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Recurrent Stroke Reduction with Patent Foramen Ovale Closure versus Medical Therapy Based on Patent Foramen Ovale Characteristics: A Meta-Analysis of Randomized Controlled Trials

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Keywords
Cryptogenic stroke · Patent foramen ovale · Device closure · Medical therapy

Abstract
Efficacy of patent foramen ovale (PFO) closure in patients with cryptogenic stroke remains a matter of debate. We performed a comprehensive meta-analysis of available randomized controlled trials (RCTs) to evaluate the efficacy and safety of PFO closure versus medical therapy (MT) based on PFO characteristics. Random-effects meta-analysis was conducted to estimate risk ratio (RR) with 95% confidence intervals (CI) for the primary end points of stroke. After systematic search, six RCTs (3,747 patients) with 1,889 patients randomized to PFO closure and 1,858 patients randomized to the MT group were included in the meta-analysis. Overall, PFO closure was associated with a significant reduction in recurrent stroke compared to MT [RR 0.41; 95% CI 0.20–0.83]. While there were no differences in mortality or major bleeding between the two groups, risk of newly diagnosed atrial fibrillation was higher in the PFO closure group compared to MT [RR 5.29; 95% CI 2.32–12.06]. Further, risk reduction in stroke with PFO closure was significant in patients with high-risk PFO characteristics [RR 0.37; 95% CI 0.16–0.87] but not in low-risk patients [RR 0.73; 95% CI 0.29–1.84]. In conclusion, among patients with cryptogenic stroke, PFO closure is associated with a significantly reduced risk of recurrent stroke compared to MT. Additionally, the benefit of PFO closure might be dependent on certain PFO characteristics.

Introduction

Cryptogenic stroke or stroke of unclear etiology accounts for approximately 25% of ischemic stroke burden [1, 2]. Patent foramen ovale (PFO) is a potential mechanism associated with paradoxical embolism among patients with cryptogenic stroke [3]. Accordingly, transcatheter closure of PFO has been hypothesized to reduce the risk of recurrent stroke in such patients [4].

Previously published randomized controlled trials (RCTs) comparing percutaneous transcatheter PFO closure to medical therapy (MT) failed to demonstrate a sig-

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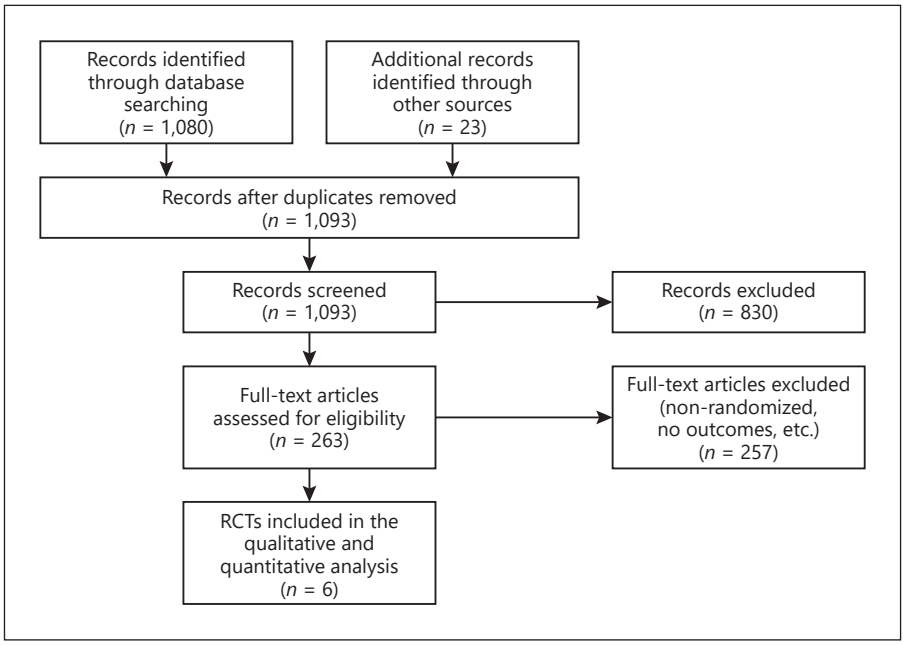

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses – flow sheet.

nificant reduction in stroke recurrence [5–7]. However, the recently reported extended follow-up of RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) and three new trials have shown a significant risk reduction in recurrent stroke with PFO closure [8–11]. Discrepant results between trials might be attributable to differences in patient selection and/or devices used for PFO closure. As such, individualized management of patients with cryptogenic stroke and PFO still remains challenging. Therefore, we performed an updated meta-analysis to study the cumulative evidence for safety and efficacy of PFO closure versus MT for stroke prevention.

Methods

We carried out a literature search using MEDLINE, EMBASE, Web of Science, and Cochrane databases of all studies published between January 1, 1990, and April 30, 2018, reporting on direct comparisons between PFO closure devices versus MT after cryptogenic stroke. We used the MeSH search headings "Cryptogenic stroke," "Stroke," "Patent foramen ovale closure," "Medical therapy," and "Recurrent" in different combinations. The review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [12].

The following criteria were applied for study inclusion: (1) RCTs comparing PFO device closure versus MT (antiplatelet or anticoagulation) in patients with cryptogenic stroke; (2) published in peer-reviewed journals; and (3) reporting at least one clinical end point based on treatment approach. Exclusion criteria were: (1) non-randomized study design and (2) non-published studies.

Two reviewers (M.T. and A.G.) independently screened the study reports for eligibility, assessed risk of bias, and collected data from each eligible study using predetermined forms. From eligible RCTs, we collected information on study characteristics (study design, year of publication, inclusion and exclusion criteria, data source, sample size, follow-up period, and primary and secondary end point definitions), baseline patient characteristics (including PFO characteristics), treatment data, and event rate of end points.

Primary end point of interest was recurrent stroke. We also compared the following secondary end points: transient ischemic attack, all-cause death, major bleeding, and newly detected atrial fibrillation (AF). End points were defined as per individual trial protocol.

Meta-analyses were conducted according to recommendations from the Cochrane Collaboration using Review Manager, version 5.3 [12]. For each clinical end point, pooled risk ratio (RR) and 95% confidence interval (CI) were calculated using random-effects models with the Mantel-Haenszel method. A p value <0.05 was assigned as the measure of statistical significance. Heterogeneity between studies was calculated using I^2 statistic. Heterogeneity was considered significant in case of $I^2 >50\%$. Forest plots were generated to show the relative effect size of PFO device closure for individual clinical end points.

We also performed meta-analyses of end point of stroke stratified by shunt size (moderate to large vs. trace/small), presence or absence of aneurysm, and medications (antiplatelet vs. anticoagulation drugs). Based on these subgroup analyses, we pooled stroke events by stratifying the patient population from the eligible RCTs into "high-risk" and "low-risk" PFO features. High-risk PFO was defined either as per trial protocol or in the presence of certain characteristics associated with increased risk of

Table 1. Baseline characteristics of included studies

	DEFENSE PFO (2018) [11]	CLOSE (2017) [9]	RESPECT (2017) [8]	REDUCE (2017) [10]	PC (2013) [7]	CLOSURE (2012) [5]
Inclusion criteria	Ischemic stroke, associated ASA, or large shunt	16–60 years; ischemic stroke within 6 months, associated ASA, or large shunt	18–60 years; ischemic stroke within 9 months, associated ASA, or moderate to large shunt	18–59 years; ischemic stroke within 6 months, associated ASA, or any size shunt	<60 years; ischemic stroke, TIA, or peripheral thromboembolism, any size shunt	18–60 years; ischemic stroke or TIA within 6 months, any size shunt
Exclusion criteria	Other mechanism of stroke, history of MI, pre-existing neurological disorder or malignancy	Other mechanism of stroke, hypercoagulable states atherosclerotic stenosis >30%	Other mechanism of stroke, hypercoagulable states including inherited thrombophilias; history of MI, uncontrolled HTN, DM, organ failure	Other mechanism of stroke, hypercoagulable states, history of MI, uncontrolled DM, HTN	Other mechanism of stroke, hypercoagulable states, severe CNS disease	Other mechanism of stroke, hypercoagulable states including inherited thrombophilias, history of MI, organ failure
Size, *n* (PFO closure/MT)	120 (60/60)	660 (238/422)	980 (499/481)	664 (441/233)	414 (204/210)	909 (447/462)
Randomization (PFO closure:MT)	1:1	1:1:1[a]	1:1	2:1[b]	1:1	1:1
Intervention	PFO closure with aspirin, DAPT, warfarin at the discretion of site	PFO closure with DAPT for 3 months, then single AP for rest of trial	PFO closure with DAPT for 1 months, then aspirin for 5 months, then AP at the discretion of site	PFO closure with clopidogrel for 3 days followed by an AP for rest of trial	PFO closure with DAPT: aspirin (100–325 mg) + triclodipine or clopidogrel for 1–6 months	PFO closure with DAPT: aspirin (81–325 mg) + clopidogrel for 6 months then aspirin for 18 months
PFO device	Amplatzer	Multiple (Amplatzer 51.5%)	Amplatzer	HELEX or Cardioform	Amplatzer	STARFlex
Medical therapy	Aspirin, aspirin + clopidogrel, aspirin + cilostazol, warfarin	AC: vitamin K antagonist (INR 2–3) or DOAC. AP: aspirin or clopidogrel or aspirin + dipyridamole for rest of trial	Aspirin, clopidogrel, warfarin, or aspirin + DIPYRIDAMOLE	Aspirin (75–325 mg), aspirin + dipyridamole, or clopidogrel	Discretion of treating physician, at least one antithrombotic drug	Warfarin (INR 2–3), aspirin (325 mg), or both
Primary outcome	Composite of stroke, vascular death, TIMI major bleeding	Fatal or nonfatal stroke	Composite of recurrent nonfatal stroke, fatal stroke, or early death	Clinical stroke and new brain infarction	Composite of death, nonfatal stroke, TIA, or peripheral embolism	Composite of stroke or TIA, death from any cause, death from neurological cause
Follow-up, years	2.8	5.3	5.9	3.2	4.0	2.0
Mean age, years	51.5	43.5	45.9	45.2	44.5	46.0
Male sex, %	55.8	57.6	54.7	60.1	49.8	51.8
DM, %	11.7	2.1	7.6	4.2	2.7	7.8
HTN, %	24.2	10	31.9	25.6	25.8	31
Smoking, %	21.7	28.9	13.3	13.3	23.9	15.2
Large shunt, %	57.5	92.7	48.8	39.3	21.7	20.8
ASA, %	10.8	34.7	35.7	20.4	23.7	36.6

CLOSE: Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; RESPECT: Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; PC: Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; CLOSURE 1: 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.

AC: anticoagulation; AP: antiplatelet; ASA: atrial septal aneurysm; CNS: central nervous system; DAPT: dual antiplatelet therapy; DM: diabetes mellitus; HTN: hypertension; INR: international normalized ratio; MI: myocardial infarction; MT: medical therapy; PFO: patent foramen ovale; TIA: transient ischemic attack; TIMI: thrombolysis in myocardial infarction.

[a] PFO closure:AP alone:AC. [b] PFO closure:AP.

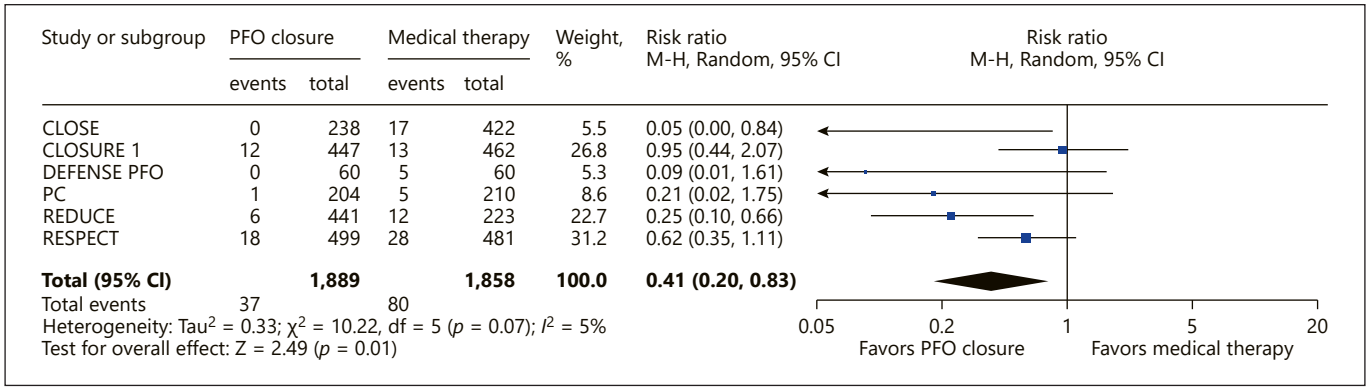

Fig. 2. Forest plot for primary end point of stroke. OR, odds ratio; CI, confidence interval.

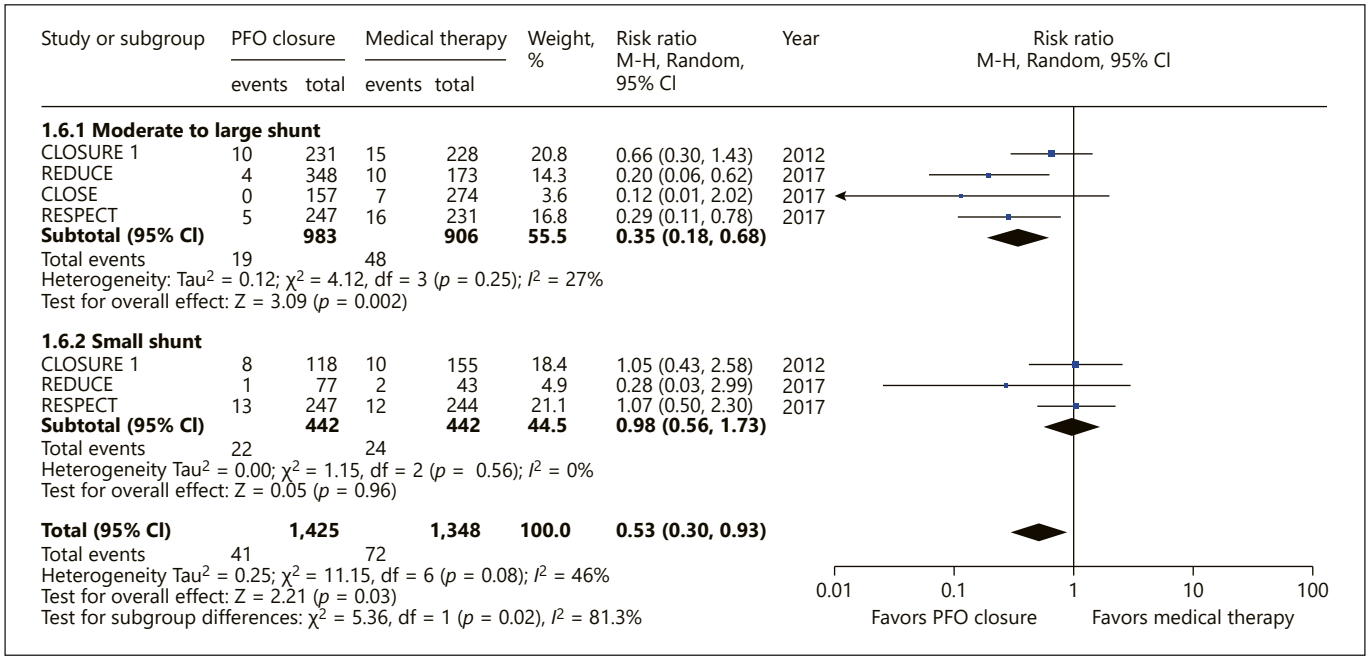

Fig. 3. Forest plot for stroke in moderate to large versus mild shunt. OR, odds ratio; CI, confidence interval.

stroke. These included either atrial septal aneurysm (septal excursion of at least 10 mm) or at least moderate to large shunt. Low-risk PFO was defined as those with a small shunt in the absence of septal aneurysm. Shunt size was defined by trials variably on the basis of number of agitated saline bubbles crossing the septum to the left side. For example, in the REDUCE and CLOSE (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence) trials, large shunt was defined respectively as at least 25 and 30 bubbles appearing in the left atrium. Finally, in case of significant heterogeneity, sensitivity analyses were performed by excluding individual studies to test the influence of single trials.

Results

As shown in Figure 1, the initial search identified 1,093 publications. Through a review of titles and abstracts, 830 studies were rejected for relevance. The remaining 263 articles were reviewed and assessed for satisfaction of the inclusion and exclusion criteria. After full-text review, six RCTs with 3,747 patients were selected for inclusion in the final analysis [5–7, 9–11]. These included 1,889 patients who were randomized to PFO device closure and 1,858 patients randomized to MT.

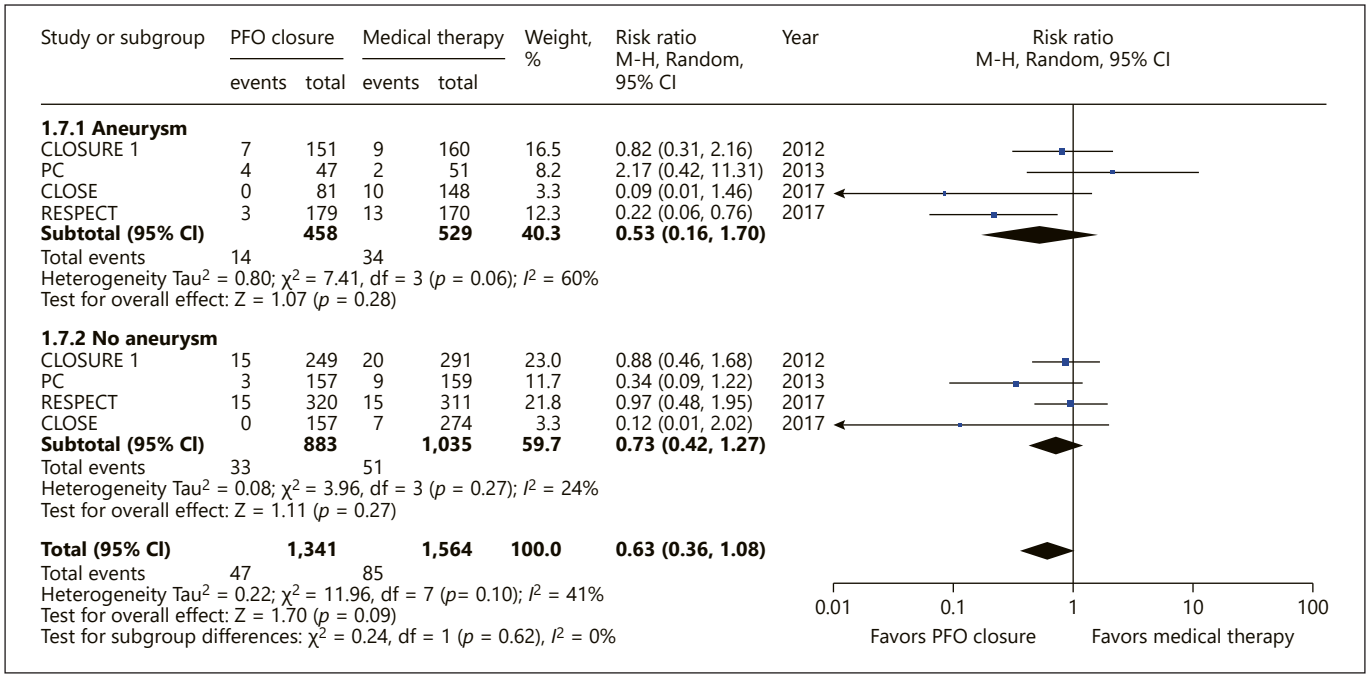

Fig. 4. Forest plot for stroke with aneurysm versus no aneurysm. OR, odds ratio; CI, confidence interval.

Study characteristics were fairly homogeneous for inclusion and exclusion criteria with a few key differences (Table 1). Baseline patient characteristics among the included studies are described in Table 1. There was some heterogeneity between trials in terms of medication use (Table 1). In the PFO arm, four trials used dual antiplatelet therapy for a variable duration (1–6 months), whereas the other two trials used either single antiplatelet therapy or left it at the physician's discretion. Details of medication use in the MT group of individual RCTs are provided in Table 1. Device use in the PFO closure arm of the different RCTs was as follows: Amplatzer device (three trials), Gore septal occluder (one trial), STARFlex device (one trial), and multiple device types (one trial). The patients were followed for a mean period of 3.9 years (interquartile range: 2–5.9 years). Mean age of the patients was 46 years, and 55% were male.

Stroke

The primary end point of stroke was reported in six RCTs (3,747 patients), with an event rate of 2% in the PFO closure group and of 4.3% in the MT group. There was a significant reduction in the risk of recurrent stroke in the closure arm compared to MT (RR 0.41; 95% CI 0.20–0.83), with mild heterogeneity ($I^2 = 51\%$) among the studies (Fig. 2). In a sensitivity analysis, the heterogeneity was no longer significant after the exclusion of the CLOSURE 1 (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) trial (RR 0.30; 95% CI 0.13–0.68; $I^2 = 43\%$).

Four trials reported subgroup analyses based on shunt size and the presence of aneurysm. Pooled estimates of the RCTs showed a significant reduction in stroke in patients with moderate to large shunt (RR 0.35; 95% CI 0.18–0.68), while such an association was lacking in patients with small shunt (RR 0.98; 95% CI 0.56–1.73) (Fig. 3). When assessed for aneurysm, there was only a nonsignificant trend towards a reduction in stroke with PFO closure regardless of the presence or absence of aneurysm with no significant interaction between subgroups (Fig. 4). Further, treatment effect of PFO closure was differential based on medication type; it was associated with a significant stroke reduction when compared to antiplatelet therapy (RR 0.39; 95% CI 0.17–0.87) but not when compared to anticoagulation (RR 0.74; 95% CI 0.20–2.71) (Fig. 5).

Consistent with the above results, compared to MT, PFO closure was associated with a significant risk reduction in stroke in the high-risk (RR 0.37; 95% CI 0.16–0.87) but not in the low-risk PFO group (RR 0.80; 95% CI 0.46–1.42) (Fig. 6).

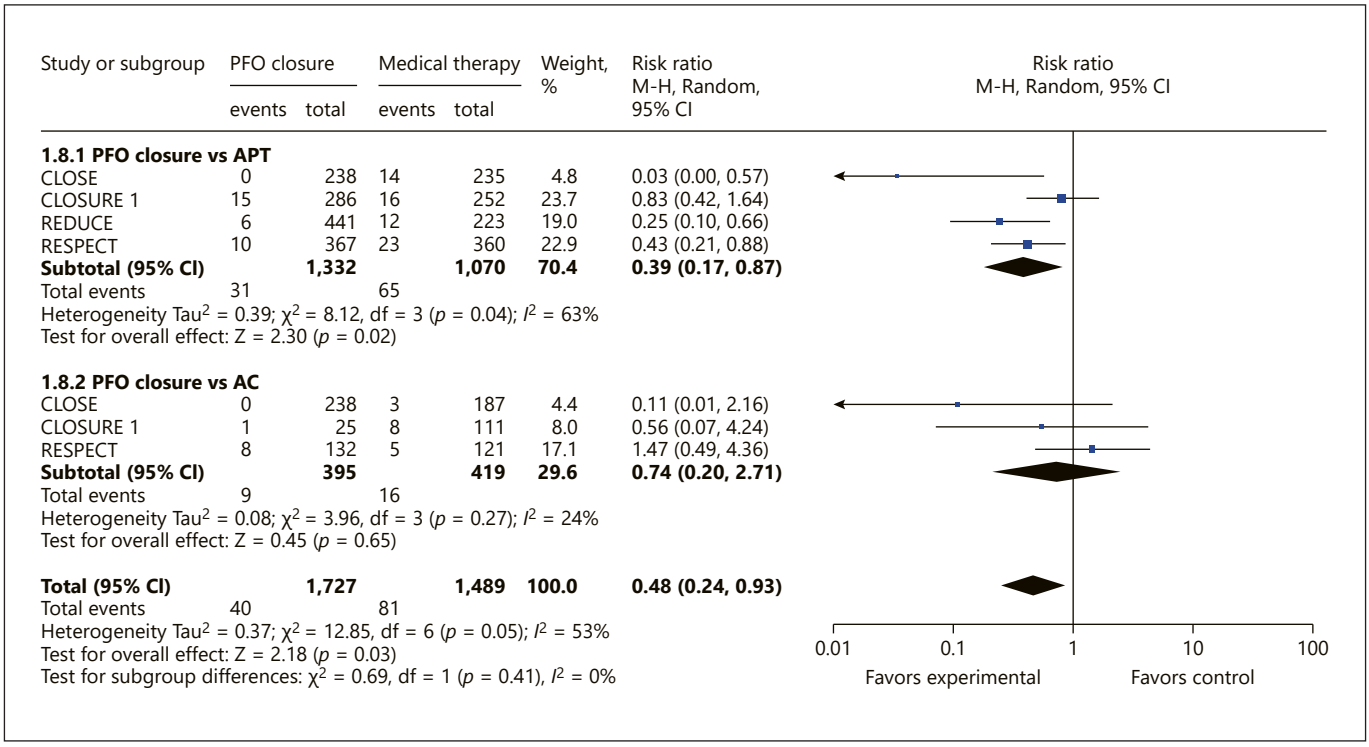

Fig. 5. Forest plot for stroke with antiplatelets versus anticoagulation. OR, odds ratio; CI, confidence interval.

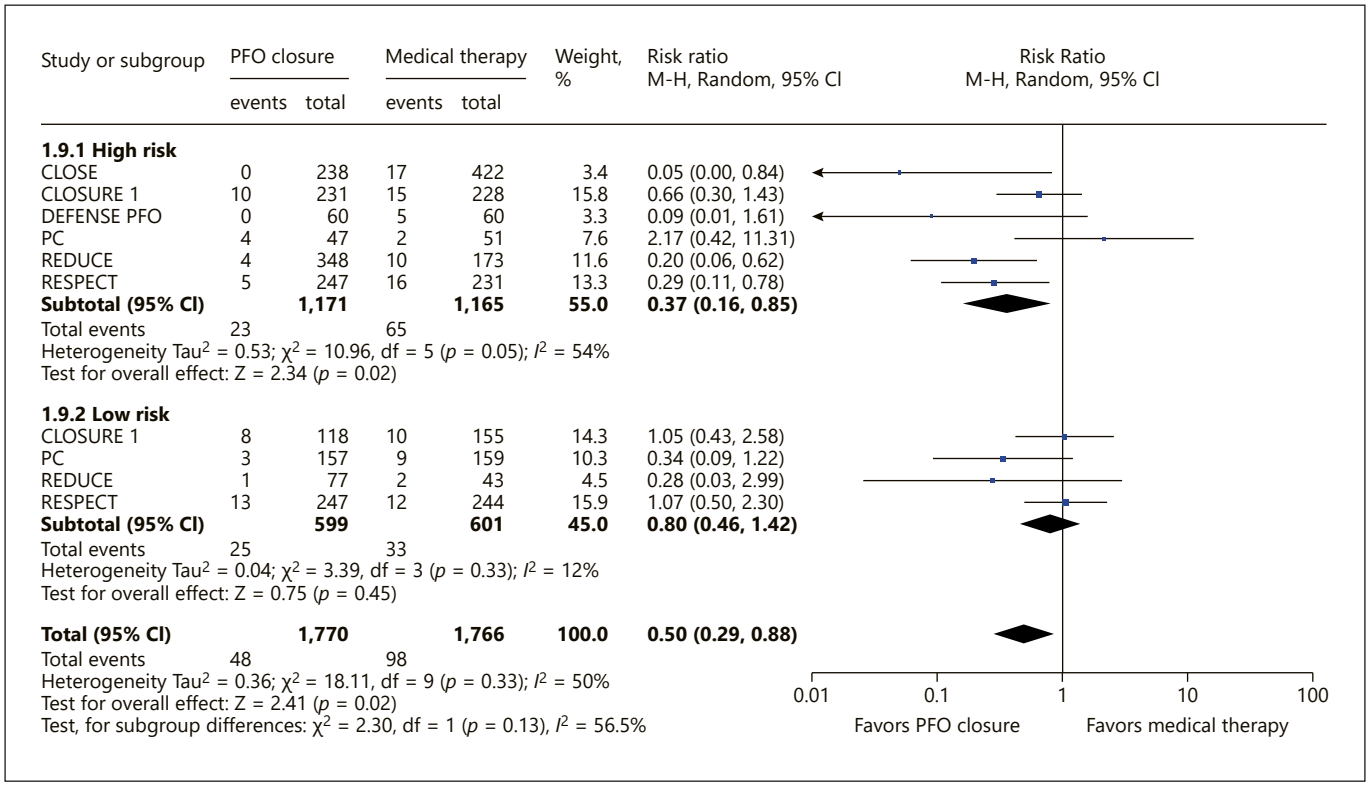

Fig. 6. Forest plot for stroke in high-risk versus low-risk groups. OR, odds ratio; CI, confidence interval.

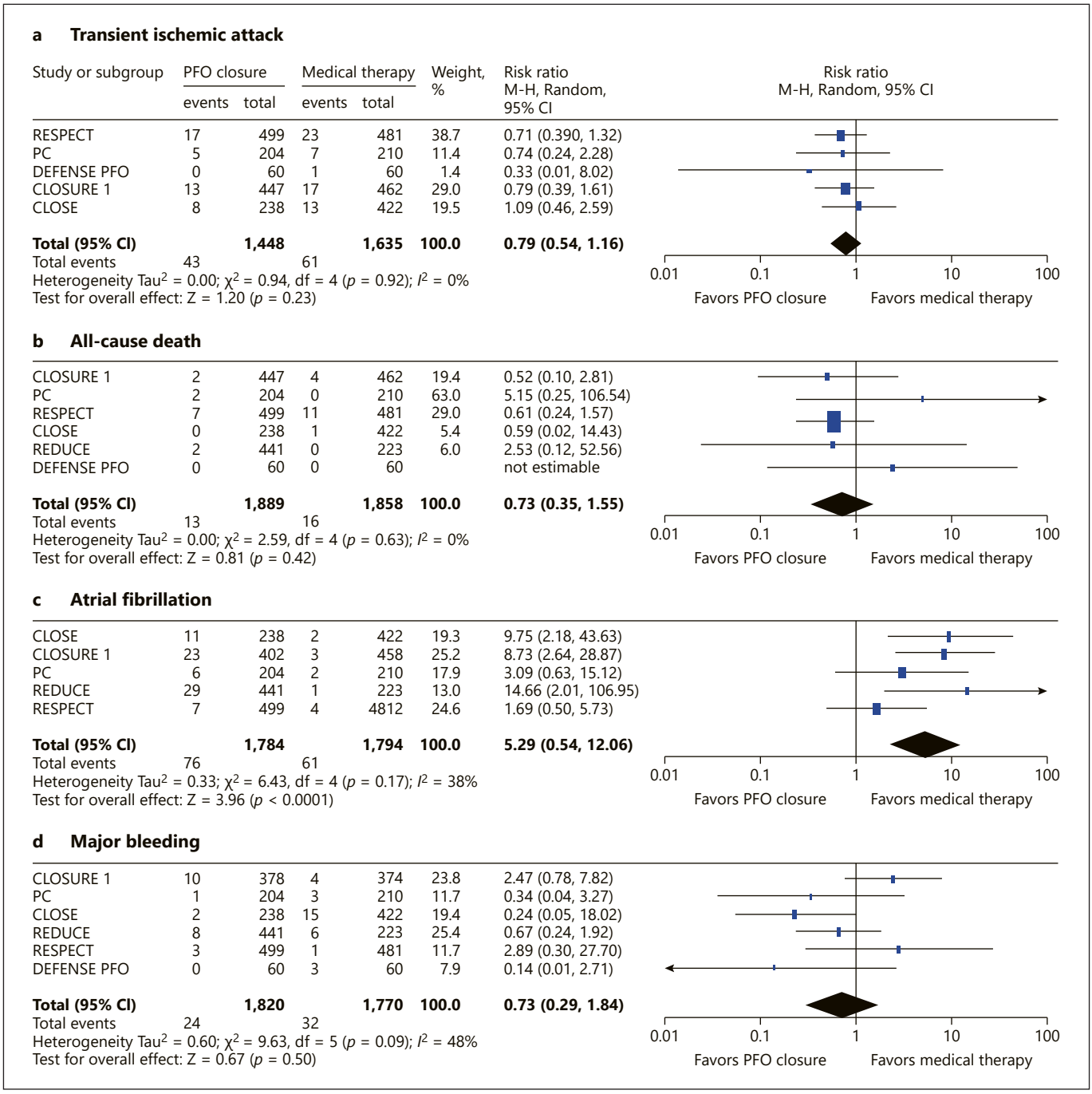

Fig. 7. Forest plot for transient ischemic attack (**a**), all-cause death (**b**), atrial fibrillation (**c**), major bleeding (**d**). OR, odds ratio; CI, confidence interval.

Secondary End Points

There were no significant differences between PFO closure and MT in terms of transient ischemic attack (RR 0.79; 95% CI 0.54–1.16; $p = 0.23$) and all-cause death (RR 0.73; 95% CI 0.35–1.55) (Fig. 7). Among five studies, PFO closure was associated with a significantly higher risk of AF compared to MT (RR 5.29; 95% CI 2.18–43.63) (Fig. 7). Finally, there was no significant difference between the two groups in terms of major bleeding (RR 0.73; 95% CI 0.29–1.84) (Fig. 7).

Discussion

Our meta-analysis of six trials including over 3,700 patients with cryptogenic stroke demonstrates a significant reduction in risk of recurrent stroke with PFO closure compared to MT. While there were no differences in risk of mortality or major bleeding, new onset AF appeared to be more common in patients undergoing PFO closure compared to MT. Further, there was significant interaction between shunt size and risk reduction in stroke with PFO closure versus MT.

Our findings consolidate the results of previous RCTs comparing device closure and MT for cryptogenic stroke [5–11]. In the long-term follow-up of the RESPECT trial, the authors found a significant 45% relative risk reduction in stroke at a mean follow-up of 5.9 years [8]. Similarly, the CLOSE and Gore REDUCE trial investigators reported a significant reduction in recurrent stroke with device closure when compared to antiplatelet therapy [9, 10]. Contrarily, two earlier trials, PC (Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) and CLOSURE 1 had failed to demonstrate a significant reduction in stroke or mortality with device therapy [5, 7]. Whereas, an individual patient-level-pooled analysis of these older trials suggested a reduction in stroke events with PFO closure [13].

We performed this meta-analysis to reconcile the contrasting results of these published studies. Our meta-analysis comprising six RCTs, which is the largest to date, reaffirms significant benefit of device closure in patients with PFO and cryptogenic stroke. Earlier trials were limited by low power and/or follow-up duration for the detection of any reduction in recurrent strokes with PFO closure compared to MT [5, 7]. Furthermore, contrasting findings between the earlier and new clinical trials could be explained by differences in patient selection and medication use. The Gore REDUCE and DEFENSE-PFO trials had more stringent criteria to exclude other pathologies (small vessel disease, hypercoaguable state, large vessel atherosclerosis, or cardiac emboli) prior to randomization [10, 11].

Importantly, patient selection in terms of PFO morphological characteristics might also play a role in the magnitude of potential benefit observed with device closure in newer studies [14]. While prior meta-analyses of five RCTs have shown benefit of PFO closure in reducing recurrent strokes, relative event risk based on stratification by different PFO characteristics has not been assessed [15–18]. Similarly, several meta-analyses comprising six RCTs and comparing stroke risk with PFO closure versus MT have been recently published; however, none of them studied the relative benefit in patients with high-risk versus low-risk PFO as described before [19–26]. In line with the CLOSE and DEFENSE-PFO trials, we performed subgroup analysis based on "high-risk" PFO characteristics such as septal aneurysm or large shunt [9, 11]. Our results are in consistence with subgroup analyses of the RESPECT trial that showed greater benefit in stroke reduction in patients with these PFO features [8]. Contrary to the same trial, we did not observe a significant interaction between presence or absence of atrial septal aneurysm and stroke reduction with PFO closure in our analysis. However, presence of septal aneurysm has been shown to be predictive of recurrent stroke in patients with PFO [27]. Heterogeneity between trials in terms of definitions and/or co-existence of aneurysm and moderate to large shunt in many patients provides a plausible explanation of our results.

Another finding that deserves mention is the potential efficacy of PFO closure in reducing stroke when testing against different antithrombotic treatments. Similar to the results of a previous trial, our analysis re-enforces that PFO closure is superior to antiplatelet therapy, whereas benefit in comparison with anticoagulation remains less conclusive [8, 9]. Of note, reflecting current guidelines, previous studies have failed to establish superiority of anticoagulation over antiplatelets for stroke reduction in patients with PFO [28, 29]. Finally, AF was significantly higher in patients undergoing PFO closure compared to MT as also noticed in previous meta-analyses [17]. The timeline of detection of AF (majority within 4 weeks of PFO closure) from several trials has suggested that the procedure itself might be associated with increased risk of transient AF [7, 9]. Nevertheless, further research is needed to evaluate patient- and procedure-related predictors of AF after PFO closure, long-term incidences of recurrent AF, and its association with stroke.

Limitations

One of the major limitations of our study is the heterogeneity between trials in the use of antithrombotic treatment in the MT group. While previous trials allowed either antiplatelet or anticoagulation use at the discretion of physicians, the CLOSE and Gore REDUCE trials tested device closure against antiplatelet medications in accordance with current practice. Henceforth, given the findings of our analysis as well as paucity of RCT data relating to effect of anticoagulation in cryptogenic stroke with PFO, further research is needed to investigate if anticoagulation could be a possible alternative to closure in se-

lected patients. Second, trials differed in terms of device type used for PFO closure, which might also explain some heterogeneity observed for the end point of stroke. Indeed, sensitivity analysis revealed no heterogeneity after exclusion of the CLOSURE 1 trial that used a device associated with high rates of thrombosis. Third, paroxysmal occult AF can be associated with stroke, yet none of the trials mandated use of prolonged monitoring to exclude this as a possible etiology. Fourth, individual studies differed slightly in terms of trial design, follow-up duration, and definitions of end points. Finally, our study is based on aggregate trial-level data and lacks patient-level data. This precluded us from performing further subanalyses or adjusted analyses for other baseline characteristics (e.g., age, gender, RoPE score, etc.).

Conclusion

Our meta-analysis confirms superior efficacy of device closure over MT for stroke reduction in patients with cryptogenic stroke and PFO. Careful evaluation for high-risk PFO characteristics might improve patient selection and enhance benefit of transcatheter closure. Further research is necessary to investigate the significance of post-closure AF as well as the role of anticoagulation in selected patients with stroke and PFO.

Disclosure Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

Aakash Garg and Mohammed Thawabi were involved in the study design, data collection, statistical analyses, and manuscript preparation. Amit Rout and Chris Sossou were involved in the data analysis and table and figure preparation. Marc Cohen and John B. Kostis were involved in the manuscript preparation and revision.

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