per protocol” subset
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5 were not reported in PC Trial manuscript. The primary author of the manuscript
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7 did not respond to email requests for further information.
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12 As previous observational studies suggest that patients with cryptogenic stroke and
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14 PFO may be at higher risk for recurrent stroke if they have a concomitant atrial
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16 septal aneurysm, we performed an additional complete case analysis for a primary
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18 composite outcome in the subset of patients with atrial septal aneurysm (data on
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20 non-fatal ischemic stroke alone not reported in any of the studies for this subset).
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22 Composite outcomes in the 3 studies included some combination of non-fatal
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24 ischemic stroke, TIA, peripheral embolism, and death.
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32 As two of the three studies used the Amplatz device and one used the STARFlex
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34 device (CLOSURE 1) we conducted a sensitivity analysis for non-fatal ischemic
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36 stroke excluding the CLOSURE study. We evaluated for subgroup difference (2
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38 Amplatz studies vs. STARFlex study) using a chi-square test.
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44 Given high rate of patients excluded from complete case analyses (most due to loss
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46 to follow-up) we also conducted 2 additional analyses: 1) Worst case scenario in
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48 which we assumed that all patients with missing data in the PFO closure arms
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50 suffered non-fatal ischemic strokes and all patients lost to follow-up in the medical
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52 arms did not; 2) Plausible worst case scenario in which all patients with missing
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54 data from the PFO closure arm were assumed to have 5 times the rate of stroke as
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3 the complete cases and b) those excluded from the medical therapy arm were
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5 assumed to have 1/5 times the rate of stroke as the complete cases.¹⁴
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10 We calculated pooled risk ratios (RR) and associated 95% confidence intervals (CI)
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12 for non-fatal ischemic stroke and TIAs using random effects models applying Mantel
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14 Haenszel method. Absolute effects (and 95% CI) were calculated by multiplying
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16 pooled RRs and 95% CI by pooled control rate of outcomes. As event rates were
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18 very low for death, atrial fibrillation, and major bleeding (leading to skewed 95%
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20 CI), pooled risk difference (RD) and 95% CI was used to calculate absolute effects
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22 for these outcomes.¹⁵ Statistical heterogeneity was assessed by the I^2 statistic.
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24 Analyses were performed using RevMan version 5.2 (Copenhagen: The Nordic
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26 Cochrane Center, The Cochrane Collaboration).
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37 Results

38 Trial Identification

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40 Our search yielded 284 abstracts - all were identified from the electronic database
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42 search- of which 47 were duplicates and excluded. We excluded an additional 229
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44 articles based on a review of the title and abstract, leaving 8 articles for full review.
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47 Of these studies, 5 were excluded – 2 were descriptions of methodology for
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49 subsequently reported RCTs, 1 was a comparison of different devices for closure but
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51 did not include a medical therapy arm, and 2 were prospective cohort studies of PFO
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3 closure. (See Appendix Figure) We included 3 randomized trials enrolling 2303
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5 patients.⁴⁻⁷
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10 Trial and Patient Characteristics

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12 Table 1 presents the characteristics of the 3 eligible studies. Two of the three
13 studies (RESPECT, PC Trial) used the Amplatz occluder device whereas the other
14 used the STARFlex device (CLOSURE I). Crossover from medical therapy to PFO
15 closure occurred in only one study (13.3%) (PC Trial). The percentage of patients in
16 the PFO closure arm undergoing a PFO closure attempt ranged from 90.6 to 96.1%
17 with success rates ranging from 89.4% to 99.1%.
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30 In the CLOSURE I study all patients undergoing PFO closure were assigned to
31 clopidogrel 75 mg per day times 6 months and aspirin 81 or 325 mg per day for 2
32 years. In the RESPECT study all patients undergoing closure received aspirin 81-
33 325 mg plus clopidogrel for one month followed by aspirin monotherapy for 5
34 months. Antiplatelet treatment thereafter was left to the discretion of the site
35 investigator. In the PC Trial, managing clinicians were counseled to recommend
36 aspirin 100 to 325 mg per day for 5 to 6 months and ticlopidine (250 to 500 mg per
37 day) or clopidogrel (75 mg to 150 mg per day) for 1 to 6 months. However at
38 discharge from PFO closure in the PC trial, 182 patients (89.2%) were using aspirin,
39 104 (51%) thienopyridines, 6 (2.9%) oral anticoagulation, and 8 (3.9%) were not
40 using antithrombotic prophylaxis.
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3 Treatment in the medical therapy arms also varied across studies. In Closure I,
4 patients assigned to medical therapy were treated with warfarin (with a target
5 international normalized ratio of 2.0 to 3.0), aspirin (325 mg daily), or both, at the
6 discretion of the principal investigator at each site (further details not provided). In
7 RESPECT five medical therapies were initially allowed (after randomization aspirin
8 alone was used in 223 patients (46.5%), warfarin alone in 121 (46.5%), clopidogrel
9 alone in 67 patients (14%), aspirin with dipyridamole in 39 patients (8.1%), and
10 aspirin with clopidogrel in 30 (6.2%). In the PC Trial antithrombotic treatment was
11 also left to the discretion of the treating physician and could have included
12 antiplatelet therapy or oral anticoagulation (after randomization, 120 (57.1%) of
13 subjects were using aspirin, 35 (16.7%) thienopyridines, 64 (30.5%) oral
14 anticoagulation, and 5 (2.4%) were not using antithrombotic prophylaxis.
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35 Adherence with medical therapy/changes in medical therapy was not clearly
36 documented in 2 of the 3 studies. In the PC trial, the percentage of patients using no
37 antithrombotic prophylaxis increased from 2.4% following randomization to 7.7%
38 at 2 years, 11.3% at 3 years, 11.1% at 4 years, and 12.8% at 5 years. The
39 distribution of other therapies changed little over 5 years.
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49 A total of 311 (13.5%) subjects were lost to follow-up or withdrew consent (range
50 within studies 12% to 18%). Loss to follow-up/withdrawal of consent was higher in
51 the medical therapy arm (n = 204, 18%) than in the PFO closure arm (n = 107, 9%).
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56 In addition, 14 patients (CLOSURE I = 12, PC Trial = 1, RESPECT = 1) were
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3 demonstrated to have no PFO after randomization and 11 patients were determined
4 to have no prior history of stroke or TIA (CLOSURE I). Therefore 336 subjects were
5 excluded from our complete case analyses.
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12 The three studies enrolled similar patients (e.g. age range from 44.5 to 46 years)
13 with some differences in medical history (Table 2). In two of the studies
14 approximately 70-80% of patients were enrolled with an index diagnosis of
15 cryptogenic stroke with most of the rest having an index diagnosis of TIA. In one
16 study (RESPECT), all patients enrolled had a diagnosis characterized as stroke but
17 patients with less than 24 hours of symptoms and radiologic evidence for infarct
18 were included in this category.
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32 Assessment of Risk of Bias

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34 Overall risk of bias was deemed high for all 3 studies due to missing data (see Figure
35 1). There is also lack of clear description regarding how compliance with medical
36 therapy was assessed – in only 1 study was medical therapy usage at different time
37 points described.
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44 Participants and study personnel were not blinded in any of the three
45 studies, which likely contributed to differential rates of loss to follow-up. It is
46 unclear if this would have led to additional bias with respect to the observed
47 outcome rates as a clinical events committee adjudicated events in all three studies.
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56 Outcomes Assessment

Non-fatal ischemic Stroke

There were a total of 22 non-fatal ischemic strokes among 1026 patients randomized to PFO closure vs. 34 strokes among 941 patients randomized to medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: $p = 0.34$, $I^2 = 8\%$) (Figure 2). Using our best estimate of baseline from the available randomized trials of 52 non-fatal ischemic strokes over 5 years in 1000 patients treated medically, PFO closure may be associated with 20 fewer strokes per 1000 treated over a period of 5 years (confidence interval 34 fewer to 4 more strokes, low confidence in estimates because of risk of bias and imprecision) (Table 3).

In a sensitivity analysis including the 2 studies using the Amplatz device, PFO closure was associated with a decreased risk of non-fatal ischemic stroke (RR 0.44, 95% 0.21, 0.93; Heterogeneity: $p = 0.42$, $I^2 = 0\%$). In the CLOSURE I Study (Starflex device), there was no difference between PFO closure and medical therapy with respect to non-fatal ischemic stroke (RR 0.87, 95% CI 0.40, 1.87). The test for interaction between these two subset analyses revealed differences consistent with chance ($\text{Chi}^2 = 1.52$, $p = 0.22$).

We conducted analyses imputing non-fatal strokes for patients excluded from the complete case analysis. In our worst-case analysis (all PFO intervention arm patients excluded from complete case analysis having non-fatal ischemic stroke, none of subjects excluded from the medical therapy arm having non-fatal ischemic stroke), RR = 4.22, 95% CI 2.93, 6.08 (Heterogeneity: $p = 0.39$, $I^2 = 0\%$). In our

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3 plausible worst case analysis in which excluded PFO closure patients had 5-fold
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5 increased rate of stroke (relative to included subjects) and excluded medical
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7 therapy patients had a 1/5 rate of stroke (relative to included subjects), PFO closure
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9 was associated with a RR = 0.96, 95% CI 0.56, 1.66 (Heterogeneity: $p = 0.28$, $I^2 =$
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11 21%). These results support rating down confidence in estimates for risk of bias
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13 related to missing data.
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20 In the 2 studies providing per-protocol event rates for non-fatal ischemic stroke
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22 there were 18 vs. 27 non-fatal ischemic strokes yielding a RR of 0.66, 95% CI 0.32,
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24 1.38 (Heterogeneity: $p = 0.23$, $I^2 = 32\%$)
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30 As previous observational studies suggest that patients with cryptogenic stroke and
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32 PFO may be at higher risk for recurrent stroke if they have a concomitant atrial
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34 septal aneurysm, we also examined pooled rates of the primary composite endpoint
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36 of the studies in this subset. There were 13 events among 378 patients with atrial
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38 septal aneurysm undergoing closure compared to 20 events among 380 patients
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40 undergoing medical therapy (RR 0.71, 95% CI 0.22, 2.27; Heterogeneity: $p = 0.11$, I^2
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42 = 55%).
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49 TIAs

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51 Pooling complete case data from the 3 studies, there were 23 vs. 28 TIAs in the PFO
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53 closure and medical treatment groups respectively (RR 0.76, 95% CI 0.44, 1.32;
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55 Heterogeneity: $p = 0.64$, $I^2 = 0\%$). PFO closure may be associated with 6 fewer TIAs
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3 over a period of 5 years (confidence interval 15 fewer to 9 more) (moderate
4 confidence because of risk of bias (Figure 3, Table 3).
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10 Total mortality

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12 There were 7 deaths per in the PFO closure arm vs. 10 deaths in the medical
13 treatment arm of the 3 studies (RD -0.00, 95% CI -0.01, 0.01; Heterogeneity: $p =$
14 0.23 , $I^2 = 31\%$). None of the deaths were deemed secondary to treatment (PFO
15 closure or antithrombotic therapy) or stroke. PFO closure may have no effect on
16 mortality over a period of 5 years (confidence interval 10 fewer to 10 more) (low
17 confidence because of risk of bias and imprecision) (Table 3).
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30 Adverse events

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32 Pooling data from all 3 studies, bleeding occurred in 13 vs. 7 patients in the PFO
33 closure vs. medical treatment arms (all were major bleeds except 2 bleeds from
34 RESPECT study not classified) (RD 0.00, 95% CI -0.01, 0.02; Heterogeneity $p = 0.12$,
35 $I^2 = 53\%$) (see Figure 4). PFO closure may have no effect on major bleeding over a
36 period of 5 years (CI 10 fewer to 20 more) (moderate confidence because of risk of
37 bias) (Table 3).
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49 Atrial fibrillation occurred in 32 patients undergoing PFO closure vs. 8 patients
50 treated with medical therapy (RD 0.02, 95% -0.02, 0.06; Heterogeneity: $p < 0.00001$,
51 $I^2 = 93\%$). PFO closure may be associated with 20 more cases of atrial fibrillation
52 per 1000 treated compared to medical therapy over a period of 5 years (CI 20 fewer
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3 to 60 more) (very low confidence because of risk of bias, inconsistency, and
4 imprecision) (Table 3). Of 23 cases of atrial fibrillation reported after PFO closure in
5 the CLOSURE I study 6 were deemed “sustained” – atrial fibrillation in the medical
6 group was not characterized. Of 8 cases of atrial fibrillation in the PC Trial occurring
7 after PFO closure 2 were transient (in PFO closure arm) and 6 required
8 cardioversion or were sustained. Atrial fibrillation was not characterized as
9 transient or sustained in the RESPECT study.
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23 We were unable to pool data regarding procedural or device related complications
24 given differences between studies in reporting styles. Serious procedural or device
25 related adverse events (in addition to bleeding, ischemic stroke, atrial fibrillation
26 which have already been captured in previous analyses) were reported in 15
27 patients in the RESPECT trial (3%). This included 8 procedural related events.
28 Major vascular events related to the procedure occurred in 13 of the 402 patients
29 (3.2%) in whom PFO closure was attempted in CLOSURE I – these included 6 major
30 bleeding episodes already captured above. The total number of serious procedural
31 related adverse events was not specifically reported in the PC Trial although it was
32 noted that no device related thrombi occurred.
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52 Discussion

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54 A decade ago a meta-analysis of observational studies suggested
55 transcatheter closure of PFO in patients with cryptogenic stroke may prevent more
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3 strokes than medical therapy.³ The authors noted important limitations in
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5 available data and highlighted the need for RCTs to resolve the issue. Since that
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7 time, thousands of patients have undergone this procedure in a non-RCT setting.
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10 We now have data from 3 RCTs comparing transcatheter PFO closure to
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12 medical therapy in patients with cryptogenic stroke or TIA and PFOs. Our analysis
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14 suggests a possible benefit of closure on the major outcome of stroke (RR 0.61, 95%
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16 CI 0.34, 1.07). Confidence in the estimate of 20 fewer strokes per 1,000 is, however,
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18 low, both because of problems with risk of bias and imprecision (confidence
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20 intervals include an increase in stroke of 4 per 1,000). Analyses for ischemic stroke
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22 restricted to “per-protocol” patients or patients with concomitant atrial septal
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24 aneurysm did not substantially change the observed risk ratios.
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29 We conducted subgroup analyses evaluating the impact of PFO closure on
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31 non-fatal stroke separately in the 2 studies using the Amplatz closure device vs. the
32
33 one study using the STARFlex device. Pooled data from the Amplatz studies
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35 suggests PFO closure may be associated a decrease in non-fatal ischemic stroke (RR
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37 0.44, 95% CI 0.21, 0.93) whereas no benefit was observed in the study using the
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39 STARFlex device. Although the subgroup hypothesis was made a priori and
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41 differences are in the anticipated direction, the analysis is based on between group
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43 differences, has not been replicated, and differences between results with the two
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45 devices is easily explained by chance ($p = 0.22$). Thus the subgroup hypothesis has
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47 low credibility.¹⁶
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53 As suggested in two other recently published analyses, our data could be
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55 interpreted to suggest a potential substantial benefit may exist for PFO closure.^{17,18}
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3 It is possible that a larger sample size and more rigorously done studies would
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5 definitively identify an important benefit in the total patient population, or in a
6
7 subgroup. Our review demonstrates, however, that such additional studies may also
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9 fail to demonstrate benefit or, in comparison to effective antithrombotic
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11 prophylaxis, an increase in strokes.
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15 Although some concern arises from possible lack of concealment of
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17 randomization in one study and the apparent failure to blind outcome adjudication
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19 in another study, the major problem in terms of risk of bias is the high loss to follow-
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21 up in these studies and the two fold greater loss to follow-up in patients in the
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23 medical therapy arms than the PFO closure arms (overall 9% in PFO and 18% in the
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25 medical therapy arms).
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30 Our primary analysis was restricted to patients with available data (complete
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32 case analysis). If event rates differed in those with missing data in intervention and
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34 control groups - of particular concern would be higher rates of events in those lost
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36 to follow-up in the PFO closure arm that the medical therapy arm - the complete
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38 case results may be misleading. In an additional analysis in which patients lost to
39
40 follow-up in the PFO arm were assumed to have 5 fold increased risk of stroke and
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42 those lost to follow-up in the medical therapy arm had a 5-fold decreased risk of
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44 stroke, there was no longer a trend favoring PFO closure (RR 0.96). This finding
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46 supports our rating down confidence in estimates of effect for risk of bias.
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51 Another issue is the rigor with which control arm clinicians encouraged
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53 compliance with antithrombotic prophylaxis in medical patients. In two of the
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55 studies dose and type of antithrombotic therapy in the medical therapy arm were
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3 left to the treating physician's discretion. Only one of the studies reported
4 adherence and/or changes over time in medical therapy in both arms. Leaving
5 therapy in the medical arm to the physician's discretion could be considered to
6 represent "usual care" for those randomized to medical therapy. Usual care may,
7 however, change over time, and differ in the jurisdictions in which the trial is
8 conducted in comparison to other jurisdictions. Patients and clinicians may,
9 therefore, be more interested in the effect of PFO closure versus a particular
10 antithrombotic regimen with a high level of adherence.
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23 Stroke occurring due to paradoxical emboli through a PFO results from
24 thrombi originating in the venous circulation or perhaps the right atrial side of an
25 associated atrial septal aneurysm. Warfarin has been shown to be more effective
26 than antiplatelet therapy for the treatment and secondary prevention of venous
27 thromboembolic events. Observational studies suggest oral anticoagulation is
28 superior to aspirin for the prevention of stroke in patients with PFO albeit with
29 increased bleeding.^{19,20} In the Patent Foramen Ovale in Cryptogenic Stroke study
30 (substudy of the randomized Warfarin-Aspirin Recurrent Stroke study) there were
31 98 patients with cryptogenic stroke and PFO - 42 were randomized to warfarin and
32 56 received aspirin.²¹ Two-year rates of recurrent stroke were lower in patients
33 receiving warfarin (9.5% vs. 17.9%,) but chance easily explains this (p = 0.28).
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49 Given the uncertainty of the optimal antithrombotic regimen, subsequent
50 trials must give this issue careful thought. One option for the medical arm would be
51 careful exploration of individual patient values and preferences. Patients highly
52 averse to bleeding risk and the burdens of anticoagulant therapy could receive only
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3 an antiplatelet agent, while those less bleeding and burden averse could receive an
4 anticoagulant. Use of an oral anticoagulant rather than warfarin in those choosing
5 anticoagulation would be a possibility. Such an approach might represent optimal
6 medical care, perhaps the appropriate comparator to PFO closure. Another option
7 would be three-arm study with both antiplatelet and anticoagulant arms
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11 We conclude that the available data warrants only low confidence in the
12 impact of PFO versus medical therapy. Thus, additional RCTs are still required –
13 two such studies are listed as actively recruiting on the NIH website
14 ClinicalTrials.gov. Ideally, when pooled across studies, sample sizes will be large
15 enough to definitively establish the impact of PFO closure versus medical therapy on
16 the most important outcome, ischemic stroke. As important, results will be more
17 compelling if the ongoing studies have implemented successful strategies to ensure
18 complete or near-complete follow-up and have paid careful attention to decisions
19 regarding medical prophylaxis and optimizing adherence in both arms of the study.
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49 Figure legends:

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51 Figure 1 Risk of bias in individual studies

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53 Figure 2 Pooled risk of non-fatal ischemic stroke with PFO closure versus medical
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3 Figure 3 Pooled risk of transient ischemic attack with PFO closure versus medical
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8 Figure 4 Pooled risk of major bleeding with PFO closure versus medical therapy
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Contributorship statement:

Dr. Frederick Spencer contributed to the conception and design of the study, the acquisition, analysis and interpretation of the data, drafting the work, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Luciane Lopes contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Mr. Sean Kennedy contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Dr. Gordon Guyatt contributed to the design of the study, the acquisition, analysis and interpretation of the data, drafting and critical revision of the work for important intellectual content, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1

Trial (patients)	Trial Type	Intervention	Medical therapy	Withdrew or Loss to Followup PFO closure (%)	Withdrew/Loss to Followup Medical Therapy (%)	Crossover from Medical Therapy to PFO Closure (%)	% PFO closure attempts/patients enrolled in PFO cohort (%)	% technical success /PFO closure attempts (%)
CLOSURE I (909)	Multicentre Randomized Open label	STARFLEX Device Clopidogrel x 6 mo ASA x 2 years	Warfarin (INR 2-3), ASA 325 per day, or both (clinician's discretion)	1.8	0.7	0	90.6	89.4
PC Trial (414)	Multicentre Randomized Open Label	Amplatz Occluder ASA 5-6 mo. Clopidogrel or ticlopidine 1-6 mo.	Antiplatelet or anticoagulation (clinician's discretion)	15.2	20	13.3	96.1	97.4
RESPECT (980)	Multicentre Randomized Open Label	Amplatz Occluder ASA 6 mo Clopidogrel 1 mo.	Antiplatelet or anticoagulation (clinician's discretion)	9.2	17.2	0	93	99.1

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Table 2 Characteristics of Patients in Eligible Studies

	CLOSURE 1	RESPECT	PC Trial
N	909	980	414
Mean Age +/- SD	46.0	45.9	44.5
Male (%)	51.8	54.7	49.8
Smoker (%)	22.1	13.3	23.9
Medical History (%)			
Diabetes	NR	7.4	2.7
Hypertension	31.0	31.4	25.8
Hyperlipidemia	44.1	39.5	27.1
Ischemic heart disease	1.1	2.9	1.9
Myocardial infarction	1.3	0.7	1
Valvular dysfunction	10.3	NR	3.1
Peripheral vascular disease	1.3	0.6	1.2
Index event (%)			
Stroke	72	100*	79.2
TIA	28	0	18.1
Peripheral arterial embolism	0	0	2.7
PFO characteristics (%)			
Moderate or higher shunt	52.9	75.2	65.6**
Atrial septal aneurysm >10 mm	37.8***	35.6	23.7

*Included patients with symptoms for less than 24 hours if new neuroradiologically relevant cerebral infarct on imaging

** 369 of 414 patients with TEE

***151/400 patients with TEE

Table 3 – GRADE assessment of quality of evidence

Bibliography:									
Quality assessment						Summary of findings			
No of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Relative effect or risk difference (95% CI)	Anticipated absolute effects Time frame: 5 years		Quality of evidence
							Risk with medical therapy	Risk difference with PFO closure (95% CI)	
Non-fatal ischemic stroke (critical outcome)									
1968 (3 RCTs)	Serious limitations¹	No serious limitations	No serious limitations	Imprecise CI includes benefit and no effect	Undetected	RR 0.61 (0.34 to 1.07)	52 per 1000²	20 fewer per 1000 (from 34 fewer to 4 more)	⊕⊕⊕⊕ LOW due to risk of bias and imprecision
TIA (important outcome)									
1968 (3 RCTs)	Serious limitations¹	No serious limitations	No serious limitations	No serious limitations ³	Undetected	RR 0.76 (0.44 to 1.32)	27 per 1000⁴	6 fewer per 1000 (from 15 fewer to 9 more)	⊕⊕⊕⊕ MODERATE due to risk of bias
Total mortality (critical outcome)⁵									
1968 (3 RCTs)	Serious limitations¹	No serious limitations	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RD 0.00 (-0.01, 0.01)	15 per 1000⁶	0 fewer per 1000 (from 10 fewer to 10 more)	⊕⊕⊕⊕ LOW due to risk of bias and imprecision
Major bleeding (important outcome)									
2254 (3 RCTs)	Serious limitations¹	No serious inconsistency	No serious limitations ³	No serious limitations	Undetected	RD 0.00 (-0.01, 0.02)	7 per 1000⁷	0 more per 1000 (10 fewer to 20 more)	⊕⊕⊕⊕ MODERATE due to risk of bias
Atrial fibrillation (important outcome)⁸									
2254 (3 RCTs)	Serious limitations¹	Serious inconsistency⁹	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RD 0.02 (-0.02, 0.06)	12 per 1000¹⁰	20 more per 1000 (20 fewer to 60 more)	⊕⊕⊕⊕ VERY LOW due to risk of bias and imprecision

¹Serious risk of bias due to substantial loss to followup in each of 3 studies; loss to followup greater in medical therapy arms. See text for other potential sources of bias in individual studies.

²Baseline rate derived from pooled Respect and PC trial data - 21 non-fatal ischemic strokes detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

³Although CI includes benefit and harm, but magnitude of extremes for this type of outcome deemed too low to appreciably impact patient decision making.

⁴Baseline rate derived from pooled Respect and PC trial data - 11 TIAs detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

⁵None of deaths due to stroke, treatment related bleeding, or device implantation

⁶Baseline rate derived from pooled Respect and PC trial data - 6 cases of total mortality detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

⁷Baseline rate derived from pooled Respect and PC trial data - 3 cases of major bleeding detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

⁸Type of atrial fibrillation (transient vs. sustained) not reported in medical therapy arms or in PFO closure arm of RESPECT study. Of 31 cases of atrial fibrillation in the remaining 2 studies 19 were characterized as transient.

⁹I² = 93%, p = <0.00001

¹⁰Baseline rate derived from pooled Respect and PC Trial data - 5 cases of atrial fibrillation detected in the medical therapy arm over a total of 2019 pt-yrs x 1000 x 5 years.

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CLOSURE I

PC Trial

RESPECT

Random sequence generation (selection bias)

Allocation concealment (selection bias)

Blinding of participants and personnel (performance bias)

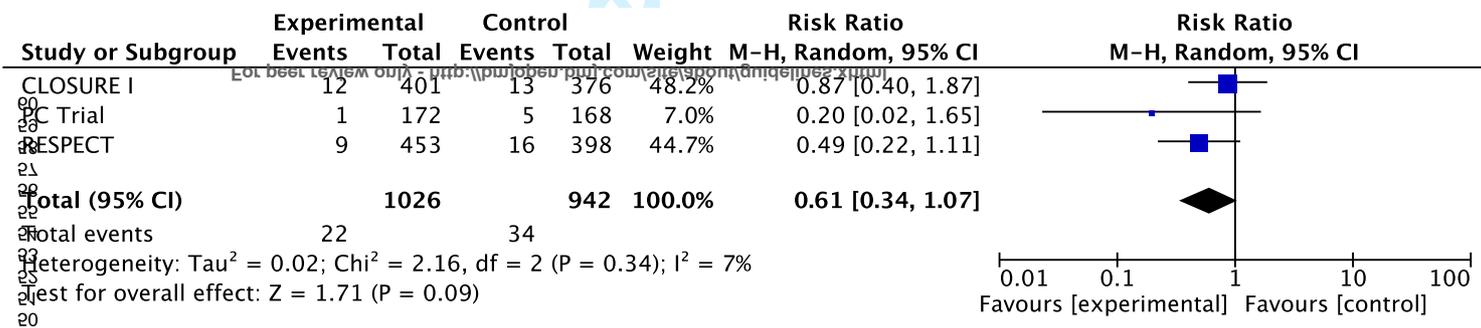
Blinding of outcome assessment (detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

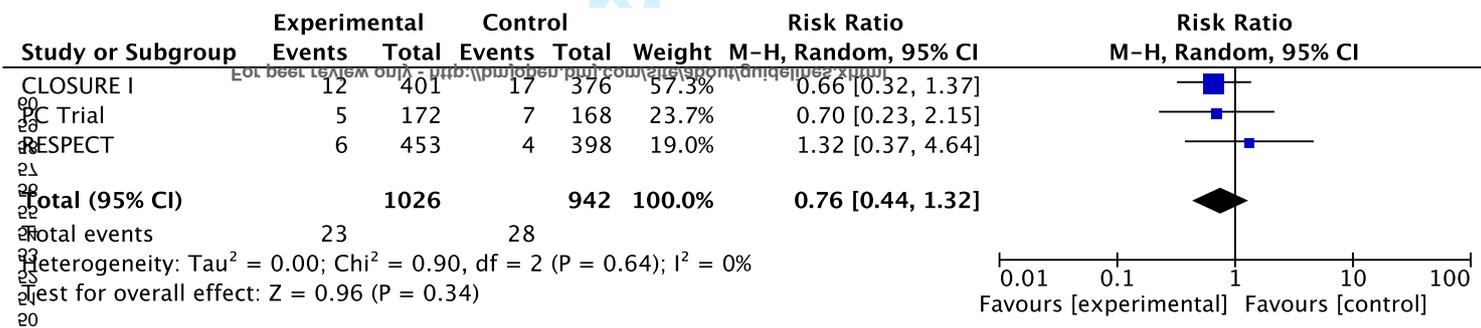
Other bias

For peer



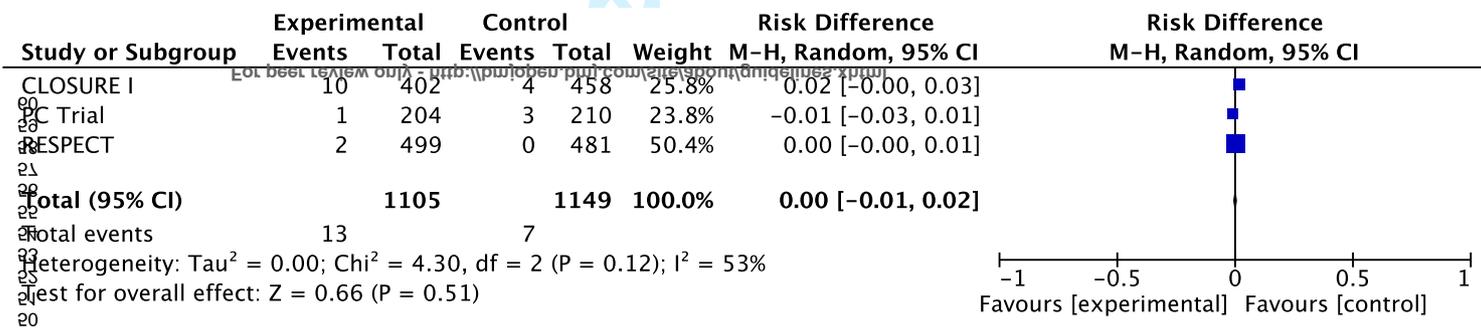
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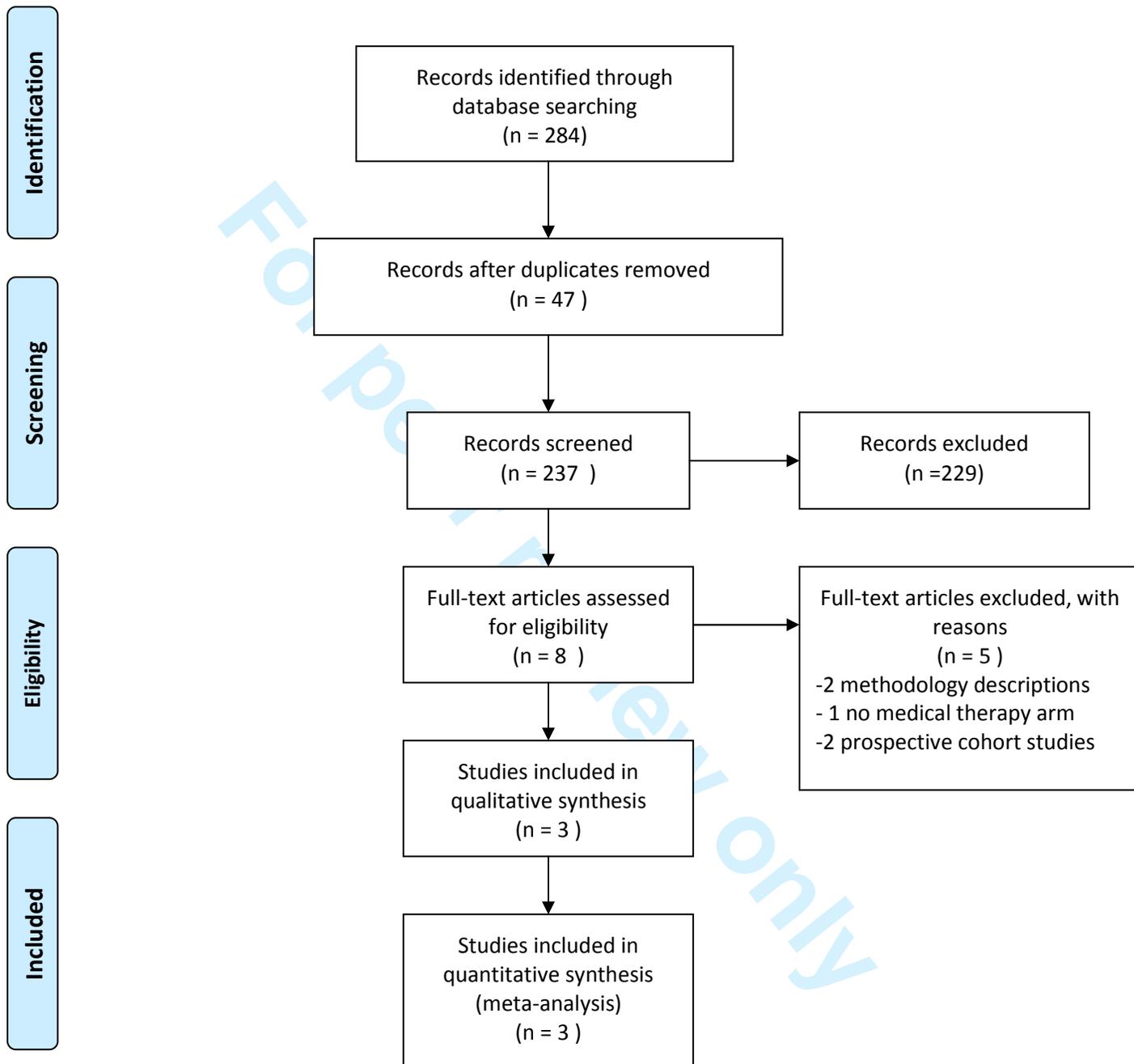
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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-11



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-14 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14 Figure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-18 Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-18 Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA



PRISMA 2009 Checklist

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Page 2 of 2

For peer review only



Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with Cryptogenic Stroke and Patent Foramen Ovale

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Manuscripts

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3 Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with
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6 Cryptogenic Stroke and Patent Foramen Ovale
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3 Abstract

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5 Objectives: To provide a comprehensive comparison of PFO closure versus medical
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7
8 therapy in patients with cryptogenic stroke or transient ischemic attack (TIA) and
9
10 demonstrated PFO.
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15 Design: Systematic review with complete case meta-analysis and sensitivity
16
17 analyses. Data sources included Medline and Embase from 1980 up to May 2013.
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19
20 All randomized controlled trials (RCTs) comparing treatment with percutaneous
21
22 catheter-based closure of PFO to anticoagulant or antiplatelet therapy in patients
23
24 with cryptogenic stroke or TIA and echocardiographically confirmed PFO or atrial
25
26 septal defect (ASD) were eligible.
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32 Participants: 1967 subjects with prior stroke or TIA and echocardiographically
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34 confirmed PFO or ASD.
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39 Primary outcome measures: The primary outcome of interest was recurrence of
40
41 ischemic stroke. We utilized data from complete cases only for the primary endpoint
42
43 and combined data from trials to estimate the pooled risk ratio (RR) and associated
44
45 95% confidence intervals (CI) calculated using random effects models.
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51 Results: We identified 284 potentially eligible articles of which 3 RCTs including
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53 2303 patients proved eligible and 1967 patients had complete data. Of the 1026
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55 patients randomized to PFO closure and followed to study conclusion 22
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3 experienced non-fatal ischemic strokes, as did 34 of 941 patients randomized to
4 medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: $p = 0.34$, $I^2 =$
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6 8%, confidence in estimates low due to risk of bias and imprecision). Analyses for
7
8 ischemic stroke restricted to “per-protocol” patients or patients with concomitant
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10 atrial septal aneurysm did not substantially change the observed risk ratios.
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Complication rates associated with either PFO closure or medical therapy were low.

Conclusions: Pooled data from 3 RCTs provides insufficient support that PFO closure is preferable to medical therapy for secondary prevention of cryptogenic stroke in patients with PFO.

Abstract word count: 279

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3 Study strengths
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- 6 • Estimation of absolute benefits and risks of treatment strategies
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- 8 • Careful assessment of risk of bias of individual studies using Cochrane
- 9 criteria
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- 13 • Evaluation of overall confidence in pooled outcome(s) estimates using
- 14 GRADE
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20 Limitations
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- 22 • Primary analysis was restricted to patients with available data (complete
- 23 case analysis). If event rates differed in those with missing data in
- 24 intervention and control groups - of particular concern would be higher
- 25 rates of events in those lost to follow-up in the PFO closure arm than the
- 26 medical therapy arm - the complete case results may be misleading
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- 35 • Individual patient-level data not available
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Introduction

Observational studies suggest that younger patients with cryptogenic stroke are more likely to have a patent foramen ovale (PFO) than the general population.^{1,2} A proposed mechanism for stroke in these patients is passage of thrombi from the venous circulation to the arterial circulation through the PFO. Although what proportion of cryptogenic strokes are due to paradoxical embolism remains unknown, percutaneous closure of PFO using devices approved for hemodynamically significant secundum atrial septal defect (ASD) has increased greatly in the last 2 decades. A systematic review of observational studies suggests PFO closure may be superior to medical therapy (antiplatelet or anticoagulant agents) for secondary prevention of stroke in patients with patent foramen ovale and cryptogenic stroke.³

In the last two years 3 three randomized control trials (RCTs) comparing PFO closure to medical therapy have been published – none showed PFO closure to be statistically superior to medical therapy for the primary composite outcome but each reported trends favoring PFO closure.⁴⁻⁶ In one study, PFO closure was superior to medical therapy for the prevention of recurrent neurologic events in prespecified per-protocol and as-treated analyses.⁵

One systematic review and meta-analysis that included the 3 RCTs, and a second meta-analysis, have addressed this issue. Both were limited, however, by failure to fully consider risk of bias issues, failure to use the GRADE approach to determine

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3 overall confidence in estimates of intervention effect, and failure to consider the
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5 limitations of composite endpoints.
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10 We therefore undertook a systematic review of all RCTs comparing percutaneous
11 PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFO
12 or ASD. As composite endpoints varied between trials, we focused on individual
13 endpoints of recurrent non-fatal stroke, recurrent TIA, death, major bleeding, and
14 atrial fibrillation. We also examined per protocol rates of recurrent stroke in
15 patients undergoing PFO closure compared to the medical therapy arm. Outcomes
16 were defined as in each study.
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30 Methods

31 Eligibility criteria

32 We included all RCTs comparing treatment with percutaneous catheter-based
33 closure of PFO to medical therapy (anticoagulant or antiplatelet therapy) in patients
34 with cryptogenic stroke or TIA and echocardiographically confirmed PFO or ASD.
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40 We excluded trials including participants with other indications for PFO/ASD
41 closure (e.g. hemodynamic significance) or other indications for anticoagulant
42 therapy (e.g. atrial fibrillation).
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51 Included articles met two prespecified criteria: 1) RCTs that compared PFO closure
52 to medical therapy (antiplatelet or anticoagulant agents); 2) Greater than 90% of
53 patients had prior unexplained stroke, TIA, or other arterial embolism, or this
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3 subset was reported separately. When more than one study reported data from a
4
5 population, we used the most complete and updated results.
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8 9 10 Data sources and search strategy

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12 We searched Medline and Embase from 1980 to May 2013. We restricted the search
13
14 to human subjects. Keywords included patent foramen ovale *or* atrial septal defect.
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16 Results were then limited to randomize controlled trial *or* controlled clinical trial *or*
17
18 phase 3 clinical trial *or* phase 4 clinical trial. For every eligible study we identified,
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20 and for studies such as review articles that included citations to potentially eligible
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22 studies, one reviewer examined the reference list.
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30 Study selection

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33 Teams of two investigators independently screened each title and abstract from this
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35 search. If either of the two screeners identified a citation as potentially relevant, we
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37 obtained the full text article for detailed review. Teams of two reviewers
38
39 independently determined the eligibility of all studies that underwent full text
40
41 evaluation. Disagreements were resolved through discussion between the two
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43 reviewers.
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50 Data abstraction

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52 Using a custom made data collection form two of three reviewers (FAS, LCL, SAK)
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54 abstracted the following information from each identified study: mean follow-up
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56 time, total patient years follow-up (overall and per cohort), number of patients
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withdrawn or lost to follow-up, number of patients crossing over from medical therapy to PFO closure, number of patients undergoing PFO closure attempt, number of patients in whom PFO closure was technically successful, procedural complications (other than major bleeding) from PFO closure, and outcome event rates.

Disagreements regarding data abstraction results were resolved through discussion between the two reviewers. The primary author abstracted additional information on study funding, eligibility criteria, patient demographics, and treatment characteristics.

Risk of Bias and Confidence in Effect Assessment

Two reviewers (FAS, LL) independently assessed, using the Cochrane risk for bias tool, seven domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the other 6 domains.⁷

We used GRADE methodology to rate confidence in estimates of effect for each outcome as high, moderate, low or very low.⁸ We used detailed GRADE guidance to assess overall risk of bias⁹, imprecision¹⁰, inconsistency¹¹, indirectness¹² and publication bias¹³, and summarized results in an evidence profile.

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6 For decisions regarding eligibility, risk of bias assessment, and data abstraction,
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8 reviewers resolved disagreement through discussion.
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10 11 12 13 Data Synthesis and Statistical Analysis

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15 We report descriptive statistics as proportions for categorical variables, and
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17 mean/median for continuous variables. Our primary analyses for non-fatal ischemic
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19 stroke, TIAs, and mortality included only patients with complete follow-up. We
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21 excluded patients for whom complete data was unavailable: those lost to follow-up,
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23 those who withdrew consent, or those who were found to not have PFO/ASD or
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25 history of TIA/stroke after randomization. For outcomes of bleeding and atrial
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27 fibrillation we used data as reported by the investigators from the intention to treat
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29 analyses.
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37 Rates of non-fatal ischemic stroke in patients treated as “per-protocol” from two of
38
39 the three studies were also abstracted and pooled. The definition of per-protocol
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41 varied from study to study (CLOSURE 1: all randomized patients who received the
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43 treatment to which they were randomized, who had no major inclusion/exclusion
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45 criteria violations, and who had a follow-up of at least 22 months; RESPECT:
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47 patients who received the randomly assigned treatment, adhered to the protocol-
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49 mandated medical treatment, and did not have a major inclusion or exclusion
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51 violation). Event rates for non-fatal ischemic stroke in the “per protocol” subset
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3 were not reported in PC Trial manuscript. The primary author of the manuscript
4 did not respond to email requests for further information.
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10 As previous observational studies suggest that patients with cryptogenic stroke and
11 PFO may be at higher risk for recurrent stroke if they have a concomitant atrial
12 septal aneurysm, we performed an additional complete case analysis for a primary
13 composite outcome in the subset of patients with atrial septal aneurysm (data on
14 non-fatal ischemic stroke alone not reported in any of the studies for this subset).
15 Composite outcomes in the 3 studies included some combination of non-fatal
16 ischemic stroke, TIA, peripheral embolism, and death.
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30 As two of the three studies used the Amplatzer device and one used the STARFlex
31 device (CLOSURE 1) we conducted a sensitivity analysis for non-fatal ischemic
32 stroke excluding the CLOSURE study. We evaluated for subgroup difference (2
33 Amplatzer studies vs. STARFlex study) using a chi-square test.
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42 Given high rate of patients excluded from complete case analyses (most due to loss
43 to follow-up) we also conducted 2 additional analyses: 1) Worst case scenario in
44 which we assumed that all patients with missing data in the PFO closure arms
45 suffered non-fatal ischemic strokes and all patients lost to follow-up in the medical
46 arms did not; 2) Plausible worst case scenario in which all patients with missing
47 data from the PFO closure arm were assumed to have 5 times the rate of stroke as
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3 the complete cases and b) those excluded from the medical therapy arm were
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5 assumed to have 1/5 times the rate of stroke as the complete cases.¹⁴
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10 We calculated pooled risk ratios (RR) and associated 95% confidence intervals (CI)
11
12 for non-fatal ischemic stroke and TIAs using random effects models applying Mantel
13
14 Haenszel method. Absolute effects (and 95% CI) were calculated by multiplying
15
16 pooled RRs and 95% CI by pooled control rate of outcomes. As event rates were
17
18 very low for death, atrial fibrillation, and major bleeding (leading to skewed 95%
19
20 CI), pooled risk difference (RD) and 95% CI was used to calculate absolute effects
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22 for these outcomes.¹⁵ Statistical heterogeneity was assessed by the I^2 statistic.
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24 Analyses were performed using RevMan version 5.2 (Copenhagen: The Nordic
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26 Cochrane Center, The Cochrane Collaboration).
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37 Results

38 Trial Identification

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40 Our search yielded 284 abstracts - all were identified from the electronic database
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42 search- of which 47 were duplicates and excluded. We excluded an additional 229
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44 articles based on a review of the title and abstract, leaving 8 articles for full review.
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47 Of these studies, 5 were excluded – 2 were descriptions of methodology for
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49 subsequently reported RCTs, 1 was a comparison of different devices for closure but
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51 did not include a medical therapy arm, and 2 were prospective cohort studies of PFO
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3 closure. (See Appendix Figure) We included 3 randomized trials enrolling 2303
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5 patients.⁴⁻⁷
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10 Trial and Patient Characteristics

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12 Table 1 presents the characteristics of the 3 eligible studies. Two of the three
13 studies (RESPECT, PC Trial) used the Amplatzer occluder device whereas the other
14 used the STARFlex device (CLOSURE I). Crossover from medical therapy to PFO
15 closure occurred in only one study (13.3%) (PC Trial). The percentage of patients in
16 the PFO closure arm undergoing a PFO closure attempt ranged from 90.6 to 96.1%
17 with success rates ranging from 89.4% to 99.1%.
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30 In the CLOSURE I study all patients undergoing PFO closure were assigned to
31 clopidogrel 75 mg per day times 6 months and aspirin 81 or 325 mg per day for 2
32 years. In the RESPECT study all patients undergoing closure received aspirin 81-
33 325 mg plus clopidogrel for one month followed by aspirin monotherapy for 5
34 months. Antiplatelet treatment thereafter was left to the discretion of the site
35 investigator. In the PC Trial, managing clinicians were counseled to recommend
36 aspirin 100 to 325 mg per day for 5 to 6 months and ticlopidine (250 to 500 mg per
37 day) or clopidogrel (75 mg to 150 mg per day) for 1 to 6 months. However at
38 discharge from PFO closure in the PC trial, 182 patients (89.2%) were using aspirin,
39 104 (51%) thienopyridines, 6 (2.9%) oral anticoagulation, and 8 (3.9%) were not
40 using antithrombotic prophylaxis.
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3 Treatment in the medical therapy arms also varied across studies. In Closure I,
4 patients assigned to medical therapy were treated with warfarin (with a target
5 international normalized ratio of 2.0 to 3.0), aspirin (325 mg daily), or both, at the
6 discretion of the principal investigator at each site (further details not provided). In
7 RESPECT five medical therapies were initially allowed (after randomization aspirin
8 alone was used in 223 patients (46.5%), warfarin alone in 121 (46.5%), clopidogrel
9 alone in 67 patients (14%), aspirin with dipyridamole in 39 patients (8.1%), and
10 aspirin with clopidogrel in 30 (6.2%). In the PC Trial antithrombotic treatment was
11 also left to the discretion of the treating physician and could have included
12 antiplatelet therapy or oral anticoagulation (after randomization, 120 (57.1%) of
13 subjects were using aspirin, 35 (16.7%) thienopyridines, 64 (30.5%) oral
14 anticoagulation, and 5 (2.4%) were not using antithrombotic prophylaxis.
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35 Adherence with medical therapy/changes in medical therapy was not clearly
36 documented in 2 of the 3 studies. In the PC trial, the percentage of patients using no
37 antithrombotic prophylaxis increased from 2.4% following randomization to 7.7%
38 at 2 years, 11.3% at 3 years, 11.1% at 4 years, and 12.8% at 5 years. The
39 distribution of other therapies changed little over 5 years.
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A total of 311 (13.5%) subjects were lost to follow-up or withdrew consent (range
within studies 12% to 18%). Loss to follow-up/withdrawal of consent was higher in
the medical therapy arm (n = 204, 18%) than in the PFO closure arm (n = 107, 9%).
In addition, 14 patients (CLOSURE I = 12, PC Trial = 1, RESPECT = 1) were

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3 demonstrated to have no PFO after randomization and 11 patients were determined
4 to have no prior history of stroke or TIA (CLOSURE I). Therefore 336 subjects were
5 excluded from our complete case analyses.
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11
12 The three studies enrolled similar patients (e.g. age range from 44.5 to 46 years)
13 with some differences in medical history (Table 2). In two of the studies
14 approximately 70-80% of patients were enrolled with an index diagnosis of
15 cryptogenic stroke with most of the rest having an index diagnosis of TIA. In one
16 study (RESPECT), all patients enrolled had a diagnosis characterized as stroke but
17 patients with less than 24 hours of symptoms and radiologic evidence for infarct
18 were included in this category.
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30 31 32 Assessment of Risk of Bias

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34 Overall risk of bias was deemed high for all 3 studies due to missing data (see Figure
35 1) – as noted 13.5% of subjects were lost to follow-up with twice as many lost to
36 follow-up in the medical arm compared to the PFO closure arm. There is also lack of
37 clear description regarding how compliance with medical therapy was assessed – in
38 only 1 study was medical therapy usage at different time points described.
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47 Participants and study personnel were not blinded in any of the three
48 studies, which likely contributed to differential rates of loss to follow-up. It is
49 unclear if this would have led to additional bias with respect to the observed
50 outcome rates as a clinical events committee adjudicated events in all three studies.
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Outcomes Assessment

Non-fatal ischemic Stroke

There were a total of 22 non-fatal ischemic strokes among 1026 patients randomized to PFO closure vs. 34 strokes among 941 patients randomized to medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: $p = 0.34$, $I^2 = 8\%$) (Figure 2). Using our best estimate of baseline from the available randomized trials of 52 non-fatal ischemic strokes over 5 years in 1000 patients treated medically, PFO closure may be associated with 20 fewer strokes per 1000 treated over a period of 5 years (confidence interval 34 fewer to 4 more strokes, low confidence in estimates because of risk of bias and imprecision) (Table 3).

In a sensitivity analysis including the 2 studies using the Amplatzer device, PFO closure was associated with a decreased risk of non-fatal ischemic stroke (RR 0.44, 95% 0.21, 0.93; Heterogeneity: $p = 0.42$, $I^2 = 0\%$). In the CLOSURE I Study (Starflex device), there was no difference between PFO closure and medical therapy with respect to non-fatal ischemic stroke (RR 0.87, 95% CI 0.40, 1.87). The test for interaction between these two subset analyses revealed differences consistent with chance ($\text{Chi}^2 = 1.52$, $p = 0.22$).

We conducted analyses imputing non-fatal strokes for patients excluded from the complete case analysis. In our worst-case analysis (all PFO intervention arm patients excluded from complete case analysis having non-fatal ischemic stroke, none of subjects excluded from the medical therapy arm having non-fatal ischemic

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3 stroke), RR = 4.22, 95% CI 2.93, 6.08 (Heterogeneity: $p = 0.39$, $I^2 = 0\%$). In our
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5 plausible worst case analysis in which excluded PFO closure patients had 5-fold
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7 increased rate of stroke (relative to included subjects) and excluded medical
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9 therapy patients had a 1/5 rate of stroke (relative to included subjects), PFO closure
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11 was associated with a RR = 0.96, 95% CI 0.56, 1.66 (Heterogeneity: $p = 0.28$, $I^2 =$
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13 21%). Although some might consider the 5 to 1 ratio we have tested beyond the
14
15 range of plausibility, there is empirical support for this choice¹⁶, and our results
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17 support rating down confidence in estimates for risk of bias related to missing data.
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25 In the 2 studies providing per-protocol event rates for non-fatal ischemic stroke
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27 there were 18 vs. 27 non-fatal ischemic strokes yielding a RR of 0.66, 95% CI 0.32,
28
29 1.38 (Heterogeneity: $p = 0.23$, $I^2 = 32\%$)
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35 As previous observational studies suggest that patients with cryptogenic stroke and
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37 PFO may be at higher risk for recurrent stroke if they have a concomitant atrial
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39 septal aneurysm, we also examined pooled rates of the primary composite endpoint
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41 of the studies in this subset. There were 13 events among 378 patients with atrial
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43 septal aneurysm undergoing closure compared to 20 events among 380 patients
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45 undergoing medical therapy (RR 0.71, 95% CI 0.22, 2.27; Heterogeneity: $p = 0.11$, I^2
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47 = 55%).
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54 TIAs
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3 Pooling complete case data from the 3 studies, there were 23 vs. 28 TIAs in the PFO
4 closure and medical treatment groups respectively (RR 0.76, 95% CI 0.44, 1.32;
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6 Heterogeneity: $p = 0.64$, $I^2 = 0\%$). PFO closure may be associated with 6 fewer TIAs
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8 over a period of 5 years (confidence interval 15 fewer to 9 more) (moderate
9
10 confidence because of risk of bias (Figure 3, Table 3).
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15 16 17 18 Total mortality

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20 There were 7 deaths in the PFO closure arm vs. 10 deaths in the medical treatment
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22 arm of the 3 studies (RD -0.00, 95% CI -0.01, 0.01; Heterogeneity: $p = 0.23$, $I^2 =$
23
24 31%). None of the deaths were deemed secondary to treatment (PFO closure or
25
26 antithrombotic therapy) or stroke. PFO closure may have no effect on mortality
27
28 over a period of 5 years (confidence interval 10 fewer to 10 more) (low confidence
29
30 because of risk of bias and imprecision) (Table 3).
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35 36 37 Adverse events

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39 Pooling data from all 3 studies, bleeding occurred in 13 vs. 7 patients in the PFO
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41 closure vs. medical treatment arms (all were major bleeds except 2 bleeds from
42
43 RESPECT study not classified) (RD 0.00, 95% CI -0.01, 0.02; Heterogeneity $p = 0.12$,
44
45 $I^2 = 53\%$) (see Figure 4). PFO closure may have no effect on major bleeding over a
46
47 period of 5 years (CI 10 fewer to 20 more) (moderate confidence because of risk of
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49 bias) (Table 3).
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3 Atrial fibrillation occurred in 32 patients undergoing PFO closure vs. 8 patients
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5 treated with medical therapy (RD 0.02, 95% -0.02, 0.06; Heterogeneity: $p < 0.00001$,
6
7 $I^2 = 93\%$). PFO closure may be associated with 20 more cases of atrial fibrillation
8
9 per 1000 treated compared to medical therapy over a period of 5 years (CI 20 fewer
10
11 to 60 more) (very low confidence because of risk of bias, inconsistency, and
12
13 imprecision) (Table 3). Of 23 cases of atrial fibrillation reported after PFO closure in
14
15 the CLOSURE I study 6 were deemed “sustained” – atrial fibrillation in the medical
16
17 group was not characterized. Of 8 cases of atrial fibrillation in the PC Trial occurring
18
19 after PFO closure 2 were transient (in PFO closure arm) and 6 required
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21 cardioversion or were sustained. Atrial fibrillation was not characterized as
22
23 transient or sustained in the RESPECT study.
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32 We were unable to pool data regarding procedural or device related complications
33
34 given differences between studies in reporting styles. Serious procedural or device
35
36 related adverse events (in addition to bleeding, ischemic stroke, atrial fibrillation
37
38 which have already been captured in previous analyses) were reported in 15
39
40 patients in the RESPECT trial (3%). This included 8 procedural related events.
41
42 Major vascular events related to the procedure occurred in 13 of the 402 patients
43
44 (3.2%) in whom PFO closure was attempted in CLOSURE I – these included 6 major
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46 bleeding episodes already captured above. The total number of serious procedural
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48 related adverse events was not specifically reported in the PC Trial although it was
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50 noted that no device related thrombi occurred.
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Discussion

A decade ago a meta-analysis of observational studies suggested transcatheter closure of PFO in patients with cryptogenic stroke may prevent more strokes than medical therapy.³ The authors noted important limitations in available data and highlighted the need for RCTs to resolve the issue. Since that time, thousands of patients have undergone this procedure in a non-RCT setting.

We now have data from 3 RCTs comparing transcatheter PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFOs. Our analysis suggests a possible benefit of closure on the major outcome of stroke (RR 0.61, 95% CI 0.34, 1.07). Confidence in the estimate of 20 fewer strokes per 1,000 is, however, low, both because of problems with risk of bias and imprecision (confidence intervals include an increase in stroke of 4 per 1,000). Analyses for ischemic stroke restricted to “per-protocol” patients or patients with concomitant atrial septal aneurysm did not substantially change the observed risk ratios.

We conducted subgroup analyses evaluating the impact of PFO closure on non-fatal stroke separately in the 2 studies using the Amplatzer closure device vs. the one study using the STARFlex device. Pooled data from the Amplatzer studies suggests PFO closure may be associated a decrease in non-fatal ischemic stroke (RR 0.44, 95% CI 0.21, 0.93) whereas no benefit was observed in the study using the STARFlex device. Although the subgroup hypothesis was made a priori and differences are in the anticipated direction, the analysis is based on between group differences, has not been replicated, and differences between results with the two

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3 devices is easily explained by chance ($p = 0.22$). Thus the subgroup hypothesis has
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5 low credibility.¹⁷
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9 There have been 3 other meta-analyses. They are limited, however, by
10 failure to fully consider risk of bias issues, failure to use the GRADE approach to
11 determine overall confidence in estimates of intervention effect, and failure to
12 consider the limitations of composite endpoints.¹⁸⁻²⁰ In the most recent of these
13 analyses, PFO closure was associated with an effect-estimate hazard ratio of 0.67
14 (95% confidence interval [CI]: 0.44 to 1.00) for the prevention of “neurologic
15 events”. However it appears that this composite endpoint included the softer
16 endpoint of TIA in addition to stroke and mortality.
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28 It is possible that a larger sample size and more rigorously done studies
29 would definitively identify an important benefit in the total patient population, or in
30 a subgroup. Our review demonstrates, however, that such additional studies may
31 also fail to demonstrate benefit or, in comparison to effective antithrombotic
32 prophylaxis, an increase in strokes.
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40 Although some concern arises from possible lack of concealment of
41 randomization in one study and the apparent failure to blind outcome adjudication
42 in another study, the major problem in terms of risk of bias is the high loss to follow-
43 up in these studies and the two fold greater loss to follow-up in patients in the
44 medical therapy arms than the PFO closure arms (overall 9% in PFO and 18% in the
45 medical therapy arms).
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54 Our primary analysis was restricted to patients with available data (complete
55 case analysis). If event rates differed in those with missing data in intervention and
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3 control groups - of particular concern would be higher rates of events in those lost
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5 to follow-up in the PFO closure arm that the medical therapy arm - the complete
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7 case results may be misleading. In an additional analysis in which patients lost to
8
9 follow-up in the PFO arm were assumed to have 5 fold increased risk of stroke and
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11 those lost to follow-up in the medical therapy arm had a 5-fold decreased risk of
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13 stroke, there was no longer a trend favoring PFO closure (RR 0.96). This finding
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15 supports our rating down confidence in estimates of effect for risk of bias.
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21 Another issue is the rigor with which control arm clinicians encouraged
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23 compliance with antithrombotic prophylaxis in medical patients. In two of the
24
25 studies dose and type of antithrombotic therapy in the medical therapy arm were
26
27 left to the treating physician's discretion. Only one of the studies reported
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29 adherence and/or changes over time in medical therapy in both arms. Leaving
30
31 therapy in the medical arm to the physician's discretion could be considered to
32
33 represent "usual care" for those randomized to medical therapy. Usual care may,
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35 however, change over time, and differ in the jurisdictions in which the trial is
36
37 conducted in comparison to other jurisdictions. Patients and clinicians may,
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39 therefore, be more interested in the effect of PFO closure versus a particular
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41 antithrombotic regimen with a high level of adherence. Unfortunately there have
42
43 been no RCTs adequately comparing specific antiplatelet or antithrombotic
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45 therapies for this indication.
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52 Stroke occurring due to paradoxical emboli through a PFO results from
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54 thrombi originating in the venous circulation or perhaps from the associated atrial
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56 septal aneurysm itself.^{21,22} Warfarin has been shown to be more effective than
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3 antiplatelet therapy for the treatment and secondary prevention of venous
4 thromboembolic events. Observational studies suggest oral anticoagulation is
5 superior to aspirin for the prevention of stroke in patients with PFO albeit with
6 increased bleeding.^{23,24} In the Patent Foramen Ovale in Cryptogenic Stroke study
7 (substudy of the randomized Warfarin-Aspirin Recurrent Stroke study) there were
8 98 patients with cryptogenic stroke and PFO - 42 were randomized to warfarin and
9 56 received aspirin.²⁵ Two-year rates of recurrent stroke were lower in patients
10 receiving warfarin (9.5% vs. 17.9%,) but chance easily explains this (p = 0.28).
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23 Given the uncertainty of the optimal antithrombotic regimen, subsequent
24 trials must give this issue careful thought. One option for the medical arm would be
25 careful exploration of individual patient values and preferences. Patients highly
26 averse to bleeding risk and the burdens of anticoagulant therapy could receive only
27 an antiplatelet agent, while those less bleeding and burden averse could receive an
28 anticoagulant. Use of an oral anticoagulant rather than warfarin in those choosing
29 anticoagulation would be a possibility. Such an approach might represent optimal
30 medical care, perhaps the appropriate comparator to PFO closure. Another option
31 would be three-arm study with both antiplatelet and anticoagulant arms
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44 We conclude that the available data warrants only low confidence in the
45 impact of PFO versus medical therapy. Thus, additional RCTs are still required –
46 two such studies are listed as actively recruiting on the NIH website
47 ClinicalTrials.gov. Ideally, when pooled across studies, sample sizes will be large
48 enough to definitively establish the impact of PFO closure versus medical therapy on
49 the most important outcome, ischemic stroke. As important, results will be more
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3 compelling if the ongoing studies have implemented successful strategies to ensure
4 complete or near-complete follow-up and have paid careful attention to decisions
5 regarding medical prophylaxis and optimizing adherence in both arms of the study.
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8 In the interval, patients should be made aware of the management options and the
9 uncertainty underlying their effectiveness.
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10
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12

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15 and gave final approval of the version to be published. He agrees to be accountable
16 for all aspects of the work in ensuring that questions related to the accuracy or
17 integrity of any part of the work are appropriately investigated and resolved.
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Figure legends:

Figure 1 Risk of bias in individual studies

Figure 2 Pooled risk of non-fatal ischemic stroke with PFO closure versus medical therapy

Figure 3 Pooled risk of transient ischemic attack with PFO closure versus medical therapy

Figure 4 Pooled risk of major bleeding with PFO closure versus medical therapy

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3 **Transparency statement:** Dr. Spencer affirms that the manuscript is an honest, accurate, and transparent account of
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For peer review only

Table 1

Trial (patients)	Trial Type	Intervention	Medical therapy	Withdrew or Loss to Followup PFO closure (%)	Withdrew/Loss to Followup Medical Therapy (%)	Crossover from Medical Therapy to PFO Closure (%)	% PFO closure attempts/patients enrolled in PFO cohort (%)	% technical success /PFO closure attempts (%)
CLOSURE I (909)	Multicentre Randomized Open label	STARFLEX Device Clopidogrel x 6 mo ASA x 2 years	Warfarin (INR 2-3), ASA 325 per day, or both (clinician's discretion)	1.8	0.7	0	90.6	89.4
PC Trial (414)	Multicentre Randomized Open Label	Amplatzer Occluder ASA 5-6 mo. Clopidogrel or ticlopidine 1-6 mo.	Antiplatelet or anticoagulation (clinician's discretion)	15.2	20	13.3	96.1	97.4
RESPECT (980)	Multicentre Randomized Open Label	Amplatzer Occluder ASA 6 mo Clopidogrel 1 mo.	Antiplatelet or anticoagulation (clinician's discretion)	9.2	17.2	0	93	99.1

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Table 2 Characteristics of Patients in Eligible Studies

	CLOSURE 1	RESPECT	PC Trial
N	909	980	414
Mean Age +/- SD	46.0	45.9	44.5
Male (%)	51.8	54.7	49.8
Smoker (%)	22.1	13.3	23.9
Medical History (%)			
Diabetes	NR	7.4	2.7
Hypertension	31.0	31.4	25.8
Hyperlipidemia	44.1	39.5	27.1
Ischemic heart disease	1.1	2.9	1.9
Myocardial infarction	1.3	0.7	1
Valvular dysfunction	10.3	NR	3.1
Peripheral vascular disease	1.3	0.6	1.2
Index event (%)			
Stroke	72	100*	79.2
TIA	28	0	18.1
Peripheral arterial embolism	0	0	2.7
PFO characteristics (%)			
Moderate or higher shunt	52.9	75.2	65.6**
Atrial septal aneurysm >10 mm	37.8***	35.6	23.7

*Included patients with symptoms for less than 24 hours if new neuroradiologically relevant cerebral infarct on imaging

** 369 of 414 patients with TEE

***151/400 patients with TEE

Table 3 – GRADE assessment of quality of evidence

Bibliography:									
Quality assessment						Summary of findings			
No of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Relative effect or risk difference (95% CI)	Anticipated absolute effects Time frame: 5 years		Quality of evidence
							Risk with medical therapy	Risk difference with PFO closure (95% CI)	
Non-fatal ischemic stroke (critical outcome)									
1968 (3 RCTs)	Serious limitations¹	No serious limitations	No serious limitations	Imprecise CI includes benefit and no effect	Undetected	RR 0.61 (0.34 to 1.07)	52 per 1000²	20 fewer per 1000 (from 34 fewer to 4 more)	⊕⊕⊕⊕ LOW due to risk of bias and imprecision
TIA (important outcome)									
1968 (3 RCTs)	Serious limitations¹	No serious limitations	No serious limitations	No serious limitations ³	Undetected	RR 0.76 (0.44 to 1.32)	27 per 1000⁴	6 fewer per 1000 (from 15 fewer to 9 more)	⊕⊕⊕⊕ MODERATE due to risk of bias
Total mortality (critical outcome)⁵									
1968 (3 RCTs)	Serious limitations¹	No serious limitations	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RD 0.00 (-0.01, 0.01)	15 per 1000⁶	0 fewer per 1000 (from 10 fewer to 10 more)	⊕⊕⊕⊕ LOW due to risk of bias and imprecision
Major bleeding (important outcome)									
2254 (3 RCTs)	Serious limitations¹	No serious inconsistency	No serious limitations ³	No serious limitations	Undetected	RD 0.00 (-0.01, 0.02)	7 per 1000⁷	0 more per 1000 (10 fewer to 20 more)	⊕⊕⊕⊕ MODERATE due to risk of bias
Atrial fibrillation (important outcome)⁸									
2254 (3 RCTs)	Serious limitations¹	Serious inconsistency⁹	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RD 0.02 (-0.02, 0.06)	12 per 1000¹⁰	20 more per 1000 (20 fewer to 60 more)	⊕⊕⊕⊕ VERY LOW due to risk of bias and imprecision

¹Serious risk of bias due to substantial loss to followup in each of 3 studies; loss to followup greater in medical therapy arms. See text for other potential sources of bias in individual studies.

²Baseline rate derived from pooled Respect and PC trial data - 21 non-fatal ischemic strokes detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

³Although CI includes benefit and harm, but magnitude of extremes for this type of outcome deemed too low to appreciably impact patient decision making.

⁴Baseline rate derived from pooled Respect and PC trial data - 11 TIAs detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

⁵None of deaths due to stroke, treatment related bleeding, or device implantation

⁶Baseline rate derived from pooled Respect and PC trial data - 6 cases of total mortality detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

⁷Baseline rate derived from pooled Respect and PC trial data - 3 cases of major bleeding detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

⁸Type of atrial fibrillation (transient vs. sustained) not reported in medical therapy arms or in PFO closure arm of RESPECT study. Of 31 cases of atrial fibrillation in the remaining 2 studies 19 were characterized as transient.

⁹I² = 93%, p = <0.00001

¹⁰Baseline rate derived from pooled Respect and PC Trial data - 5 cases of atrial fibrillation detected in the medical therapy arm over a total of 2019 pt-yrs x 1000 x 5 years.

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For peer review only

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8 Systematic Review of Percutaneous Closure versus Medical Therapy in Patients with
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10 Cryptogenic Stroke and Patent Foramen Ovale
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Abstract

~~Background: Three randomized control trials (RCTs) comparing patient foramen ovale (PFO) closure to medical therapy have been published—none showed PFO closure to be statistically superior to medical therapy but each reported trends favoring PFO closure.~~

Objectives: To provide a comprehensive comparison of PFO closure versus medical therapy in patients with cryptogenic stroke or transient ischemic attack (TIA) and demonstrated PFO.

Design: Systematic review with complete case meta-analysis and sensitivity analyses. Data sources included

~~Data sources:—~~Medline and, Embase from 1980 up to May 2013.

~~Eligibility criteria:—~~All randomized controlled trials (RCTs) comparing treatment with percutaneous catheter-based closure of PFO to ~~medical therapy~~ (anticoagulant or antiplatelet therapy) in patients with cryptogenic stroke or TIA and echocardiographically confirmed PFO or atrial septal defect (ASD) were eligible.

Participants: 1967 subjects with prior stroke or TIA and echocardiographically confirmed PFO or ASD.

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Methods Primary outcome measures: The primary outcome of interest was recurrence of ischemic stroke. We utilized data from complete cases only for the primary endpoint and combined data from trials to estimate the pooled risk ratio (RR) and associated 95% confidence intervals (CI) calculated using random effects models.

Results: We identified 284 potentially eligible articles of which 3 RCTs including 2303 patients proved eligible and 1967 patients had complete data. Of the 1026 patients randomized to PFO closure and followed to study conclusion 22 experienced non-fatal ischemic strokes, as did 34 of 941 patients randomized to medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: $p = 0.34$, $I^2 = 8\%$, confidence in estimates low due to risk of bias and imprecision). Analyses for ischemic stroke restricted to “per-protocol” patients or patients with concomitant atrial septal aneurysm did not substantially change the observed risk ratios. Complication rates associated with either PFO closure or medical therapy were low.

Conclusions: Pooled data from 3 RCTs provides ~~insufficient~~ little support ~~for that~~ PFO closure ~~is preferable to~~ ~~over~~ medical therapy for secondary prevention of cryptogenic stroke in patients with PFO.

Abstract word count: ~~299~~279

Data sharing: No additional data are available.

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26 Study strengths

- 27 • Estimation of absolute benefits and risks of treatment strategies
- 28 • Careful assessment of risk of bias of individual studies using Cochrane
- 29 criteria
- 30 • Evaluation of overall confidence in pooled outcome(s) estimates using
- 31 GRADE
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40 Limitations

- 41 • Primary analysis was restricted to patients with available data (complete
- 42 case analysis). If event rates differed in those with missing data in
- 43 intervention and control groups - of particular concern would be higher
- 44 rates of events in those lost to follow-up in the PFO closure arm that the
- 45 medical therapy arm - the complete case results may be misleading
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- 51 • Individual patient-level data not available
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Introduction

Observational studies suggest that younger patients with cryptogenic stroke are more likely to have a patent foramen ovale (PFO) than the general population.^{1,2} A proposed mechanism for stroke in these patients is passage of thrombi from the venous circulation to the arterial circulation through the PFO. Although what proportion of cryptogenic strokes are due to paradoxical embolism remains unknown, percutaneous closure of PFO using devices approved for hemodynamically significant secundum atrial septal defect (ASD) has increased greatly in the last 2 decades. A systematic review of observational studies suggests PFO closure may be superior to medical therapy (antiplatelet or anticoagulant agents) for secondary prevention of stroke in patients with patent foramen ovale and cryptogenic stroke.³

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In the last two years 3 three randomized control trials (RCTs) comparing PFO closure to medical therapy have been published – none showed PFO closure to be statistically superior to medical therapy for the primary composite outcome but each reported trends favoring PFO closure.⁴⁻⁶ In one study, PFO closure was superior to medical therapy for the prevention of recurrent neurologic events in prespecified per-protocol and as-treated analyses.⁵

One systematic review and meta-analysis that included the 3 RCTs, and a second meta-analysis, have addressed this issue. Both were limited, however, by failure to fully consider risk of bias issues, failure to use the GRADE approach to determine overall confidence in estimates of intervention effect, and failure to consider the limitations of composite endpoints.

We therefore undertook a systematic review of all RCTs comparing percutaneous PFO closure to medical therapy in patients with cryptogenic stroke or TIA and PFO or ASD. As composite endpoints varied between trials, we focused on individual endpoints of recurrent non-fatal stroke, recurrent TIA, death, major bleeding, and atrial fibrillation. We also examined per protocol rates of recurrent stroke in patients undergoing PFO closure compared to the medical therapy arm. Outcomes were defined as in each study.

Methods

Eligibility criteria

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8 We included all RCTs comparing treatment with percutaneous catheter-based
9 closure of PFO to medical therapy (anticoagulant or antiplatelet therapy) in patients
10 with cryptogenic stroke or TIA and echocardiographically confirmed PFO or ASD.
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13 We excluded trials including participants with other indications for PFO/ASD
14 closure (e.g. hemodynamic significance) or other indications for anticoagulant
15 therapy (e.g. atrial fibrillation).
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22 Included articles met two prespecified criteria: 1) RCTs that compared PFO closure
23 to medical therapy (antiplatelet or anticoagulant agents); 2) Greater than 90% of
24 patients had prior unexplained stroke, TIA, or other arterial embolism, or this
25 subset was reported separately. When more than one study reported data from a
26 population, we used the most complete and updated results.
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31 32 33 34 Data sources and search strategy

35 We searched Medline and Embase from 1980 to May 2013. We restricted the search
36 to human subjects. Keywords included patent foramen ovale *or* atrial septal defect.
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38 Results were then limited to randomize controlled trial *or* controlled clinical trial *or*
39 phase 3 clinical trial *or* phase 4 clinical trial. For every eligible study we identified,
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41 and for studies such as review articles that included citations to potentially eligible
42 studies, one reviewer examined the reference list.
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49 50 Study selection

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Teams of two investigators independently screened each title and abstract from this search. If either of the two screeners identified a citation as potentially relevant, we obtained the full text article for detailed review. Teams of two reviewers independently determined the eligibility of all studies that underwent full text evaluation. Disagreements were resolved through discussion between the two reviewers.

Data abstraction

Using a custom made data collection form two of three reviewers (FAS, LCL, SAK) abstracted the following information from each identified study: mean follow-up time, total patient years follow-up (overall and per cohort), number of patients withdrawn or lost to follow-up, number of patients crossing over from medical therapy to PFO closure, number of patients undergoing PFO closure attempt, number of patients in whom PFO closure was technically successful, procedural complications (other than major bleeding) from PFO closure, and outcome event rates.

Disagreements regarding data abstraction results were resolved through discussion between the two reviewers. The primary author abstracted additional information on study funding, eligibility criteria, patient demographics, and treatment characteristics.

Risk of Bias and Confidence in Effect Assessment

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Two reviewers (FAS, LL) independently assessed, using the Cochrane risk for bias tool, seven domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the other 6 domains.⁷

We used GRADE methodology to rate confidence in estimates of effect for each outcome as high, moderate, low or very low.⁸ We used detailed GRADE guidance to assess overall risk of bias⁹, imprecision¹⁰, inconsistency¹¹, indirectness¹² and publication bias¹³, and summarized results in an evidence profile.

For decisions regarding eligibility, risk of bias assessment, and data abstraction, reviewers resolved disagreement through discussion.

Data Synthesis and Statistical Analysis

We report descriptive statistics as proportions for categorical variables, and mean/median for continuous variables. Our primary analyses for non-fatal ischemic stroke, TIAs, and mortality included only patients with complete follow-up. We excluded patients for whom complete data was unavailable: those lost to follow-up, those who withdrew consent, or those who were found to not have PFO/ASD or history of TIA/stroke after randomization. For outcomes of bleeding and atrial

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8 fibrillation we used data as reported by the investigators from the intention to treat
9 analyses.
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13 Rates of non-fatal ischemic stroke in patients treated as “per-protocol” from two of
14 the three studies were also abstracted and pooled. The definition of per-protocol
15 varied from study to study (CLOSURE 1: all randomized patients who received the
16 treatment to which they were randomized, who had no major inclusion/exclusion
17 criteria violations, and who had a follow-up of at least 22 months; RESPECT:
18 patients who received the randomly assigned treatment, adhered to the protocol-
19 mandated medical treatment, and did not have a major inclusion or exclusion
20 violation). Event rates for non-fatal ischemic stroke in the “per protocol” subset
21 were not reported in PC Trial manuscript. The primary author of the manuscript
22 did not respond to email requests for further information.
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36 As previous observational studies suggest that patients with cryptogenic stroke and
37 PFO may be at higher risk for recurrent stroke if they have a concomitant atrial
38 septal aneurysm, we performed an additional complete case analysis for a primary
39 composite outcome in the subset of patients with atrial septal aneurysm (data on
40 non-fatal ischemic stroke alone not reported in any of the studies for this subset).
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46 Composite outcomes in the 3 studies included some combination of non-fatal
47 ischemic stroke, TIA, peripheral embolism, and death.
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As two of the three studies used the ~~Amplatz~~Amplatz device and one used the STARFlex device (CLOSURE 1) we conducted a sensitivity analysis for non-fatal ischemic stroke excluding the CLOSURE study. We evaluated for subgroup difference (2 ~~Amplatz~~Amplatz studies vs. STARFlex study) using a chi-square test.

Given high rate of patients excluded from complete case analyses (most due to loss to follow-up) we also conducted 2 additional analyses: 1) Worst case scenario in which we assumed that all patients with missing data in the PFO closure arms suffered non-fatal ischemic strokes and all patients lost to follow-up in the medical arms did not; 2) Plausible worst case scenario in which all patients with missing data from the PFO closure arm were assumed to have 5 times the rate of stroke as the complete cases and b) those excluded from the medical therapy arm were assumed to have 1/5 times the rate of stroke as the complete cases.¹⁴

We calculated pooled risk ratios (RR) and associated 95% confidence intervals (CI) for non-fatal ischemic stroke and TIAs using random effects models applying Mantel Haenszel method. Absolute effects (and 95% CI) were calculated by multiplying pooled RRs and 95% CI by pooled control rate of outcomes. As event rates were very low for death, atrial fibrillation, and major bleeding (leading to skewed 95% CI), pooled risk difference (RD) and 95% CI was used to calculate absolute effects for these outcomes.¹⁵ Statistical heterogeneity was assessed by the I^2 statistic. Analyses were performed using RevMan version 5.2 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration).

Results

Trial Identification

Our search yielded 284 abstracts - all were identified from the electronic database search- of which 47 were duplicates and excluded. We excluded an additional 229 articles based on a review of the title and abstract, leaving 8 articles for full review.

Of these studies, 5 were excluded – 2 were descriptions of methodology for subsequently reported RCTs, 1 was a comparison of different devices for closure but did not include a medical therapy arm, and 2 were prospective cohort studies of PFO closure. (See Appendix Figure) We included 3 randomized trials enrolling 2303 patients.⁴⁻⁷

Trial and Patient Characteristics

Table 1 presents the characteristics of the 3 eligible studies. Two of the three studies (RESPECT, PC Trial) used the ~~Amplatz~~Amplatzer occluder device whereas the other used the STARFlex device (CLOSURE I). Crossover from medical therapy to PFO closure occurred in only one study (13.3%) (PC Trial). The percentage of patients in the PFO closure arm undergoing a PFO closure attempt ranged from 90.6 to 96.1% with success rates ranging from 89.4% to 99.1%.

In the CLOSURE I study all patients undergoing PFO closure were assigned to clopidogrel 75 mg per day times 6 months and aspirin 81 or 325 mg per day for 2

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9 years. In the RESPECT study all patients undergoing closure received aspirin 81-
10 325 mg plus clopidogrel for one month followed by aspirin monotherapy for 5
11 months. Antiplatelet treatment thereafter was left to the discretion of the site
12 investigator. In the PC Trial, managing clinicians were counseled to recommend
13 aspirin 100 to 325 mg per day for 5 to 6 months and ticlopidine (250 to 500 mg per
14 day) or clopidogrel (75 mg to 150 mg per day) for 1 to 6 months. However at
15 discharge from PFO closure in the PC trial, 182 patients (89.2%) were using aspirin,
16 104 (51%) thienopyridines, 6 (2.9%) oral anticoagulation, and 8 (3.9%) were not
17 using antithrombotic prophylaxis.
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28 Treatment in the medical therapy arms also varied across studies. In Closure I,
29 patients assigned to medical therapy were treated with warfarin (with a target
30 international normalized ratio of 2.0 to 3.0), aspirin (325 mg daily), or both, at the
31 discretion of the principal investigator at each site (further details not provided). In
32 RESPECT five medical therapies were initially allowed (after randomization aspirin
33 alone was used in 223 patients (46.5%), warfarin alone in 121 (46.5%), clopidogrel
34 alone in 67 patients (14%), aspirin with dipyridamole in 39 patients (8.1%), and
35 aspirin with clopidogrel in 30 (6.2%). In the PC Trial antithrombotic treatment was
36 also left to the discretion of the treating physician and could have included
37 antiplatelet therapy or oral anticoagulation (after randomization, 120 (57.1%) of
38 subjects were using aspirin, 35 (16.7%) thienopyridines, 64 (30.5%) oral
39 anticoagulation, and 5 (2.4%) were not using antithrombotic prophylaxis.
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9 Adherence with medical therapy/changes in medical therapy was not clearly
10 documented in 2 of the 3 studies. In the PC trial, the percentage of patients using no
11 antithrombotic prophylaxis increased from 2.4% following randomization to 7.7%
12 at 2 years, 11.3% at 3 years, 11.1% at 4 years, and 12.8% at 5 years. The
13 distribution of other therapies changed little over 5 years.
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20 A total of 311 (13.5%) subjects were lost to follow-up or withdrew consent (range
21 within studies 12% to 18%). Loss to follow-up/withdrawal of consent was higher in
22 the medical therapy arm (n = 204, 18%) than in the PFO closure arm (n = 107, 9%).
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24 In addition, 14 patients (CLOSURE I = 12, PC Trial = 1, RESPECT = 1) were
25 demonstrated to have no PFO after randomization and 11 patients were determined
26 to have no prior history of stroke or TIA (CLOSURE I). Therefore 336 subjects were
27 excluded from our complete case analyses.
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36 The three studies enrolled similar patients (e.g. age range from 44.5 to 46 years)
37 with some differences in medical history (Table 2). In two of the studies
38 approximately 70-80% of patients were enrolled with an index diagnosis of
39 cryptogenic stroke with most of the rest having an index diagnosis of TIA. In one
40 study (RESPECT), all patients enrolled had a diagnosis characterized as stroke but
41 patients with less than 24 hours of symptoms and radiologic evidence for infarct
42 were included in this category.
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51 Assessment of Risk of Bias
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8 Overall risk of bias was deemed high for all 3 studies due to missing data (see Figure
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10 1) – as noted 13.5% of subjects were lost to follow-up with twice as many lost to
11 follow-up in the medical arm compared to the PFO closure arm. There is also lack of
12 clear description regarding how compliance with medical therapy was assessed – in
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14 only 1 study was medical therapy usage at different time points described.
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18 Participants and study personnel were not blinded in any of the three
19 studies, which likely contributed to differential rates of loss to follow-up. It is
20 unclear if this would have led to additional bias with respect to the observed
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22 outcome rates as a clinical events committee adjudicated events in all three studies.
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28 Outcomes Assessment

29 Non-fatal ischemic Stroke

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31 There were a total of 22 non-fatal ischemic strokes among 1026 patients
32 randomized to PFO closure vs. 34 strokes among 941 patients randomized to
33 medical therapy (Risk Ratio 0.61, 95% CI 0.34, 1.07; Heterogeneity: $p=0.34$, $I^2 =$
34 8%) (Figure 2). Using our best estimate of baseline from the available randomized
35 trials of 52 non-fatal ischemic strokes over 5 years in 1000 patients treated
36 medically, PFO closure may be associated with 20 fewer strokes per 1000 treated
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38 over a period of 5 years (confidence interval 34 fewer to 4 more strokes, low
39 confidence in estimates because of risk of bias and imprecision) (Table 3).
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49 In a sensitivity analysis including the 2 studies using the [AmplatzAmplatzer](#) device,
50 PFO closure was associated with a decreased risk of non-fatal ischemic stroke (RR
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8 0.44, 95% 0.21, 0.93; Heterogeneity: $p = 0.42$, $I^2 = 0\%$). In the CLOSURE I Study
9 (Starflex device), there was no difference between PFO closure and medical therapy
10 with respect to non-fatal ischemic stroke (RR 0.87, 95% CI 0.40, 1.87). The test for
11 interaction between these two subset analyses revealed differences consistent with
12 chance ($\text{Chi}^2 = 1.52$, $p = 0.22$).
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20 We conducted analyses imputing non-fatal strokes for patients excluded from the
21 complete case analysis. In our worst-case analysis (all PFO intervention arm
22 patients excluded from complete case analysis having non-fatal ischemic stroke,
23 none of subjects excluded from the medical therapy arm having non-fatal ischemic
24 stroke), RR = 4.22, 95% CI 2.93, 6.08 (Heterogeneity: $p = 0.39$, $I^2 = 0\%$). In our
25 plausible worst case analysis in which excluded PFO closure patients had 5-fold
26 increased rate of stroke (relative to included subjects) and excluded medical
27 therapy patients had a 1/5 rate of stroke (relative to included subjects), PFO closure
28 was associated with a RR = 0.96, 95% CI 0.56, 1.66 (Heterogeneity: $p = 0.28$, $I^2 =$
29 21%). [Although some might consider the 5 to 1 ratio we have tested beyond the
30 range of plausibility, there is empirical support for this choice¹⁶, and our](#) These
31 results support rating down confidence in estimates for risk of bias related to
32 missing data.
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48 In the 2 studies providing per-protocol event rates for non-fatal ischemic stroke
49 there were 18 vs. 27 non-fatal ischemic strokes yielding a RR of 0.66, 95% CI 0.32,
50 1.38 (Heterogeneity: $p = 0.23$, $I^2 = 32\%$)
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As previous observational studies suggest that patients with cryptogenic stroke and PFO may be at higher risk for recurrent stroke if they have a concomitant atrial septal aneurysm, we also examined pooled rates of the primary composite endpoint of the studies in this subset. There were 13 events among 378 patients with atrial septal aneurysm undergoing closure compared to 20 events among 380 patients undergoing medical therapy (RR 0.71, 95% CI 0.22, 2.27; Heterogeneity: $p = 0.11$, $I^2 = 55\%$).

TIAs

Pooling complete case data from the 3 studies, there were 23 vs. 28 TIAs in the PFO closure and medical treatment groups respectively (RR 0.76, 95% CI 0.44, 1.32; Heterogeneity: $p = 0.64$, $I^2 = 0\%$). PFO closure may be associated with 6 fewer TIAs over a period of 5 years (confidence interval 15 fewer to 9 more) (moderate confidence because of risk of bias (Figure 3, Table 3)).

Total mortality

There were 7 deaths ~~per~~ in the PFO closure arm vs. 10 deaths in the medical treatment arm of the 3 studies (RD -0.00, 95% CI -0.01, 0.01; Heterogeneity: $p = 0.23$, $I^2 = 31\%$). None of the deaths were deemed secondary to treatment (PFO closure or antithrombotic therapy) or stroke. PFO closure may have no effect on mortality over a period of 5 years (confidence interval 10 fewer to 10 more) (low confidence because of risk of bias and imprecision) (Table 3).

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10 Adverse events

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12 Pooling data from all 3 studies, bleeding occurred in 13 vs. 7 patients in the PFO
13 closure vs. medical treatment arms (all were major bleeds except 2 bleeds from
14 RESPECT study not classified) (RD 0.00, 95% CI -0.01, 0.02; Heterogeneity $p = 0.12$,
15 $I^2 = 53\%$) (see Figure 4). PFO closure may have no effect on major bleeding over a
16 period of 5 years (CI 10 fewer to 20 more) (moderate confidence because of risk of
17 bias) (Table 3).
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26 Atrial fibrillation occurred in 32 patients undergoing PFO closure vs. 8 patients
27 treated with medical therapy (RD 0.02, 95% -0.02, 0.06; Heterogeneity: $p < 0.00001$,
28 $I^2 = 93\%$). PFO closure may be associated with 20 more cases of atrial fibrillation
29 per 1000 treated compared to medical therapy over a period of 5 years (CI 20 fewer
30 to 60 more) (very low confidence because of risk of bias, inconsistency, and
31 imprecision) (Table 3). Of 23 cases of atrial fibrillation reported after PFO closure in
32 the CLOSURE I study 6 were deemed “sustained” – atrial fibrillation in the medical
33 group was not characterized. Of 8 cases of atrial fibrillation in the PC Trial occurring
34 after PFO closure 2 were transient (in PFO closure arm) and 6 required
35 cardioversion or were sustained. Atrial fibrillation was not characterized as
36 transient or sustained in the RESPECT study.
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49 We were unable to pool data regarding procedural or device related complications
50 given differences between studies in reporting styles. Serious procedural or device
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8 related adverse events (in addition to bleeding, ischemic stroke, atrial fibrillation
9 which have already been captured in previous analyses) were reported in 15
10 patients in the RESPECT trial (3%). This included 8 procedural related events.
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12 Major vascular events related to the procedure occurred in 13 of the 402 patients
13 (3.2%) in whom PFO closure was attempted in CLOSURE I – these included 6 major
14 bleeding episodes already captured above. The total number of serious procedural
15 related adverse events was not specifically reported in the PC Trial although it was
16 noted that no device related thrombi occurred.
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28 Discussion

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30 A decade ago a meta-analysis of observational studies suggested
31 transcatheter closure of PFO in patients with cryptogenic stroke may prevent more
32 strokes than medical therapy.³ The authors noted important limitations in
33 available data and highlighted the need for RCTs to resolve the issue. Since that
34 time, thousands of patients have undergone this procedure in a non-RCT setting.
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39 We now have data from 3 RCTs comparing transcatheter PFO closure to
40 medical therapy in patients with cryptogenic stroke or TIA and PFOs. Our analysis
41 suggests a possible benefit of closure on the major outcome of stroke (RR 0.61, 95%
42 CI 0.34, 1.07). Confidence in the estimate of 20 fewer strokes per 1,000 is, however,
43 low, both because of problems with risk of bias and imprecision (confidence
44 intervals include an increase in stroke of 4 per 1,000). Analyses for ischemic stroke
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8 restricted to “per-protocol” patients or patients with concomitant atrial septal
9 aneurysm did not substantially change the observed risk ratios.

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12 We conducted subgroup analyses evaluating the impact of PFO closure on
13 non-fatal stroke separately in the 2 studies using the ~~Amplatz~~Amplatzer closure
14 device vs. the one study using the STARFlex device. Pooled data from the
15 ~~Amplatz~~Amplatzer studies suggests PFO closure may be associated a decrease in
16 non-fatal ischemic stroke (RR 0.44, 95% CI 0.21, 0.93) whereas no benefit was
17 observed in the study using the STARFlex device. Although the subgroup hypothesis
18 was made a priori and differences are in the anticipated direction, the analysis is
19 based on between group differences, has not been replicated, and differences
20 between results with the two devices is easily explained by chance ($p = 0.22$). Thus
21 the subgroup hypothesis has low credibility.¹⁷

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24 ~~As suggested in-~~There have been 3 other meta-analyses. They are limited,
25 however, by failure to fully consider risk of bias issues, failure to use the GRADE
26 approach to determine overall confidence in estimates of intervention effect, and
27 failure to consider the limitations of composite endpoints. ~~two other recently~~
28 published analyses, our data could be interpreted to suggest a potential substantial
29 benefit may exist for PFO closure.¹⁸⁻²⁰ In the most recent of these analyses, PFO
30 closure was associated with an effect-estimate hazard ratio of 0.67 (95% confidence
31 interval [CI]: 0.44 to 1.00) for the prevention of “neurologic events”. However it
32 appears that this composite endpoint included the softer endpoint of TIA in addition
33 to stroke and mortality.

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36 It is possible that a larger sample size and more rigorously done studies

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8 would definitively identify an important benefit in the total patient population, or in
9 a subgroup. Our review demonstrates, however, that such additional studies may
10 also fail to demonstrate benefit or, in comparison to effective antithrombotic
11 prophylaxis, an increase in strokes.
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16 Although some concern arises from possible lack of concealment of
17 randomization in one study and the apparent failure to blind outcome adjudication
18 in another study, the major problem in terms of risk of bias is the high loss to follow-
19 up in these studies and the two fold greater loss to follow-up in patients in the
20 medical therapy arms than the PFO closure arms (overall 9% in PFO and 18% in the
21 medical therapy arms).
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28 Our primary analysis was restricted to patients with available data (complete
29 case analysis). If event rates differed in those with missing data in intervention and
30 control groups - of particular concern would be higher rates of events in those lost
31 to follow-up in the PFO closure arm than the medical therapy arm - the complete
32 case results may be misleading. In an additional analysis in which patients lost to
33 follow-up in the PFO arm were assumed to have 5 fold increased risk of stroke and
34 those lost to follow-up in the medical therapy arm had a 5-fold decreased risk of
35 stroke, there was no longer a trend favoring PFO closure (RR 0.96). This finding
36 supports our rating down confidence in estimates of effect for risk of bias.
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45 Another issue is the rigor with which control arm clinicians encouraged
46 compliance with antithrombotic prophylaxis in medical patients. In two of the
47 studies dose and type of antithrombotic therapy in the medical therapy arm were
48 left to the treating physician's discretion. Only one of the studies reported
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8 adherence and/or changes over time in medical therapy in both arms. Leaving
9 therapy in the medical arm to the physician's discretion could be considered to
10 represent "usual care" for those randomized to medical therapy. Usual care may,
11 however, change over time, and differ in the jurisdictions in which the trial is
12 conducted in comparison to other jurisdictions. Patients and clinicians may,
13 therefore, be more interested in the effect of PFO closure versus a particular
14 antithrombotic regimen with a high level of adherence. Unfortunately there have
15 been no RCTs adequately comparing specific antiplatelet or antithrombotic
16 therapies for this indication.

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26 Stroke occurring due to paradoxical emboli through a PFO results from
27 thrombi originating in the venous circulation or perhaps from the right atrial side of
28 an-associated atrial septal aneurysm itself.^{21,22} Warfarin has been shown to be more
29 effective than antiplatelet therapy for the treatment and secondary prevention of
30 venous thromboembolic events. Observational studies suggest oral anticoagulation
31 is superior to aspirin for the prevention of stroke in patients with PFO albeit with
32 increased bleeding.^{23,24} In the Patent Foramen Ovale in Cryptogenic Stroke study
33 (substudy of the randomized Warfarin-Aspirin Recurrent Stroke study) there were
34 98 patients with cryptogenic stroke and PFO - 42 were randomized to warfarin and
35 56 received aspirin.²⁵ Two-year rates of recurrent stroke were lower in patients
36 receiving warfarin (9.5% vs. 17.9%,) but chance easily explains this (p = 0.28).
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48 Given the uncertainty of the optimal antithrombotic regimen, subsequent
49 trials must give this issue careful thought. One option for the medical arm would be
50 careful exploration of individual patient values and preferences. Patients highly
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averse to bleeding risk and the burdens of anticoagulant therapy could receive only
an antiplatelet agent, while those less bleeding and burden averse could receive an
anticoagulant. Use of an oral anticoagulant rather than warfarin in those choosing
anticoagulation would be a possibility. Such an approach might represent optimal
medical care, perhaps the appropriate comparator to PFO closure. Another option
would be three-arm study with both antiplatelet and anticoagulant arms

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We conclude that the available data warrants only low confidence in the
impact of PFO versus medical therapy. Thus, additional RCTs are still required –
two such studies are listed as actively recruiting on the NIH website
ClinicalTrials.gov. Ideally, when pooled across studies, sample sizes will be large
enough to definitively establish the impact of PFO closure versus medical therapy on
the most important outcome, ischemic stroke. As important, results will be more
compelling if the ongoing studies have implemented successful strategies to ensure
complete or near-complete follow-up and have paid careful attention to decisions
regarding medical prophylaxis and optimizing adherence in both arms of the study.

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[In the interval, patients should be made aware of the management options and the uncertainty underlying their effectiveness.](#)

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Figure legends:

Figure 1 Risk of bias in individual studies

Figure 2 Pooled risk of non-fatal ischemic stroke with PFO closure versus medical therapy

Figure 3 Pooled risk of transient ischemic attack with PFO closure versus medical therapy

Figure 4 Pooled risk of major bleeding with PFO closure versus medical therapy

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Contributorship statement:

Dr. Frederick Spencer contributed to the conception and design of the study, the acquisition, analysis and interpretation of the data, drafting the work, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Luciane Lopes contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Mr. Sean Kennedy contributed to the design of the study, the acquisition, analysis and interpretation of the data, critical revision of the work for important intellectual content, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Gordon Guyatt contributed to the design of the study, the acquisition, analysis and interpretation of the data, drafting and critical revision of the work for important intellectual content, and gave final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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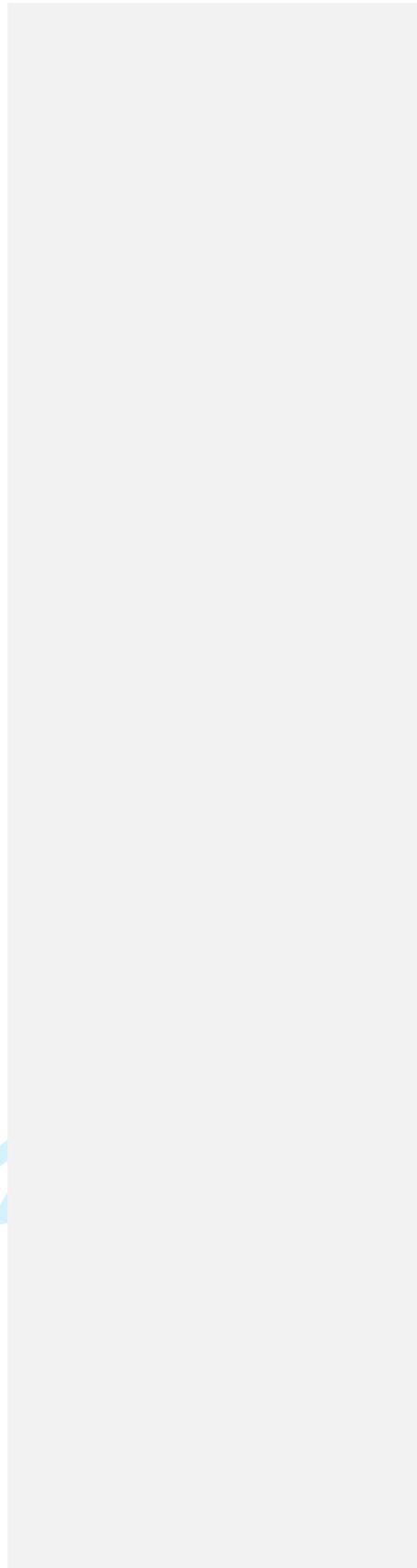


Table 1

Trial (patients)	Trial Type	Intervention	Medical therapy	Withdrew or Loss to Followup PFO closure (%)	Withdrew/Loss to Followup Medical Therapy (%)	Crossover from Medical Therapy to PFO Closure (%)	% PFO closure attempts/patients enrolled in PFO cohort (%)	% technical success /PFO closure attempts (%)
CLOSURE I (909)	Multicentre Randomized Open label	STARFLEX Device Clopidogrel x 6 mo ASA x 2 years	Warfarin (INR 2-3), ASA 325 per day, or both (clinician's discretion)	1.8	0.7	0	90.6	89.4
PC Trial (414)	Multicentre Randomized Open Label	Amplatz Amplatzer Occluder ASA 5-6 mo. Clopidogrel or ticlopidine 1-6 mo.	Antiplatelet or anticoagulation (clinician's discretion)	15.2	20	13.3	96.1	97.4
RESPECT (980)	Multicentre Randomized Open Label	Amplatz Amplatzer Occluder ASA 6 mo Clopidogrel 1 mo.	Antiplatelet or anticoagulation (clinician's discretion)	9.2	17.2	0	93	99.1

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Table 2 Characteristics of Patients in Eligible Studies

	CLOSURE 1	RESPECT	PC Trial
N	909	980	414
Mean Age +/- SD	46.0	45.9	44.5
Male (%)	51.8	54.7	49.8
Smoker (%)	22.1	13.3	23.9
Medical History (%)			
Diabetes	NR	7.4	2.7
Hypertension	31.0	31.4	25.8
Hyperlipidemia	44.1	39.5	27.1
Ischemic heart disease	1.1	2.9	1.9
Myocardial infarction	1.3	0.7	1
Valvular dysfunction	10.3	NR	3.1
Peripheral vascular disease	1.3	0.6	1.2
Index event (%)			
Stroke	72	100*	79.2
TIA	28	0	18.1
Peripheral arterial embolism	0	0	2.7
PFO characteristics (%)			
Moderate or higher shunt	52.9	75.2	65.6**
Atrial septal aneurysm >10 mm	37.8***	35.6	23.7

*Included patients with symptoms for less than 24 hours if new neuroradiologically relevant cerebral infarct on imaging
** 369 of 414 patients with TEE

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***151/400 patients with TEE

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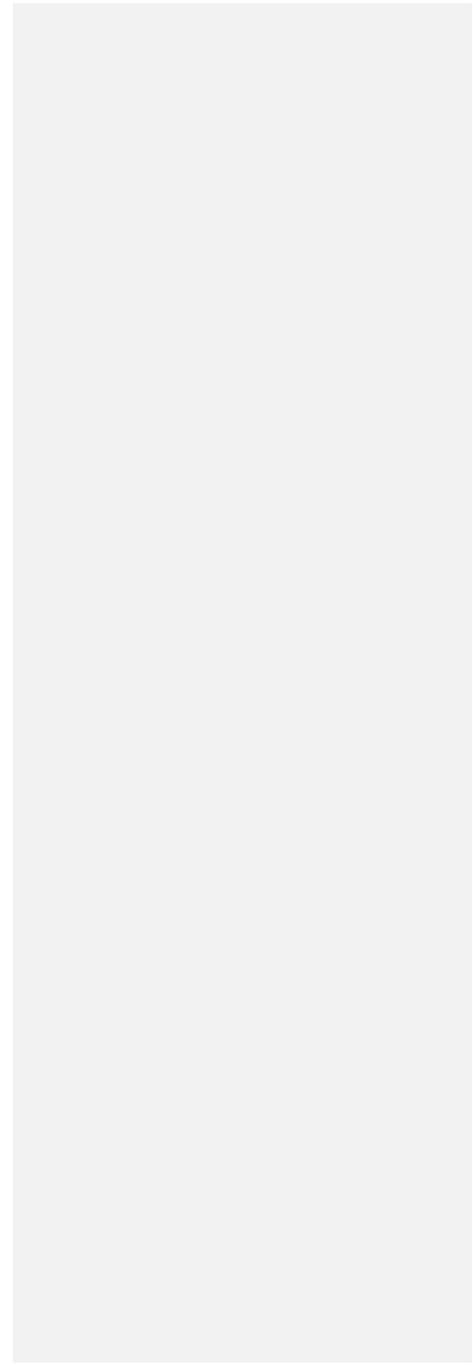


Table 3 – GRADE assessment of quality of evidence

Bibliography:									
Quality assessment						Summary of findings			
No of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Relative effect or risk difference (95% CI)	Anticipated absolute effects Time frame: 5 years		Quality of evidence
							Risk with medical therapy	Risk difference with PFO closure (95% CI)	
Non-fatal ischemic stroke (critical outcome)									
1968 (3 RCTs)	Serious limitations ¹	No serious limitations	No serious limitations	Imprecise CI includes benefit and no effect	Undetected	RR 0.61 (0.34 to 1.07)	52 per 1000 ²	20 fewer per 1000 (from 34 fewer to 4 more)	⊕⊕○○ LOW due to risk of bias and imprecision
TIA (important outcome)									
1968 (3 RCTs)	Serious limitations ¹	No serious limitations	No serious limitations	No serious limitations ³	Undetected	RR 0.76 (0.44 to 1.32)	27 per 1000 ⁴	6 fewer per 1000 (from 15 fewer to 9 more)	⊕⊕⊕○ MODERATE due to risk of bias
Total mortality (critical outcome)⁵									
1968 (3 RCTs)	Serious limitations ¹	No serious limitations	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RD 0.00 (-0.01, 0.01)	15 per 1000 ⁶	0 fewer per 1000 (from 10 fewer to 10 more)	⊕⊕○○ LOW due to risk of bias and imprecision
Major bleeding (important outcome)									
2254 (3 RCTs)	Serious limitations ¹	No serious inconsistency	No serious limitations ³	No serious limitations	Undetected	RD 0.00 (-0.01, 0.02)	7 per 1000 ⁷	0 more per 1000 (10 fewer to 20 more)	⊕⊕⊕○ MODERATE due to risk of bias
Atrial fibrillation (important outcome)⁸									
2254 (3 RCTs)	Serious limitations ¹	Serious inconsistency ⁹	No serious limitations	Imprecise CI includes benefit and harm	Undetected	RD 0.02 (-0.02, 0.06)	12 per 1000 ¹⁰	20 more per 1000 (20 fewer to 60 more)	⊕○○○ VERY LOW due to risk of bias and imprecision

¹Serious risk of bias due to substantial loss to followup in each of 3 studies; loss to followup greater in medical therapy arms. See text for other potential sources of bias in individual studies.

²Baseline rate derived from pooled Respect and PC trial data - 21 non-fatal ischemic strokes detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

³Although CI includes benefit and harm, but magnitude of extremes for this type of outcome deemed too low to appreciably impact patient decision making.

⁴Baseline rate derived from pooled Respect and PC trial data - 11 TIAs detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

⁵None of deaths due to stroke, treatment related bleeding, or device implantation

⁶Baseline rate derived from pooled Respect and PC trial data - 6 cases of total mortality detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

⁷Baseline rate derived from pooled Respect and PC trial data - 3 cases of major bleeding detected in medical therapy arm over a total of 2019 patient years x 1000 x 5 years

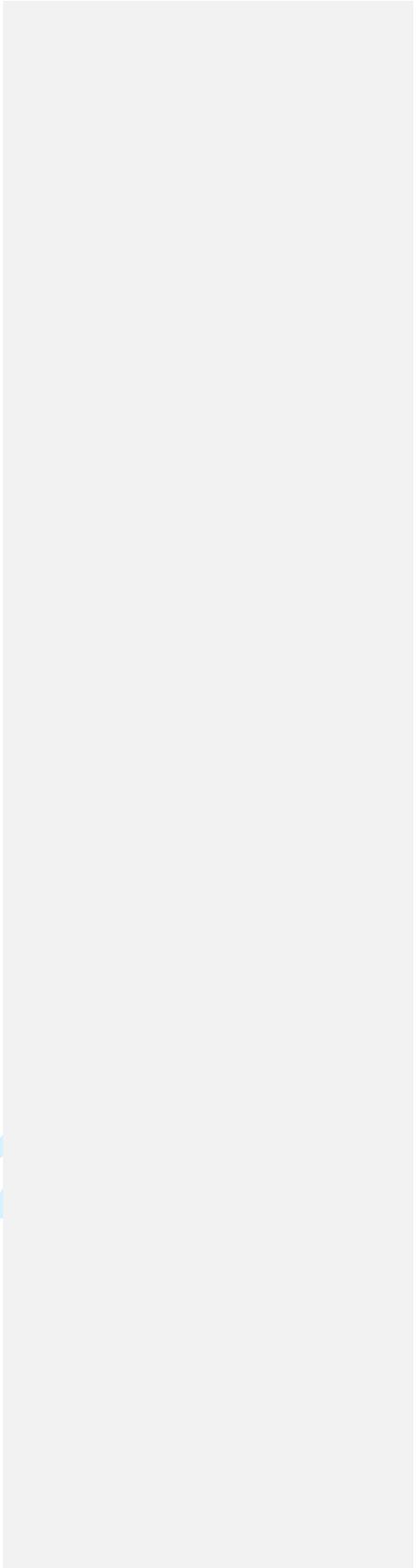
⁸Type of atrial fibrillation (transient vs. sustained) not reported in medical therapy arms or in PFO closure arm of RESPECT study. Of 31 cases of atrial fibrillation in the remaining 2 studies 19 were characterized as transient.

⁹ $p = 93\%$, $p = <0.00001$

¹⁰Baseline rate derived from pooled Respect and PC Trial data - 5 cases of atrial fibrillation detected in the medical therapy arm over a total of 2019 pt-yrs x 1000 x 5 years.

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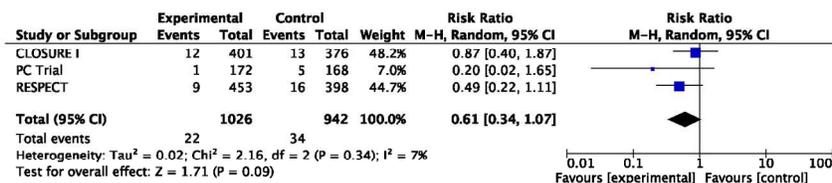


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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
CLOSURE I	+	+	?	?	-	+	+
PC Trial	+	+	?	+	-	+	+
RESPECT	?	-	?	+	-	+	+
Sensitivity Analysis							

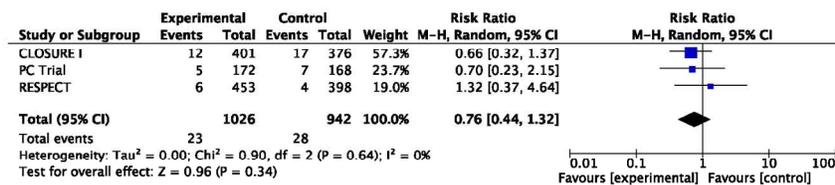
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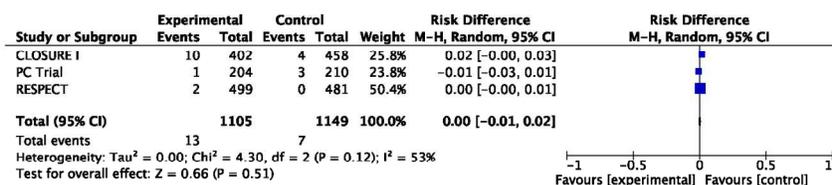
Pooled risk of non-fatal ischemic stroke with PFO closure versus medical therapy
209x279mm (200 x 200 DPI)

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Pooled risk of transient ischemic attack with PFO closure versus medical therapy
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Pooled risk of major bleeding with PFO closure versus medical therapy
209x279mm (200 x 200 DPI)



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-11



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-14 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14 Figure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-18 Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-18 Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA



PRISMA 2009 Checklist

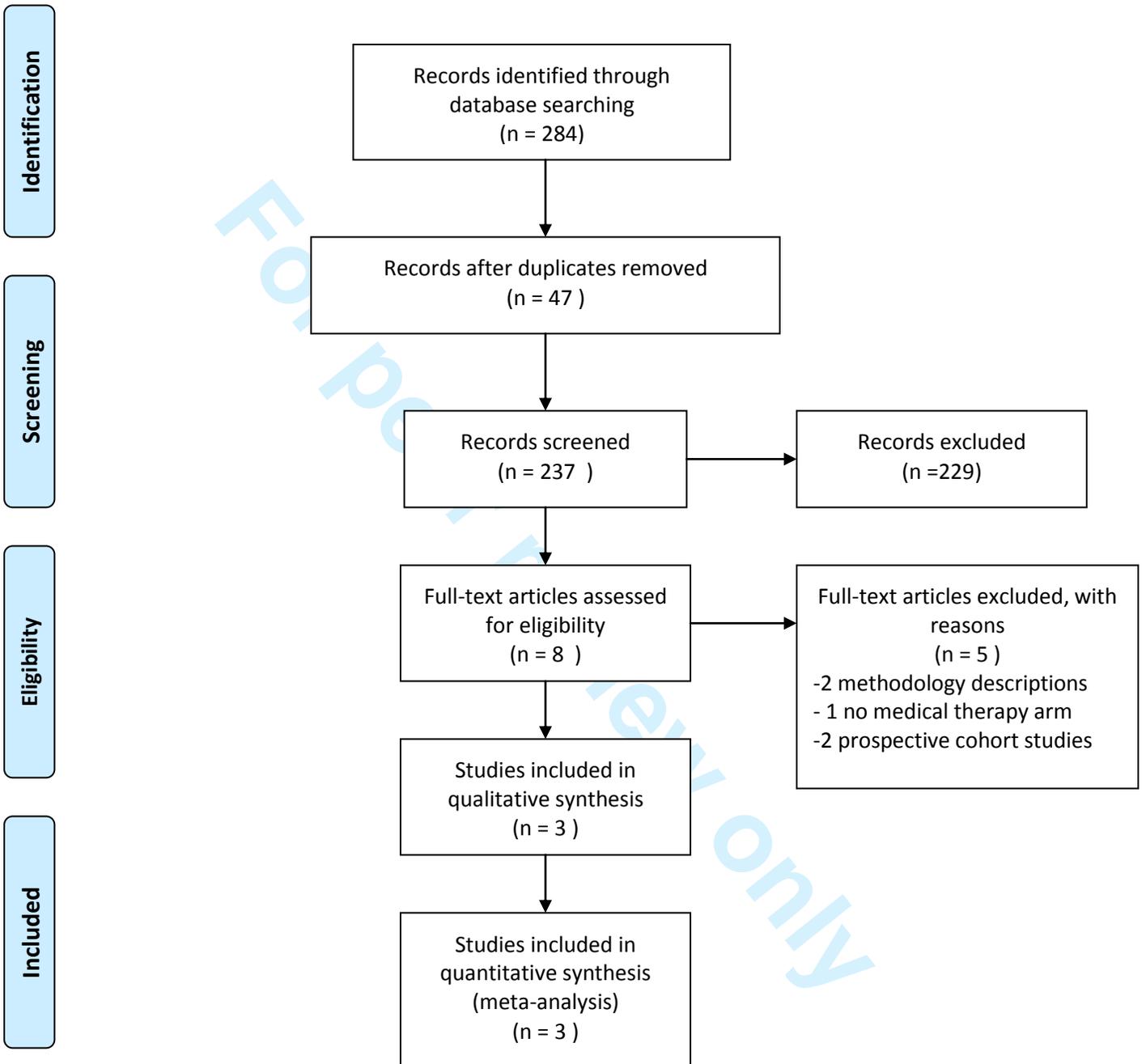
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