SUPPLEMENTAL MATERIAL*


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* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.
Part 1: Protocol for review

Device Closure Versus Medical Therapy Alone for Patent Foramen Ovale in Patients with Cryptogenic Stroke: A Systematic Review and Meta-Analysis

Review question(s):

To compare the efficacy and safety of transcatheter patent foramen ovale (PFO) closure with medical therapy alone (MTA) for the prevention of recurrent strokes in patients with cryptogenic stroke and PFO.

Searches:

We will perform a literature search using PubMed and the Cochrane Library from inception to September 2017 without language restriction. In addition, abstracts from major international cardiology meetings will be reviewed. Searches will be performed using various combinations of the following terms: “patent foramen ovale,” “PFO,” “device,” “closure,” “medical therapy,” “stroke,” “transient ischemic attack,” “TIA,” and “clinical trial.”

At the recommendation of the editor, the protocol was amended to include a literature search from inception to October 2017. In addition, we will hand-search the references of all meta-analyses published over last five years in this subject as identified by PubMed and Google Scholar searches. Finally, we will search www.clinicaltrials.gov for ongoing trials and to evaluate for possible publication bias.

Types of study to be included

Randomized studies comparing device closure with medical therapy alone.

Condition or domain being studied;
Patients with PFO and cryptogenic stroke.

**Intervention(s), exposure(s):**

Medical therapy alone (with antiplatelet therapy, oral anticoagulants, or a combination of both).

**Comparator(s)/ control:**

Transcatheter device closure.

**Outcome(s):**

**Primary efficacy endpoint:** Recurrent stroke

**Secondary efficacy endpoints:** Transient ischemic attack (TIA) and all-cause mortality

**Safety endpoints:** Incidence of atrial fibrillation/flutter, procedure-related vascular complications, and major bleeding.

At the recommendation of the editor, the protocol was amended to change recurrent stroke to “outcomes of main interest.” In addition, endpoints for all-cause mortality and vascular complication were removed because of low event rates.

**Risk of bias (quality) assessment**

The risk of bias will be assessed according to the Cochrane Collaboration for randomized trials.

**Strategy for data synthesis:**

Data will be extracted and presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Studies will be selected, and data extracted independently by two reviewers (RS and MN). Disagreements will be resolved by consensus.
Studies will be evaluated carefully for duplicate or overlapping data. The pooled RR will be calculated using the DerSimonian-Laird method for random effects.

At the recommendation of the editor, the protocol was amended to calculate pooled risk difference using the Knapp-Hartung estimator. In addition, for zero events “treatment arm continuity correction” will be done.

**Analysis of subgroups or subsets**

If heterogeneity is discovered, a sensitivity analysis will be performed by excluding one study at a time and evaluating the impact on summary results.

At the recommendation of the editor, the protocol was amended to exclude the CLOSURE I trial from the analysis.

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**Funding sources/sponsors**

None

**Conflicts of interest**

None

**Language**

English

**Country**

United States of America

**Protocol developed:** September 16, 2017

**Protocol amended:** November 2, 2017
Part 2: Lists of meta-analyses reviewed


### Part 3: Inclusion and exclusion criteria of the RCTs.

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<th>Trials</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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| **PC (2013)** | 1. Age <60 years old.  
2. Presence of PFO (with or without ASA) documented by TEE with a right--to--left shunt during the bubble test or color Doppler flow imaging either spontaneously or with a Valsalva or cough maneuver.  
3. Ischemic stroke verified clinically and neuroradiologically by magnetic resonance, computed tomography or angiography in the absence of another identifiable cause of stroke (see exclusion criteria).  
4. Symptoms of TIA and neuroradiologically identified intracranial ischemic lesion in the absence of another identifiable cause of stroke (see exclusion criteria).  
5. Clinically and radiologically verified extracranial peripheral thromboembolism in the absence of another identifiable cause of thromboembolism (see exclusion criteria).  
6. Sufficient recovery from the thromboembolic index event to | 1. Any identifiable cause for the thromboembolic event other than PFO. The following causes must be specifically excluded in all patients enrolled in this study:  
   - **Cardiac:** mural thrombus, dilated cardiomyopathy, prosthetic heart valve, mitral stenosis, bacterial and nonbacterial endocarditis, cardiac myxoma, atherosclerosis of the aorta, chronic or paroxysmal atrial fibrillation (12 lead ECG, transesophageal echocardiography, >24-hour ECG monitoring in case of suspected arrhythmias). **Peripheral Vascular System:** significant atherosclerosis or dissection of the aorta (TEE, MR, CT).  
   - **Cerebrovascular System:** clinically relevant atherosclerosis or dissection of the intracranial and extracranial arteries (Duplex ultrasound of the carotid arteries, contrast MR or CT head scan). Any preexisting neurological disorder or significant intracranial disease (i.e. multiple sclerosis, arteriovenous malformations, previous intracranial hemorrhage).  
   - **Vasculitis:** significant collagen vascular disease, giant cell arteritis, vasculitis, systemic necrotizing vasculitis (history, physical examination, erythrocyte sedimentation rate, C--reactive protein, antinuclear antibodies). |
allow independent daily activities.

7. The physician implanting the device in case of allocation to percutaneous PFO closure agrees to implant an Amplatzer PFO Occluder. Other commercially available devices for percutaneous PFO closure are not to be used in this study.

- **Hematologic**: hyperviscosity syndromes (erythrocytosis with hematocrit >50%, leukocytosis with white blood cell count >150 000 per μl, thrombocytosis with platelets >106 per μl, paraproteinemia), hypercoagulable states (coagulation status including prothrombin time, INR, activated partial thromboplastin time, complete blood cell count, serum protein electrophoresis, anticardiolipin antibodies)

2. Contraindication for chronic oral anticoagulant oral antiplatelet therapy:
   - Severe bleeding disorder within past 3 months prior to randomization: gastrointestinal bleeding, gross hematuria, known coagulopathy, platelet disorder.
   - Significant retinopathy (hemorrhages, exudates)
   - Significant intracranial disease
   - Previous intracranial hemorrhage

3. Patients who are on chronic anticoagulant therapy for another disease entity (e.g. prosthetic heart valve) other than paradoxical embolism.

4. Previous surgical or percutaneous PFO closure.

5. Drug or alcohol abuse <48 hours prior to the thromboembolic index event.

6. Septicemia or severe localized infection.

7. Pregnancy.

8. Severe central nervous system disease (seizure disorder, inflammatory disease of the central nervous system, severe disability from previous
| RESPECT - Extended (2017) | stroke, i.e. Barthel--index <50, Modified Rankin scale >3)  
9. No informed consent  
10. Follow-up over the next 5 years not possible (e.g. severe co-morbid diseases with limited life expectancy, unreliable patient, etc.) |
|---|---|
| **1.** Subjects who have had a cryptogenic stroke within the last 270 days with stroke defined as follows: acute focal neurological deficit, presumed to be due to focal ischemia, and either symptoms persisting 24 hours or greater, or symptoms persisting less than 24 hours but associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct.  
2. Subjects who have been diagnosed with a Patent Foramen Ovale (defined as visualization of microbubbles per TEE in the left atrium within three cardiac cycles from the right atrial opacification at | **1.** Atherosclerosis or other arteriopathy of the intracranial and extracranial vessels of >50% of lumen diameter supplying the involved lesion.  
2. Intracardiac thrombus or tumor.  
3. Acute or recent (within 6 months) myocardial infarction or unstable angina.  
4. Left ventricular aneurysm or akinesis.  
5. Mitral valve stenosis or severe mitral regurgitation irrespective of etiology.  
6. Aortic valve stenosis (gradient >40 mmHg) or severe aortic valve regurgitation.  
7. Mitral or aortic valve vegetation or prosthesis.  
8. Aortic arch plaques protruding >4mm into the lumen.  
9. Left ventricular dilated cardiomyopathy with LVEF <35%.  
10. Subjects with other source of right to left shunts identified at baseline, including an atrial septal defect and/or fenestrated septum.  
11. Septal defect and/or fenestrated septum.  
12. Atrial fibrillation/atrial flutter (chronic or intermittent.  
13. Pregnant or desire to become pregnant within the next year.  
14. Age <18 years and age >60 years. |
3. Subjects willing to participate in follow-up visits

15. Active endocarditis, or other untreated infections.
16. Organ failure (kidney, liver or lung)
   - Kidney failure: Poor urine output of less than 1 cc/kg/hr with elevated BUN levels (above the normal reference range for the laboratory at the investigational site).
   - Liver failure: Liver enzymes outside the normal reference range for the laboratory at the investigational site: poor liver function as assessed by elevated PT (above the normal reference range for the laboratory at the investigational site) and low total protein and albumin (below the normal reference range for the laboratory at the investigational site).
   - Lung failure: Respiratory failure is retention of carbon dioxide more than 60 mmHg, poor oxygenation with oxygen tension less than 40 mmHg in room air or the need for assisted ventilation.
17. Uncontrolled hypertension or uncontrolled diabetes mellitus.
18. Uncontrolled hypertension: Sustained elevated systemic blood pressure to more than 160/90 with medications.
19. 160/90 with medications.
20. Uncontrolled diabetes: Continued elevated glucose levels in spite of administration of 25 insulin/levels of more than 200mg with presence of glucose in the urine.
21. Lacunar infarct probably due to intrinsic small vessel as qualifying event
   - Lacunar infarct Definition: Ischemic stroke in
the distribution of a single, small deep penetrating vessel in a patient with any of the following: 1) a history of hypertension (except in the first week post stroke); 2) history of diabetes mellitus; 3) Age \( \geq 50 \); or 4) MRI or CT shows leukoaraiosis greater than symmetric, well-defined periventricular caps or bands (European Task Force on Age-Related White Matter Changes rating scale score \( > 0 \)).

22. Arterial dissection as qualifying event.

23. Signs of progressive neurological dysfunction.

24. Subjects who test positive with one of the following hypercoagulable states; Anticardiolipin Ab of the IgG or IgM, Lupus anticoagulant, B2-glycoprotein-1 antibodies or persistently elevated fasting plasma homocysteine despite medical therapy.

25. Subjects with contraindication to aspirin or clopidogrel therapy.

26. Anatomy in which the AMPLATZER PFO Occluder would interfere with intracardiac or intravascular structures such as valves or pulmonary veins.

27. Malignancy or other illness where life expectancy is less than 2 years.

28. Subjects who will not be available for follow-up for the duration of the trial.

29. Inability to obtain Informed Consent from patient or legally authorized representative.

30. Stroke with poor outcome at time of enrollment (Modified Rankin score \( > 3 \)).

31. Subjects who are not able to discontinue the use of
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<th><strong>CLOSE (2017)</strong></th>
<th>anticoagulation if randomized to closure.</th>
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<td>1. Males or females, 16 ≤ age ≤ 60 years.</td>
<td>1. Another cause for stroke associated with PFO.</td>
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<td>2. Recent (≤ 6 months) ischemic stroke (or retinal ischemia), initial or recurrent, confirmed by cerebral imaging (presence of signs of recent infarction corresponding to the clinical signs) regardless of the duration of symptoms (less than or greater than 24 hours).</td>
<td>2. Isolated ASD or ASD associated with PFO but with a hemodynamically significant left-to-right shunt requiring closure.</td>
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<td>3. Modified Rankin score ≤ 3.</td>
<td>3. Previous surgical or endovascular treatments of PFO or ASA.</td>
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<td>4. Absence of another identifiable cause of stroke (or retinal ischemia) on a thorough etiological work.</td>
<td>4. Known or suspected pregnancy (beta-hCG assay must be performed before inclusion).</td>
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<td>5. Presence of a PFO with at least one of the following characteristics:</td>
<td>5. Breastfeeding.</td>
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<td>• PFO with large shunt &gt; 30 microbubbles on TTE or TEE detected either spontaneously or exclusively during provocation maneuvers &gt; 30 microbubbles on TTE or TOE.</td>
<td>6. Follow-up impossible or expected poor compliance.</td>
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<td>• PFO associated with atrial septal aneurysm on TEE: base of aneurysm ≥ 15 mm and excursion &gt; 10 mm.</td>
<td>7. Patient not covered by national health insurance.</td>
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<td>11. Related to the drug treatments of the study:</td>
<td>8. Presence of other medical problems that would either lead to inability to complete the study or interfere with the assessment of outcomes.</td>
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<td>• Indication for long-term anticoagulant or antiplatelet therapy for another reason.</td>
<td>9. Participation in another study.</td>
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<td>• Contraindication to: aspirin, clopidogrel, or oral anticoagulants (3-arm study); aspirin or clopidogrel (2-arm study, closure vs. antiplatelet therapy); oral anticoagulants or all antiplatelet drugs (2-arm study, oral anticoagulants vs. antiplatelet therapy).</td>
<td>10. Patient unable to understand the informed consent form.</td>
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<tr>
<td>• Increased bleeding risk: severe liver failure, active peptic ulcer, proliferative diabetic</td>
<td>11. Related to the drug treatments of the study:</td>
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retinopathy, history of severe bleeding (e.g.: gastrointestinal bleeding, macroscopic hematuria, intraocular bleeding, intracranial or cerebral hemorrhage), or other history of bleeding or coagulopathy, work and sports activities associated with high-risk of injury and bleeding.

12. Related to the endovascular treatment:
   - Active infection requiring antibiotic therapy (possible inclusion after cure and 4 weeks after stopping antibiotics).
   - Presence of very large or multiperforated ASA, for which the procedure is considered difficult or at high risk.
   - Presence of thrombus or occlusion between the femoral venous access and the right atrium.
   - Presence of an inferior vena cava filter.
   - Severe pulmonary artery hypertension.

| REDUCE (2017) | 1. Patient has had a cryptogenic, ischemic stroke, or transient ischemic attack (TIA), of presumed embolic etiology, verified by a neurologist within 180 days prior to randomization, meeting either criteria a or b:   | 1. Patient has a life expectancy of less than one year. |
| | a. Patient has a diagnosis of ischemic stroke (clinical symptoms persisting ≥24 hours). | 2. Patient is experiencing severe disability, defined as modified Rankin Scale core greater than or equal to 3, at the time of randomization. |
| | OR | 3. Patient has neurological deficits not due to stroke that may affect the patient’s neurologic assessments. |
| | 4. Patient has other potential source(s) of cardio-embolism, for example: atrial fibrillation (AFib) or atrial flutter (AFlu), prosthetic heart valve, severe native valve disease, left ventricular ejection fraction of <40%, severe ventricular wall | 4. Patient has other potential source(s) of cardio-embolism, for example: atrial fibrillation (AFib) or atrial flutter (AFlu), prosthetic heart valve, severe native valve disease, left ventricular ejection fraction of <40%, severe ventricular wall |
b. Patient has a diagnosis of TIA (clinical symptoms persisting <24 hours) and has MRI evidence of infarction. For MRI-incompatible patients (i.e., patients that are claustrophobic and/or have implants that are contraindicated for MR) a CT scan of the brain will be accepted.

2. Patient is diagnosed with a patent foramen ovale (PFO), confirmation of which is achieved by transesophageal echocardiography (TEE) with bubble study demonstrating spontaneous right-to-left shunting or right-to-left shunting during Valsalva maneuver.

3. There is an absence of an identifiable source of thromboembolism in the systemic arterial circulation.

4. Patient is at least 18 years and less than 60 years of age (subjects cannot have reached their 60th birthday prior to randomization/enrollment).

5. Patient has had a prior myocardial infarction.

6. Patient has uncontrolled diabetes mellitus at the time of randomization, in the opinion of the investigator.

7. Patient has pulmonary hypertension (mean pulmonary artery pressure >25 mmHg).

8. Patient has uncontrolled systemic hypertension at the time of screening, in the opinion of the investigator.

9. Patient presented with a lacunar stroke syndrome (e.g., small deep infarction <1.5 cm in diameter and/or a typical lacunar syndrome such as pure motor hemiparesis, pure sensory stroke, clumsy hand-dysarthria syndrome, or ataxic-hemiparesis syndrome).

10. Patient has intracranial pathology that makes the patient inappropriate for study participation based on discretion of the Investigator (e.g., brain tumor other than meningioma, arterio-venous malformation (AVM) or cerebral hemorrhage, cerebral venous sinus thrombosis on CT or MRI, or cerebral aneurysm > 7 mm).

11. Patient has active autoimmune disease (e.g., lupus erythematosus disseminata, rheumatoid arthritis, polyarteritis nodosa, primary cerebral vasculitis).

12. Patient has active infection that cannot be treated
5. Patient has vascular imaging that rules out other potential sources of cerebral thromboembolism (e.g., dissection of the aorta or neck vessels, carotid stenosis > 50% and/or presence of ulcerated plaques, or intracranial stenosis > 50%).

6. Patient has no evidence of hypercoagulable state, which requires anticoagulation therapy. This determination will be based on the evaluation of, at a minimum: platelet count, Prothrombin Time (PT) or International Normalized Ratio (INR), Activated Partial Thromboplastin Time (aPTT), and Antiphospholipid Antibodies. All test results are to be evaluated based on the laboratory normals established at the institution. A thorough history of thromboembolic events in first degree family members must be obtained for all patients. For patients who have a first degree family member with such an event prior to age 55, or whose family history is unknown, the following additional tests are required and must be interpreted as successfully prior to randomization.

13. Patient abuses alcohol and/or drugs [e.g., on average >5 units or drinks (60 grams) of alcohol/day] or abuses alcohol and/or drugs in the opinion of the Investigator.

14. Patient is pregnant, lactating, or intent on becoming pregnant through 24-months after randomization.

15. Patient has contraindication to study medications, including antiplatelet therapy.

16. Patient requires chronic anticoagulation therapy that cannot be discontinued prior to randomization, in the opinion of the Investigator. Testing for prothrombotic disorders may be performed at the discretion of the treating physicians but is not required for this study.

17. Patient is currently participating in another clinical device or drug trial that has not completed its primary endpoint or that will clinically confound the current study endpoints or does not permit subjects to participate in other studies. Typically, subjects that are involved in the long-term surveillance phase of a clinical study are eligible.

18. Patient has other anatomic or co-morbid conditions that could, in the Investigator’s opinion, limit the patient’s ability to participate in the study or to comply with follow-up requirements, or impact the scientific soundness of the study results.

7. Patient is willing and capable of complying with the study protocol requirements, including the specified follow-up period, and can be contacted by telephone.

8. Patient or patient’s legal representative (or person designated acceptable under local Ethics committee requirements) is willing to provide written informed consent prior to enrollment in study.

19. Patient has a known sensitivity to contrast media that cannot be controlled adequately with pre-medications.

20. Patient has had any major surgical procedure within 30 days preceding randomization.

21. Patient plans to have a major elective surgical procedure within 30 days after randomization or within 30 days of a PFO closure procedure.

22. Patient has the need for any concomitant procedure, based on the results of the screening evaluations, during the PFO closure procedure that may confound detection of device-related adverse events.

23. In the opinion of the Investigator, patient has anatomic criteria identified during the screening evaluation and/or the screening transesophageal echocardiogram (TEE) that are unfavorable for successful placement of the GORE® HELEX® Septal Occluder / GORE® CARDIOFORM Septal Occluder or the patient has contraindications for device placement, which may include:
   o Inability to accommodate a 10 Fr delivery catheter
   o The need for trans-septal puncture
   o Requires placement of more than one device
   o PFO estimated to be too large for successful device placement
   o Device would impinge on cardiac structure(s)