

Sónia Patrícia Pinto Pereira

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The role of patent foramen ovale closure in the secondary prevention of cryptogenic stroke. A meta-analysis report.

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The role of patent foramen ovale closure in the secondary prevention of cryptogenic stroke. A meta-analysis report.

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## **Dedicatória**

Ao meu orientador deixo um sentido agradecimento por toda a sua dedicação, por todo o tempo despendido e pela forma célere e didática como sempre atuou durante a concretização deste trabalho.

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Aos meus Pais, aos meus irmãos, ao meu namorado e à minha melhor amiga.

É fácil conquistar o apoio e admiração das pessoas quando somos bem-sucedidos, difícil é ter quem nos apoie e quem invista em nós quando ainda estamos muito longe da meta. Estas pessoas que acabei de mencionar, acreditaram sempre nas minhas capacidades, investiram em mim, motivaram-me e desejaram o meu sucesso tanto quanto eu. Estas são as pessoas incríveis a quem serei eternamente grata.

**The role of Patent Foramen Ovale Closure in the Secondary prevention of Cryptogenic  
Stroke. A meta-analysis report.**

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## **Abstract**

### **Background**

Randomized clinical trials have been performed to determine if patent foramen ovale (PFO) closure is superior to medical therapy for secondary prevention of recurrent cryptogenic stroke. Our purpose with the current study is evaluate the best management for these patients.

### **Methods**

We performed a search in Medline (PubMed) and in ISI Web of Knowledge databases for all randomized controlled trials that compared PFO closure with medical therapy for preventing recurrent stroke in patients who presented with cryptogenic stroke and who had a documented PFO. The parameters chosen for analysis and meta-analysis were stroke, transient ischemic attack (TIA) and atrial fibrillation (AF).

### **Results**

We included in this study a total of six randomized trials enrolling 3750 patients. Unlike other published meta-analysis on the same topic, in this case only clinical trial data and not follow-up data were used. PFO closure, as compared with medical therapy alone, demonstrated superiority in reducing the rate of recurrent stroke (risk ratio [RR], 0.37; 95% confidence interval [CI], 0.17 to 0.78;  $P = 0.01$ ). PFO closure did not offer a significant benefit in prevention of TIA (RR, 0.96; 95% CI, 0.64 to 1.44;  $P = 0.85$ ). Among patients assigned to closure group, an increased risk of AF was seen (RR, 4.64; 95% CI, 2.38 to 9.01;  $P < 0.01$ ).

### **Conclusions**

In patients with cryptogenic stroke who had a PFO, a protective effect of closure was seen concerning the risk of recurrent stroke, but not regarding the prevention of TIA.

**Key Words:** Patent Foramen Ovale, Device closure, Medical Therapy, Cryptogenic Stroke

## Introduction

Stroke remains one of the more important causes of death and morbidity worldwide (1). Between 20% and 30% of ischemic strokes have no identifiable cause after exclusion of all potential causes, and they are denominated cryptogenic strokes (2). In people who suffer a cryptogenic stroke, 40% to 50% of patients have a patent foramen ovale (PFO); this association suggest that some cryptogenic strokes, particularly in younger patients, may be due to paradoxical embolism, which consists in the passage of a thrombus from the venous to the atrial system through a patent foramen ovale (3, 4).

The options to implement secondary prevention of recurrent stroke for patients with a PFO who have had a cryptogenic stroke have been the administration of antithrombotic medications or percutaneous closure of PFO, however it was not initially clear whether percutaneous closure is superior to medical therapy (5, 6). The results of early studies gave no room for an excessive optimism. These relatively modest results have been attributed to reasons that include the choice of closure device, off-protocol closure device use within the medical therapy arms, patient selection criteria, slow enrolment (1, 3, 5, 7, 8), among other factors.

In the years 2017 and 2018, three new clinical trials were published, and demonstrated that percutaneous PFO closure as compared with medical therapy reduce the risk of recurrent stroke (6, 9, 10). Some of these results, impressive as they are, have been obtained by the selective inclusion of patients with high-risk PFO features, including the size of the PFO, or the presence of an atrial septal aneurysm - making PFO closure particularly persuasive in these patients. However, restricting device closure entirely to patients with high-risk characteristics of PFO may be too conservative (11).

Concerning the clinical trials currently published, several meta-analyses were carried out (12-19), but all of them included data from a follow-up study (2) rather than the original clinical trial data – data that the authors themselves considered to be exploratory. In the present report, we conducted

an updated meta-analysis including only data from the primary analysis of clinical trials evaluating the role of PFO closure in the secondary prevention of recurrent stroke.

## **Methods**

### Search strategy

The study started with a search on Medline (PubMed) database, using the query “patent foramen ovale” AND “stroke” AND “closure” with the filter “clinical trial”. The search took place during the month of July 2018, and no articles were excluded based on publication date. The query resulted in 40 articles being found. A further search was carried out in a second database, ISI Web of Knowledge, using the same query, with the filter “article”, in December 2018, yielding 840 articles (Figure 1, supplementary file 1). Additional studies that were evaluated were found after searching the references of previous review articles and other relevant sources, including articles related to the topic in question as well as articles citing the selected articles.

### Inclusion criteria

Only human studies were included, and only interventional studies comparing PFO closure with medical therapy were considered within the scope of this review.

### Exclusion criteria

Excluded were: mechanistic studies; animal studies; studies of PFO physiology; case reports; editorials; review papers; study protocols; non-randomized studies; duplicate studies, if found; systematic reviews and/or meta-analyses; sub-group analyses of included studies; follow-up data of included studies; cost analyses or surveys; comparison between medical treatments; comparison between closure devices; studies of PFO closure only; guidelines; genetic or pathological studies.

### Summary measures

We aimed at presenting an overview of clinical trials evaluating interventional studies comparing PFO closure with medical therapy. Meta-analysis was carried out by using the Comprehensive

Meta-analysis Software, V.2.0 (Biostat, New Jersey, USA). Random-effects analyses were carried out, given the considerable heterogeneity of some of the data. The parameters chosen for analysis and for the meta-analysis were stroke, transient ischemic attack (TIA) and atrial fibrillation (AF), and risk ratios (RR) were calculated. Results were reviewed by a biostatistician (CS).

#### Quality assessment of studies and data extraction

Study quality and eligibility were independently assessed by two researchers. Different opinions regarding the relevance of articles were solved by consensus between the authors. Global article quality assessment was carried out according to the method used by Haffar and colleagues (supplementary file 2) (20).

### **Results**

A total of six articles were identified and selected for further study (3, 5, 6, 8-10). Inter-observer agreement was 100%.

Between 2012 and 2018, six randomized controlled trials (RCTs) comparing PFO closure with medical therapy alone for secondary prevention of patients with cryptogenic stroke and PFO were published. These studies involved a total of 3750 patients who were randomly assigned to either closure with the percutaneous device (closure group) or medical therapy alone (medical-therapy group). Concerning acronyms, CLOSURE 1 denotes “Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale”, RESPECT “Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment”, PC trial “Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale (PFO) Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism”, CLOSE “Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence”, REDUCE “GORE HELEX Septal Occluder / GORE CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA

in Patients With Patent Foramen Ovale (PFO) - The Gore REDUCE Clinical Study”, DEFENSE PFO “Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale”). The main aspects of selected studies are shown in Table 1. In the closure group, device implantation was performed soon after randomization and, after the procedure, all patients were given antithrombotic therapy at discretion of the site investigator but always in accordance with the guideline recommendations. The mean follow-up duration varied between RCTs from 2 to 5.3 years.

The data of patients enrolled in each RCT are listed in Table 2. After randomization, a total of 1889 patients were assigned to closure arm and 1671 patients were assigned to medical therapy arm. The mean age was 46 years in both sides. Furthermore, dropouts were observed in each study and similar rate of serious adverse events were seen between the two treatment arms. Efficacy and safety endpoints are illustrated in Table 3.

Clinical endpoints under evaluation in the present report were stroke, TIA and incidence of AF during the follow-up period.

When compared to medical treatment only, PFO closure significantly reduced the rate of recurrent stroke (RR, 0.37; 95% confidence interval [CI], 0.17 to 0.78;  $P = 0.01$ ; I squared 51.12; Figure 2). However, PFO closure did not offer any significant benefit in the prevention of TIA (RR, 0.96; 95% CI, 0.64 to 1.44;  $P = 0.85$ ; I squared 0.00; Figure 3).

Each study demonstrated a relatively low frequency of device and procedure-related complications. PFO closure increased the risk of AF (RR, 4.64; 95% CI, 2.38 to 9.01;  $P < 0.01$ ; I squared 3.84, Figure 4). Importantly, in most cases AF was peri-procedural.

Data on risk difference and annualized risk difference concerning the three outcomes under evaluation are presented in Supplement 2.

## Discussion

Controversy has persisted after the first reports were published on whether PFO closure reduces the risk of recurrent stroke for patients with cryptogenic stroke and documented PFO, when compared with medical therapy. Since 2012, six randomized controlled trials were published, with the aim of comparing these two forms of secondary prevention (3, 5, 6, 8-10). In the present updated meta-analysis, PFO closure in cryptogenic strokes was shown to be superior to medical therapy in reducing recurrent stroke, although the risk of TIA was similar between the two groups. We also confirmed that patients who underwent transcatheter closure were more likely to develop transient AF as compared with medical-therapy group. Our findings are in line with the results of recent meta-analysis (12-19). However, the present study includes data of the RESPECT trial published in 2013 as opposed to recent meta-analysis, which selected the RESPECT long-term results, published in 2017, and that are not the primary results of a controlled trial, rather of a follow-up study.

All six studies included young to middle age patients with PFO documented on transesophageal echocardiography (TE) and cryptogenic stroke, usually in the six months prior to randomization. Three RCTs conducted earlier, which were published in 2012 and 2013, failed to show superiority of PFO closure over medical treatment to decrease stroke recurrence or TIA (3, 5, 8). These relatively modest results have been attributed to several limitations which include choice of the closure device, off-protocol closure device use within the medical therapy arms, patient selection criteria, low sample size, slow enrolment, short duration of follow-up (1, 3, 5, 7, 8), among other factors. Although in the first trials PFO closure did not show greater benefit than medical therapy alone, more recent studies did observe its superiority (6, 9, 10).

The REDUCE trial had a smaller number of patients with uncontrolled vascular risk factors than previous trials, that had less rigorous exclusion criteria; CLOSE and DEFENSE-PFO trials only included patients with high-risk anatomic PFO features. Therefore, better and stricter patient's

selection in more recent RCTs may have increased the probability to have strokes attributable to PFO and consequently may have increased the likelihood that PFO closure would be effective.

PFO presumably provides an anatomic substrate for paradoxical embolism, which may be the cause of most of the cryptogenic strokes (21). Our findings confirm that PFO closure significantly decreased the rate of recurrent ischemic stroke. The risk of TIA, however, was unaltered, pointing in the direction of a different patho-physiology of TIA in this setting (possibly unrelated to paradoxical embolism) and the potential misclassification of non-ischemic events as TIA. Each study demonstrated a low frequency of device and procedure-related complications but a significant increase of AF in the interventional group was seen, which could in theory increase the risk of recurrent stroke. However, the most cases of atrial fibrillation occurred early after the procedure with no recurrence during follow-up.

The key to an appropriate treatment strategy could be to detect which patients may derive more benefit from PFO closure. Recent studies have shown some characteristics that make the potential benefit of the patient more likely, but more studies will be needed to clarify this issue (22). The decision to choose a given type of treatment should be multidisciplinary and shared with the patient, considering the preferences of each person.

The major sources of data heterogeneity are presented in Table 1 – differences in inclusion criteria, in device used, in medical therapy, and in mean follow-up. Patients requiring long-term anticoagulation therapy were mostly excluded from the clinical trials. Thus, the population of patients under anticoagulation therapy does not seem to have a proven benefit with PFO closure for the time being.

### **Limitations**

The included studies were all open label and not double blind, which might impact the results with differential evaluation of suspected events and unequal referral of those events to the adjudication committees. As stated above, there was non-uniformity in the follow-up period, patients'

characteristics, inclusion criteria and closure device used between included studies. TIA was only a primary endpoint in two of the clinical trials, namely, PC trial and CLOSURE I trial.

Preference of some patients and physicians prompted a differential dropout of studies and crossovers between the two treatments groups that may have biased the trials results. Thus, PFO closure was not performed in all patients initially assigned and not all patients who underwent the procedure had a successful closure. If residual shunts persisted, this might mask the real efficacy of PFO closure in prevention of recurrent strokes. Similarly, some patients of medical group underwent PFO closure with devices approved by the Food and Drug Administration (FDA) for other indications (off-label use).

In the medical-therapy groups, there was lack of standardization in the type and doses of the medical therapy used in each site and the use of anticoagulant treatment was more frequent as compared with closure group. In addition, discontinuation of antithrombotic treatment was allowed after PFO closure in many trials, which may have increased the risk of non-PFO-related stroke in these studies. Finally, the definitions used for reporting of AF varied among trials and may not be directly comparable.

## **Conclusions**

At the present stage, PFO closure seems to be superior to medical treatment in reducing recurrent stroke in patients with cryptogenic stroke. Comparable risks of TIA have been seen in studies published so far. Furthermore, even if a significantly higher risk of new-onset AF was seen with closure, studies suggested that it was usually periprocedural. These findings suggest that PFO closure is a better strategy for secondary prevention of recurrent stroke in patients with a cryptogenic stroke and PFO.

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**Declaration of Conflicting Interests**

The authors declared no potential conflicts of interest.

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**Table 1.** The main aspects of selected studies

	<b>Total number of Patients</b>	<b>Inclusion criteria</b>	<b>Device and additional therapy</b>	<b>Medical therapy</b>	<b>Follow- up Duration (Years)</b>	<b>Primary outcomes</b>
<b>CLOSURE 1 (2012)</b>	909	<b>1.</b> 18 to 60 yr of age  <b>2.</b> PFO documented on TE  <b>3.</b> CS or TIA within the previous 6 mo	STARFlex Septal Closure System + clopidogrel 75 mg/day, 6 mo, + aspirin, 81 or 325 mg/day, 2 yr	Aspirin or warfarin or both	2	A composite of stroke or TIA <2 yr and death (death for any cause < 30 days or death for neurologic causes between 31 days and 2 yr)
<b>RESPECT (2013)</b>	980	<b>1.</b> 18 to 60 yr of age  <b>2.</b> PFO documented on TE  <b>3.</b> CS within the previous 270 days	Amplatzer PFO Occluder + 81 to 325 mg of aspirin plus clopidogrel for 1 mo, followed by aspirin monotherapy for 5 mo	Aspirin or clopidogrel or aspirin + ER- dipyridamole or warfarin	Mean: 2.6 ± 2.0	A composite of ischemic stroke or early death after randomization
<b>PC TRIAL (2013)</b>	414	<b>1.</b> <60 yr of age  <b>2.</b> PFO documented on TE  <b>3.</b> CS, TIA with cerebral ischemic lesion, or PTE	Amplatzer PFO Occluder + 100- 325 mg/day aspirin for at least 5 to 6 mo + either 250-500 mg/day ticlopidine or 75- 150 mg/day clopidogrel for 1 to 6 mo	Antiplatelet therapy or oral anticoagulation	Mean: 4.1 <sup>A</sup> 4.0 <sup>B</sup>	A composite of death, nonfatal stroke, TIA or PTE

<b>CLOSE</b> (2017)	663	<p><b>1.</b> 16 to 60 yr of age</p> <p><b>2.</b> PFO with atrial septal aneurysm or large interatrial shunt</p> <p><b>3.</b> CS within the previous 6 mo</p>	<p>One randomization arm: any of eleven different devices + dual antiplatelet therapy (75 mg of aspirin plus 75 mg of clopidogrel per day) for 3 mo, followed by single antiplatelet therapy throughout the remainder of the trial.</p>	<p>Two further randomization arms: antiplatelet therapy alone (antiplatelet-only group), or oral anticoagulation (anticoagulation group). Antiplatelet regimen: aspirin, clopidogrel, or aspirin combined with ER-dipyridamole. Patients with contraindications to anticoagulants or to PFO closure were randomly assigned to the alternative no contraindicated treatment or to antiplatelet therapy</p>	<p>Mean: 5.3 ± 2.0</p>	Fatal or nonfatal stroke
<b>REDUCE</b> (2017)	664	<p><b>1.</b> 18 to 59 yr of age</p> <p><b>2.</b> PFO documented on TE</p> <p><b>3.</b> CS within the previous 180 days</p>	<p>Helex Septal Occluder or Cardioform Septal Occluder + Antiplatelet therapy as in the medical therapy arm + clopidogrel at the time of the</p>	<p>75-325 mg/day aspirin or 50-100 mg/day Aspirin + 225-400 mg/day dipyridamole or 75 mg/day clopidogrel</p>	<p>Mean: 3.2</p>	Two coprimary end points of clinical ischemic stroke and new brain infarction

			procedure and for 3 days			
<b>DEFENSE</b> <b>PFO</b> (2018)	120	1. High-risk PFO - PFO with atrial septal aneurysm, hypermobility (phasic septal excursion into either atrium $\geq 10$ mm), or PFO size (maximum separation of the septum primum from the secundum) $\geq 2$ mm 2. CS within the previous 6 mo	Amplatzer PFO Occluder + dual antiplatelet regimen (aspirin 100 mg/day in combination with clopidogrel 75 mg/day) for at least 6 mo; anticoagulation therapy allowed as alternative	Aspirin or aspirin + clopidogrel or aspirin + cilostazol or warfarin	Median: 2.8	Composite of stroke, vascular death, or major bleeding

A. Closure group; B. Control group; CS. Cryptogenic ischemic stroke; ER. Extended-release; mg. milligram; mm. millimetre; mo. Month; PFO. Patent foramen ovale; PTE. Peripheral thromboembolic event; TE. transesophageal echocardiography; TIA. transient ischemic attack; yr. year. For acronyms see text.

**Table 2.** Data concerning patients enrolled in each study

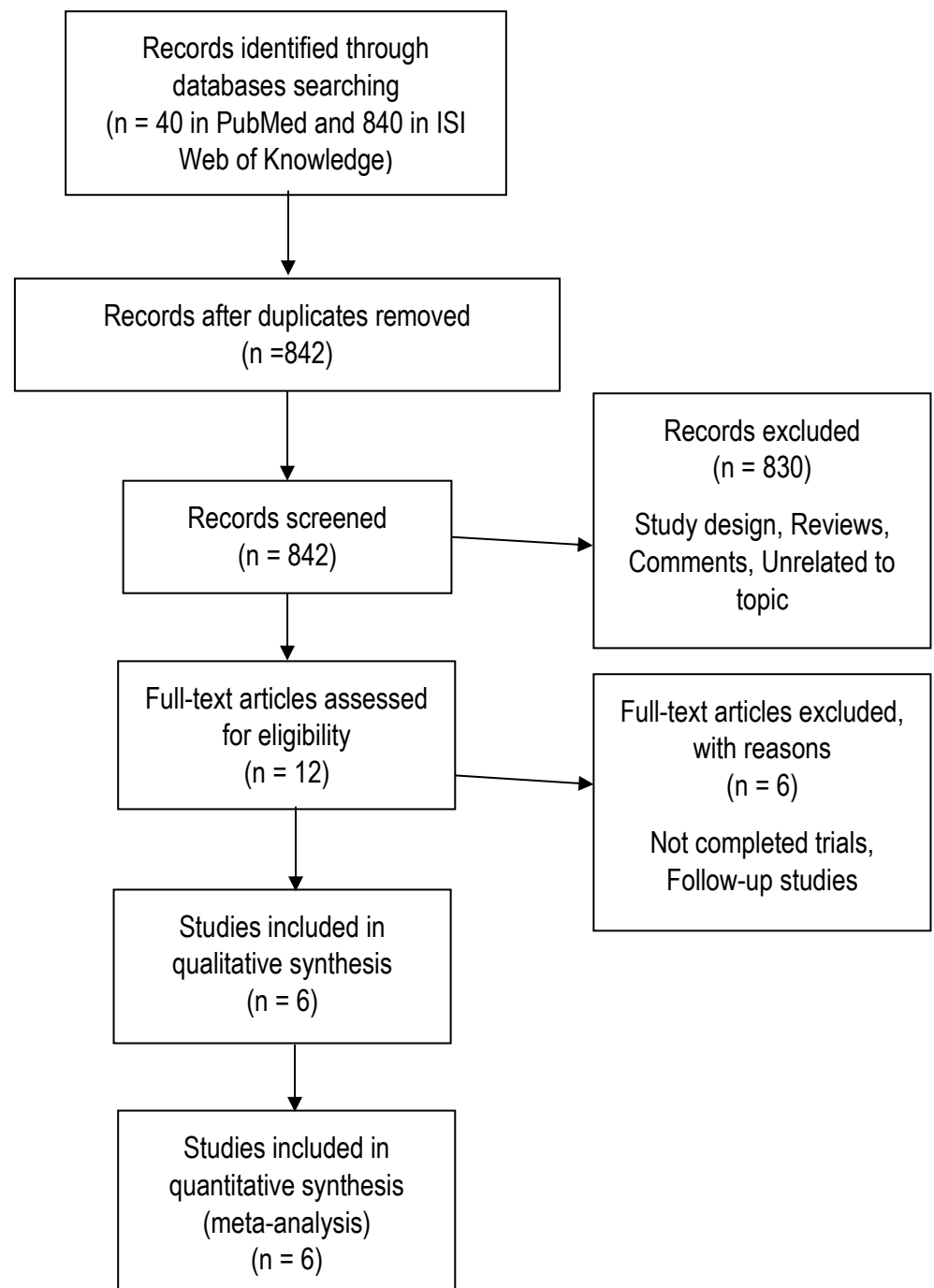
Study	Number of patients		Mean age (years)		Dropouts (number of patients)		Serious Adverse events (%)	
	Closure	Control	Closure	Control	Closure	Control	Closure	Control
<b>CLOSURE</b> 1	447	462	46.3 ± 9.6	45.7 ± 9.1	69	87	16.9	16.6
<b>RESPECT</b>	499	481	45.7 ± 9.7	46.2 ± 10.0	46	83	23.0	21.6
<b>PC TRIAL</b>	204	210	44.3 ± 10.2	44.6 ± 10.1	31	42	21.1	17.6
<b>CLOSE</b>	238	235	42.9 ± 10.1	43.8 ± 10.5	21	12	35.7	33.2
<b>REDUCE</b>	441	223	45.4 ± 9.3	44.8 ± 9.6	39	33	23.1	27.8
<b>DEFENSE</b> PFO	60	60	49 ± 15	54 ± 12	-	-	-	-

Data concerning number of patients, mean age, dropouts and serious adverse events of patients enrolled in each study. For acronyms see text

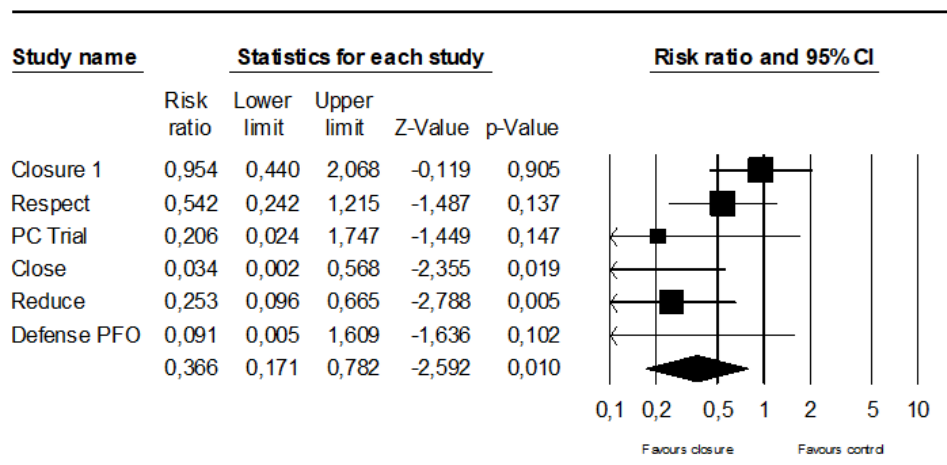
**Table 3.** Efficacy and safety endpoints

Study	Stroke		TIA		AF	
	Closure	Control	Closure	Control	Closure	Control
<b>CLOSURE</b> 1	12(447)	13(462)	13(447)	17(462)	23(402)	3(458)
<b>RESPECT</b>	9(499)	16(481)	6(499)	4(481)	3(499)	3(481)
<b>PC TRIAL</b>	1(204)	5(210)	5(204)	7(210)	6(204)	2(210)
<b>CLOSE</b>	0(238)	14(235)	8(238)	8(235)	11(238)	2(235)
<b>REDUCE</b>	6(441)	12(223)	21(441)	8(223)	29(441)	1(223)
<b>DEFENSE</b> <b>PFO</b>	0(60)	5(60)	0(60)	1(60)	2(60)	0(60)

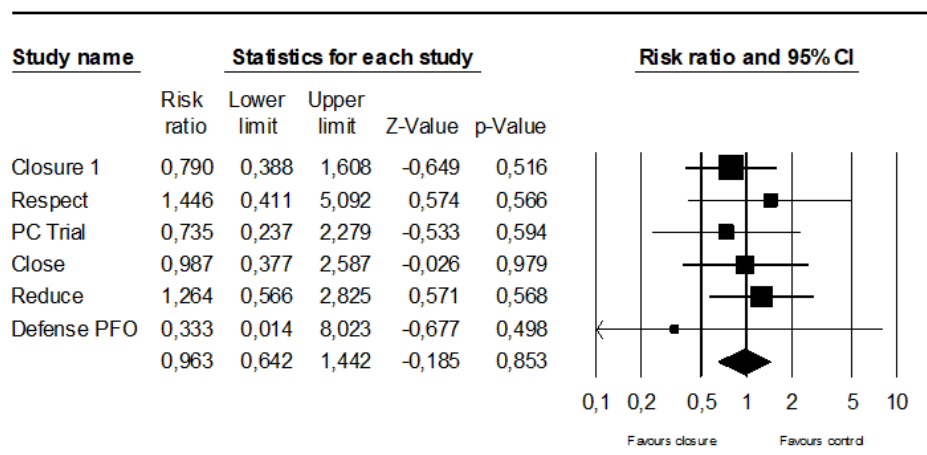
Data concerning stroke, transient ischemic attack (TIA) and atrial fibrillation (AF), in patients involved in trials comparing closure of patent foramen ovale versus medical therapy (total number of patients in brackets). For acronyms see text.



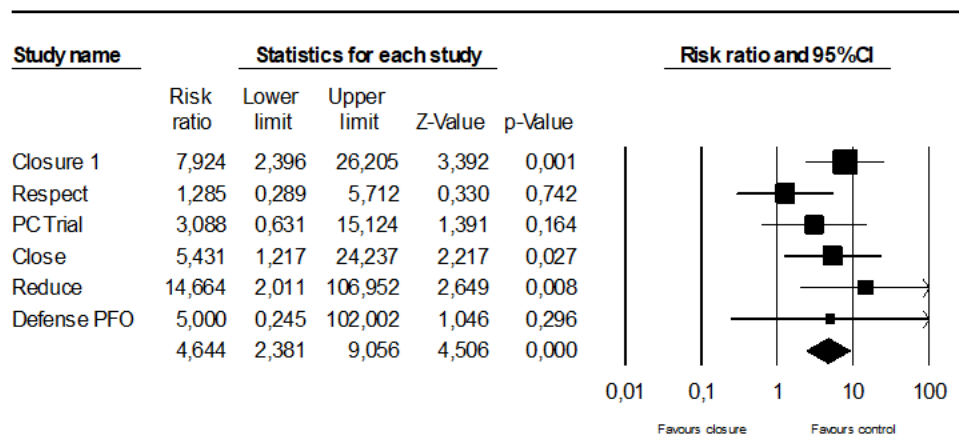
**Figure 1.** Flow Diagram of Studies selection



**Figure 2.** Risk Ratios for recurrent stroke in six major trials. CI confidence interval. For references and trial acronyms see text.



**Figure 3.** Risk Ratios for transient ischemic attack in six major trials. CI confidence interval. For references and trial acronyms see text.



**Figure 4.** Risk Ratios for atrial fibrillation in six major trials. CI confidence interval. For references and trial acronyms see text.

## Supplement 1

### Supplementary file 1.

Search strategy:

1. Medline (PubMed) database - query “patent foramen ovale” AND “stroke” AND “closure” with the filter “clinical trial”.
2. ISI Web of Knowledge - query “patent foramen ovale” AND “stroke” AND “closure” with the filter “article”.

### Supplementary file 2. Article quality assessment

Study	Did the patient(s) represent the whole case(s) of the medical center	Was the diagnosis correctly made	Were other important diagnosis excluded	Were all important data cited in the report	Was the outcome correctly ascertained	Global quality assessment
<b>CLOSURE 1</b>	Yes	Yes	Yes	Yes	Yes	Good
<b>RESPECT</b>	Yes	Yes	Yes	Yes	Yes	Good
<b>PC TRIAL</b>	Yes	Yes	Yes	Yes	Yes	Good
<b>CLOSE</b>	Yes	Yes	Yes	Yes	Yes	Good
<b>REDUCE</b>	Yes	Yes	Yes	Yes	Yes	Good
<b>DEFENSE PFO</b>	Yes	Yes	Yes	No	Yes	Moderate

Article quality assessment according to the method used by Haffar *et al.* For acronyms and complete references see text.

## Supplement 2

**Supplementary Table 1.** Data on risk difference concerning the three outcomes under evaluation

Study	Stroke	TIA	AF
CLOSURE 1	-0.13	-0.77	5.07
RESPECT	-1.52	0.37	-0.02
PC TRIAL	-1.89	-0.88	1.99
CLOSE	-5.96	-0.04	3.77
REDUCE	-4.02	0.95	6.13
DEFENSE PFO	-8.33	-1.67	3.33

Risk difference per 100 patients enrolled in clinical trials comparing foramen ovale closure with medical therapy in patients with ischemic stroke. For acronyms see text.

**Supplementary Table 2.** Data on annualized risk difference concerning the three outcomes under evaluation

Study	Stroke	TIA	AF
CLOSURE 1	-0.06	-0.39	2.53
RESPECT	-0.59	0.14	-0.01
PC TRIAL	-0.47	-0.22	0.50
CLOSE	-1.12	-0.01	0.71
REDUCE	-1.26	0.30	1.91
DEFENSE PFO	-2.98	-0.60	1.19

Annualized risk difference per 100 patients enrolled in clinical trials comparing foramen ovale closure with medical therapy in patients with ischemic stroke. Calculations based on number of years given in each trial for either mean or mean number of years of follow-up. For acronyms see text.

**ANEXO**

# **Manuscript Submission Guidelines: Therapeutic Advances in Cardiovascular Disease**

This Journal is a member of the Committee on Publication Ethics.

This Journal recommends that authors follow the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals formulated by the International Committee of Medical Journal Editors (ICMJE).

All articles are listed on PubMed.

Please read the guidelines below then visit the Journal's submission site <http://mc.manuscriptcentral.com/tac> to upload your manuscript. Please note that manuscripts not conforming to these guidelines may be returned. Remember you can log in to the submission site at any time to check on the progress of your paper through the peer review process.

Only manuscripts of sufficient quality that meet the aims and scope of Therapeutic Advances in Cardiovascular Disease will be reviewed.

As part of the submission process you will be required to warrant that you are submitting your original work, that you have the rights in the work, that you are submitting the work for first publication in the Journal and that it is not being considered for publication elsewhere and has not already been published elsewhere, and that you have obtained and can supply all necessary permissions for the reproduction of any copyright works not owned by you.

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If your paper is accepted, you must include a link on your preprint to the final version of your paper.

#### Further information

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There will be no article processing charge (APC) payable for an introductory period.

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**Review Articles.** These manuscripts are usually commissioned by the Editors, but the following types of high-quality review will be considered:

(a) General reviews that provide a synthesis of an area that fits within the aims and scope of the journal;

(b) Perspective reviews – review articles that address important new areas of general interest and afford the author the opportunity to present a forward-looking perspective on the topic;

(c) Drug reviews – review articles focusing on the available evidence for the use of a particular drug or combination therapy.

Systematic Reviews – these should answer a specific research question and be reported according to the PRISMA guidelines. They should also include a PRISMA flow chart as a cited figure and a completed PRISMA checklist as a supplementary file (please see section 2.8).

Meta-analyses – these should answer a specific research question and be reported according to the PRISMA guidelines. They should also include a PRISMA flow chart as a cited figure and a completed PRISMA checklist as a supplementary file (please see section 2.8).

Case Reports – these structured reports should describe an unusual case and include a full review of the pertinent literature and a section on implications for clinical care.

Case Series – these descriptive structured reports (which do not involve formal hypotheses or pre-specified methodology or analyses) of a small group of patients should include a full review of the pertinent literature and a section on implications for clinical care.

Study Protocols – these can be for forthcoming or ongoing research. Information on trial registration (where applicable) and ethics approval should be included in the manuscript.

Letters to the Editor – these brief opinion pieces should be as concise as possible, usually no more than 1000 words.

The journal considers the results of rigorous, well-designed studies that demonstrate “no effect” or that fail to replicate previous work (“negative data”) as important to the advancement of science.

Therapeutic Advances in Cardiovascular Disease welcomes short reports on null or negative results as long as the papers are based on strong hypothesis testing.

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Made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data,

Drafted the article or revised it critically for important intellectual content,

Approved the version to be published,

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Authors should meet the conditions of all of the points above. When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship.

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It is the policy of Therapeutic Advances in Cardiovascular Disease to require a declaration of conflicting interests from all authors enabling a statement to be carried within the paginated pages of all published articles.

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For research articles, authors are also required to state in the methods section whether participants provided informed consent and whether the consent was written or verbal.

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#### 4.8 Reporting guidelines

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# **Apêndice**

Checklist according to the PRISMA statement (<http://www.prisma-statement.org/>).

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Report identified in the sub-title as a meta-analysis.	1
<b>ABSTRACT</b>			
Structured summary	2	Structured summary provided; not all aspects of the checklist are included due to space limitations.	2
<b>INTRODUCTION</b>			
Rationale	3	Rationale for the review in the context of what is already known is described.	3
Objectives	4	An explicit statement of questions being addressed is included in the introduction, including the type of study to be included in the literature search – randomized controlled clinical trials addressing the issue of interest.	3
<b>METHODS</b>			
Protocol and registration	5	No registered review protocol exists.	N/A
Eligibility criteria	6	Study characteristics, report characteristics and criteria for eligibility are specified.	4
Information sources	7	Information sources are described, as well as date of search.	4
Search	8	Full electronic search strategy for one database is presented.	4
Study selection	9	The process for selecting studies is stated.	4
Data collection process	10	Method of data extraction from reports is described.	4

Data items	11	All variables for which data were sought are listed and defined.	4
Risk of bias in individual studies	12	<p>No methods were used for assessing risk of bias of individual studies, since the reports were considered of high quality, published in highly prestigious peer-reviewed journals. Each individual study was evaluated by the authors.</p> <p>The set of articles selected for analysis corresponds to the sets chosen by other authors that have carried out similar analysis, with one exception, as explained in the text.</p> <p>A limitation of the present report is that different clinical trials used different methods to select patients. This was an intentional deviation from earlier studies that some more recent authors deliberately chose to carry out, in order to try and select patients concerning whom the intervention under study could be more favorable.</p> <p>The matter is discussed in the text, including in the section on limitations.</p>	N/A
Summary measures	13	The principal summary measures are stated.	5
Synthesis of results	14	Methods of handling data are described.	N/A
Risk of bias across studies	15	See comment on topic 12, above.	N/A
Additional analyses	16	No additional analyses were carried out.	N/A
<b>RESULTS</b>			
Study selection	17	Number of studies screened, assessed for eligibility, and included in the review, with a flow diagram, are given.	5 Figure 1
Study characteristics	18	Characteristics for which data were extracted are presented for each study.	5-6 Tables 1 and 2

Risk of bias within studies	19	See comment on topic 12, above.	N/A
Results of individual studies	20	For each study, a summary data and effect estimate, and confidence intervals are presented for each outcome considered.	6 Table 3
Synthesis of results	21	Results of each meta-analysis done, including confidence intervals, are presented.	Figures 2, 3 and 4
Risk of bias across studies	22	See comment on topic 12, above.	N/A
Additional analysis	23	Data on risk difference and annualized risk difference concerning the three outcomes under evaluation	Supplement 2
<b>DISCUSSION</b>			
Summary of evidence	24	The main findings were summarized.	7-8
Limitations	25	Limitations of the study are discussed.	8-9
Conclusions	26	A general interpretation of the results is provided.	9
<b>FUNDING</b>			
Funding	27	No funding was received.	9

N/A - not applicable