American Heart Journal 199 (2018) 44–50

Contents lists available at ScienceDirect

American Heart Journal

Clinical Investigations

Transcatheter closure of patent foramen ovale following cryptogenic stroke: An updated meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 16 January 2018
Accepted 16 January 2018
Available online xxxx

ABSTRACT

Background: Transcatheter closure of patent foramen ovale (PFO) after cryptogenic stroke has long been a contentious issue. Herein, we pool aggregate data examining safety and efficacy of transcatheter closure of PFO compared with medical therapy following initial cryptogenic stroke.

Methods: We searched for randomized clinical trials (RCT) that compared device closure with medical management and reported on subsequent stroke and adverse events. Stroke was considered as the primary efficacy endpoint, whereas bleeding and atrial fibrillation were considered primary safety endpoints. Data were pooled by the random effects model and I2 was used to assess heterogeneity.

Results: A total of 5 RCT investigating 3630 patients met inclusion criteria. Pooled analysis revealed that device closure compared to medical management was associated with a significant reduction in stroke (RR = 0.3, 95% CI = 0.02–0.57). There was, however, a significant increase in atrial arrhythmias with device therapy (RR = 4.8, 95% CI = 2.2–10.7). We found no increase in bleeding (RR = 0.80, 95% CI = 0.5–1.4), death (RR = 0.76, 95% CI = 0.3–1.99) or "any adverse events" (RR = 1.02, 95% CI = 0.85–1.23) with device therapy. Sub-group analysis revealed that device closure significantly reduced the incidence of the composite primary endpoint among patients who had moderate to large shunt sizes (RR = 0.22, 95% CI = 0.02–0.42).

Conclusions: Transcatheter closure is associated with a significant reduction in the risk of stroke compared to medical management at the expense of an increased risk of atrial arrhythmias.

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Despite extensive evaluation, approximately one third of strokes have no discernible etiology and are referred to as "cryptogenic."[1] Patent foramen ovale (PFO) is identified almost twice as commonly in individuals with cryptogenic stroke compared with matched patients without stroke, suggesting an association between PFO and cryptogenic stroke.[2] Mechanistically, stroke in PFO is believed to occur through paradoxical embolism, where a blood clot traverses the PFO and enters the systemic circulation and eventually occludes part of the cerebral circulation. Prevention of thrombosis through long-term antiplatelet and anticoagulant therapy requires patient compliance and increases bleeding risk. Occlusion of PFO, thereby interrupting the embolic pathway, presents an attractive therapeutic target. The availability of devices designed specifically for occlusion of atrial septal defects and early epidemiological evidence suggesting a significant benefit of closure when compared to medical therapy following cryptogenic stroke, resulted in a considerable number of off-label closures being performed over the past decade. However the recent American Academy of Neurology guidelines state clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting.[3]

Three different randomized controlled trials (RCT) were initially conducted to examine the impact of PFO occlusion on subsequent stroke risk.[4-6] These studies led to the publication of at least 17 systematic reviews and meta-analyses of the impact of device-based PFO closure, each with conflicting results and recommendations.[7-10] To further complicate the matters, stroke guidelines have made transcatheter PFO closure a 2B recommendation,[3] whereas the FDA recently approved the Amplatzer PFO occluder device as first line therapy for patients who experience an initial cryptogenic stroke. Therefore, the transcatheter closure of PFO remains a contentious topic among clinicians.

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https://doi.org/10.1016/j.ahj.2018.01.008
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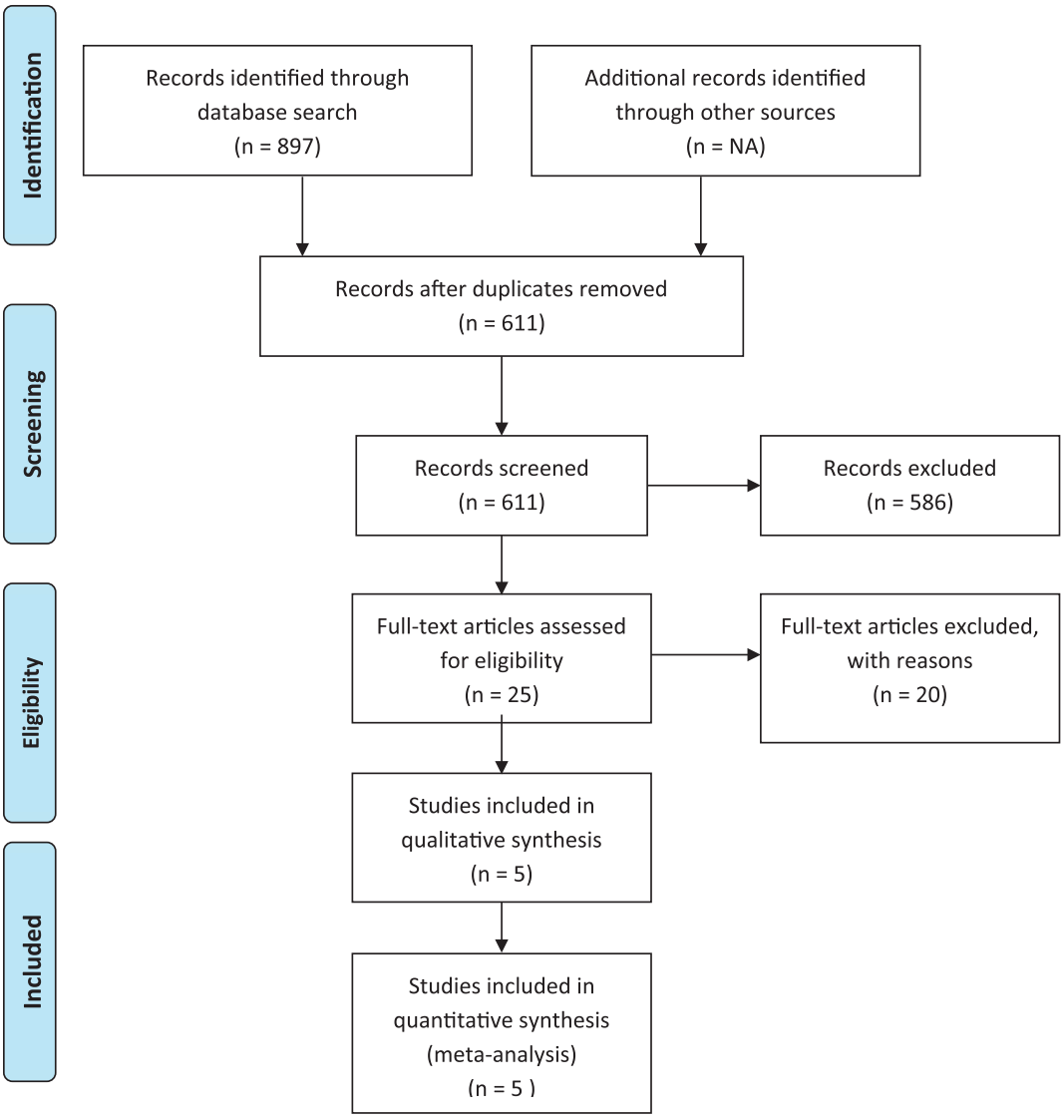

Figure 1. Prisma Chart.

Recently, results from 2 additional well-designed RCT and the extended long-term follow up from a prior RCT comparing device closure of PFO versus medical management were published. To better guide current clinical decision making, we conducted an updated systematic review and meta-analysis of RCT to further address this management conundrum.

Methods

We conducted a systematic review of the literature from the PubMed, Embase and the Cochrane database of controlled trials (CENTRAL) to identify RCT that compared device closure of PFO with medical management. A variety of search terms as medical subject headings (MESH) and keywords were employed including "patent foramen ovale", "PFO", "heart septal defects (atrial)", "inter-atrial shunt", "right to left shunt", "transcatheter closure", "septal occluder device", "cryptogenic stroke", "ischemic stroke", "atrial septal aneurysm", "ASA", "recurrent stroke", "recurrent TIA", "recurrent thromboembolism", "transient ischemic attack" and "TIA". The search was conducted from the inception of these databases until September of 2017. No restriction of language was placed. To ensure no important studies were missed, we also looked for the conference proceedings from the American College of Cardiology, American Heart Association and European Society of Cardiology.

Our systematic review was conducted in accordance with the PRISMA guidelines. Only RCT were included in our analysis. We defined occurrence of stroke as the key primary efficacy endpoint and transient ischemic attack as the secondary efficacy endpoint. We accepted the primary study investigator's definition of stroke or TIA. Atrial tachyarrhythmias, bleeding and death were the safety endpoints of our study. Two independent reviewers extracted and verified the data. A standardized data collection form was used to extract data from each study. In case of any discrepancy, the original reference article was further reviewed and a third reviewer was consulted.

Quality assessment of studies was done as per Cochrane Collaboration's tool for the ascertainment of bias, while publication bias was assessed using funnel plot and Egger's regression symmetry testing. The studies were pooled as per the random-effects model. We defined a-priori that the differences in the device utilized, definition of stroke, comorbidities among patients and specific medical management strategy (anti-platelet agents versus anticoagulation) would account for the clinical heterogeneity of the findings. Statistical heterogeneity across studies was quantified using Cochran x2 and the I2 statistics.

For efficacy endpoints of stroke and TIA, relative risk (RR) was used as a measure of effect. RR< 1 favored device closure. Safety end points that were analyzed included the total number of adverse events, atrial fibrillation, deaths and bleeding events. OR with 95% confidence interval

Table I
Quality assessment.

	CLOSE	REDUCE	RESPECT	PC	CLOSURE
Random sequence generation	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Allocation concealment	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding	Unclear	Unclear	Unclear	Yes	Unclear
Incomplete outcome data	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Selective reporting	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Other bias (ITT analysis)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

Table II
Characteristics of the randomized clinical trials comparing transcatheter closure to medical management.

Trial name	# of patients	Type of device	Centers	Mean follow-up (years)	Primary end point(s)	Secondary end point(s)
CLOSURE	909	STARFlex Septal Closure System	North America	2	Stroke or TIA, all-cause mortality at 30 days, death from neurological cause from day 31 to 2 years	Major bleeding, death from any cause, stroke, TIA, and transient neurologic events of uncertain cause.
PC	414	Amplatzer PFO Occluder	Europe, Canada, Brazil, Australia	4.1	Death, stroke, TIA, peripheral embolism	Cardiovascular death, new arrhythmias (particularly new-onset atrial fibrillation), myocardial infarction, hospitalization related to the patent foramen ovale or its treatment, device problems, and bleeding
RESPECT	980	Amplatzer PFO Occluder	North America	5.9	Fatal or non-fatal ischemic stroke or early mortality	Complete closure of PFO at 6 months, absence of recurrent symptomatic nonfatal ischemic stroke or cardiovascular death, and absence of TIA
CLOSE	663	Multiple devices – investigator choice	France, Germany	5.3	Ischemic stroke	Composite of ischemic stroke, transient ischemic attack or systemic embolism; systemic embolism; all-cause mortality; death from vascular-related causes; success of device implantation and success of PFO closure.
REDUCE	664	Gore Helex; Gore Cardioform	United States, Europe	3.2	Ischemic stroke or new cerebral infarction on imaging	Success of PFO closure and adverse events, classified by the local investigators as serious or not serious

Table III
Baseline demographics of the included studies.

Trial name	Treatment of Control Group	Mean Age (years)	Males (%)	Caucasion (%)	Previous Stroke
CLOSURE	Antiplatelet/Anti-coagulation. Patients assigned to medical therapy were treated with warfarin (with a target international normalized ratio of 2.0 to 3.0), aspirin (325 mg daily), or both, at the discretion of the principal investigator at each site.	46.3/45.7	52.1/51.5	89/89.6	NA
PC	Antiplatelet therapy or oral anticoagulation, provided that patients received at least one antithrombotic drug.	44.3/44.6	45.1/54.3	NA	NA
RESPECT	Aspirin or warfarin or clopidogrel or aspirin combined with extended-release dipyridamole.	45.7/46.2	53.7/55.7	NA	53/51
CLOSE	Anti-platelet only. They could receive could receive aspirin, clopidogrel, or aspirin combined with extended release dipyridamole	42.9/43.8	57.6/60.4	NA	10/7
REDUCE	Antiplatelet therapy could consist of aspirin alone (75 to 325 mg once daily), a combination of aspirin (50 to 100 mg daily) and dipyridamole (225 to 400 mg daily), or clopidogrel (75 mg once daily)	45.4/44.8	59.2/61.9	NA	42/13

*Closure/Medical.

(CI) were used as the common measures of association. All statistical tests were two-sided and used a significance level of $P < .05$.All data were analyzed using STATA-10 (Stata Corporation, Lakeway Drive, College Station, Texas, USA).

No extramural funding was used to support this work. The authors were solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

We identified a total of 6 randomized controlled trials for inclusion.[4-6,11-13] However, the RESPECT trial published the initial data and subsequent long term follow-up and only the recent iteration with long-term results was included to avoid duplication. Therefore, a total of 5 RCTs were included accounting for a total of 3630 patients. The search strategy is shown in the PRISMA flow sheet (Figure 1). Overall, the studies were deemed to be of low-risk of bias as per the Cochrane Collaboration's tool for risk of bias (Table I). Tables II and III summarize the demographic and clinical characteristics of the included studies. There was little evidence of publication bias in our analysis (Supplementary Figure).

Pooled analysis of RCT showed that device closure leads to significantly decreased risk (RR = 0.30, 95% CI = 0.02–0.57, I2 = 67.7%, P = .034) of stroke compared with medical therapy (Figure 2). On using the old RESPECT trial instead of the new follow up study, the results remained statistically significant (RR = 0.25, 95% CI = 0.01–0.50, I2 = 56.4%, P = .04). However, device closure did not significantly decrease (RR = 0.73, 95% CI = 0.44–1.03 I2 = 0%, P = .43) the risk for subsequent transient ischemic attack (Figure 3).

No statistically significant difference was observed in the incidence of bleeding (OR = 0.94, 95% CI = 0.48–1.86, I2 = 29.5%, P = .87;

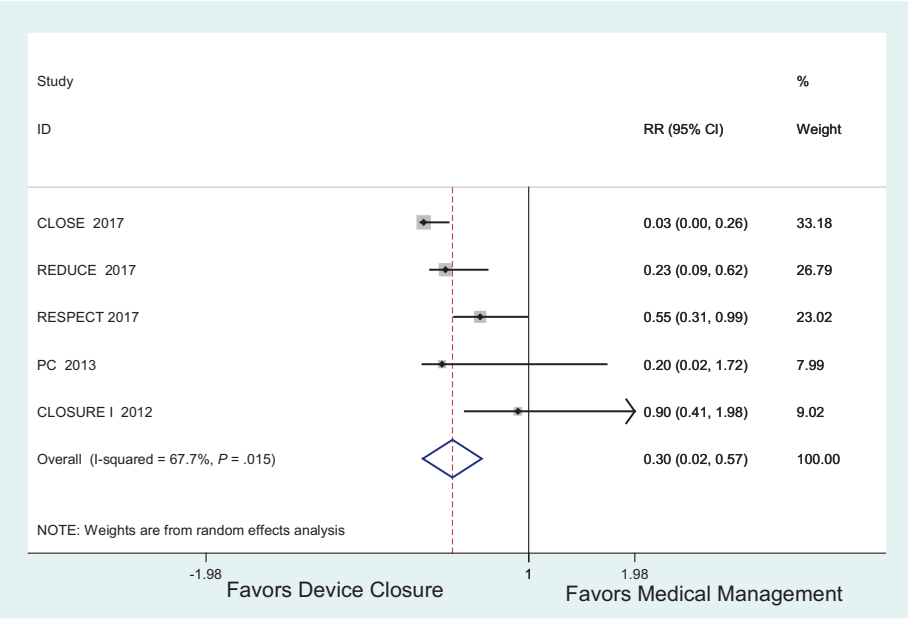

Figure 2. Stroke Endpoint.

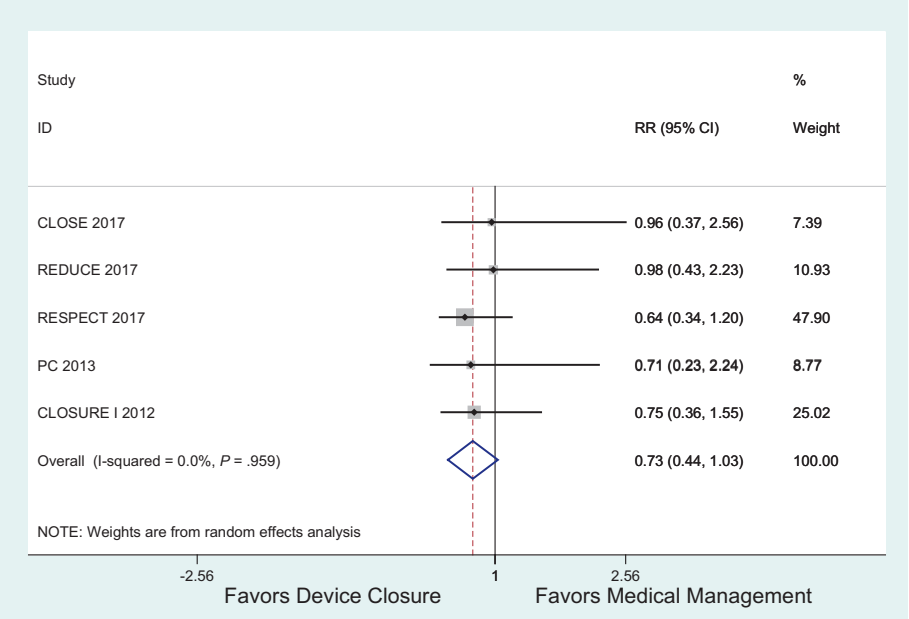

Figure 3. Transient Ischemic Attack Endpoint.

Figure 4A) or any adverse events (OR = 1.08, 95% CI = 0.92–1.26, I2 = 8.4%, $P = .37$; Figure 4B). Device closure was, however, associated with a significantly increased risk of atrial tachyarrhythmias (OR = 4.86, 95% CI = 2.20–10.73, I2 = 31.3%, $P < .001$; Figure 4C). The overall risk of mortality was similar in the device closure and medical therapy groups (OR = 0.76, 95% CI = 0.35–1.65, I2 = 0%, $P = .48$).

On sub-group analysis, we found that device closure significantly reduced the incidence of the composite primary endpoint among patients who had moderate to large shunt sizes (RR = 0.22, 95% CI = 0.02–0.42, I2 = 0%, $P = .028$; Figure 5B) or were men (RR = 0.35, 95% CI = 0.11–0.59, I2 = 0%, $P = .005$; Figure 5D). We observed no significant benefit of device closure among patients who had concomitant atrial septal aneurysm (RR = 0.7, 95% CI = 0.2–2.2, I2 = 0%, $P = .5$; Figure 5A). There was a significant reduction of stroke in patients younger than 45 years of age (RR = 0.4, 95% CI = 0.18–0.8, I2 = 0%, $P = .01$); Figure 5C).

Discussion

Our study suggests that the transcatheter closure of patent foramen ovale is associated with significantly reduced risk of stroke compared with medical management either in the form of antiplatelet or anticoagulation following cryptogenic stroke. These findings are important and represent a significant shift from the previous data, which either did not support or weakly supported the beneficial effects of transcatheter closure. We did not observe a reduction in transient ischemic attack with device closure. This may be related to the differing definition of TIA in each trial, though it also speaks to the difficulty in interpreting new or

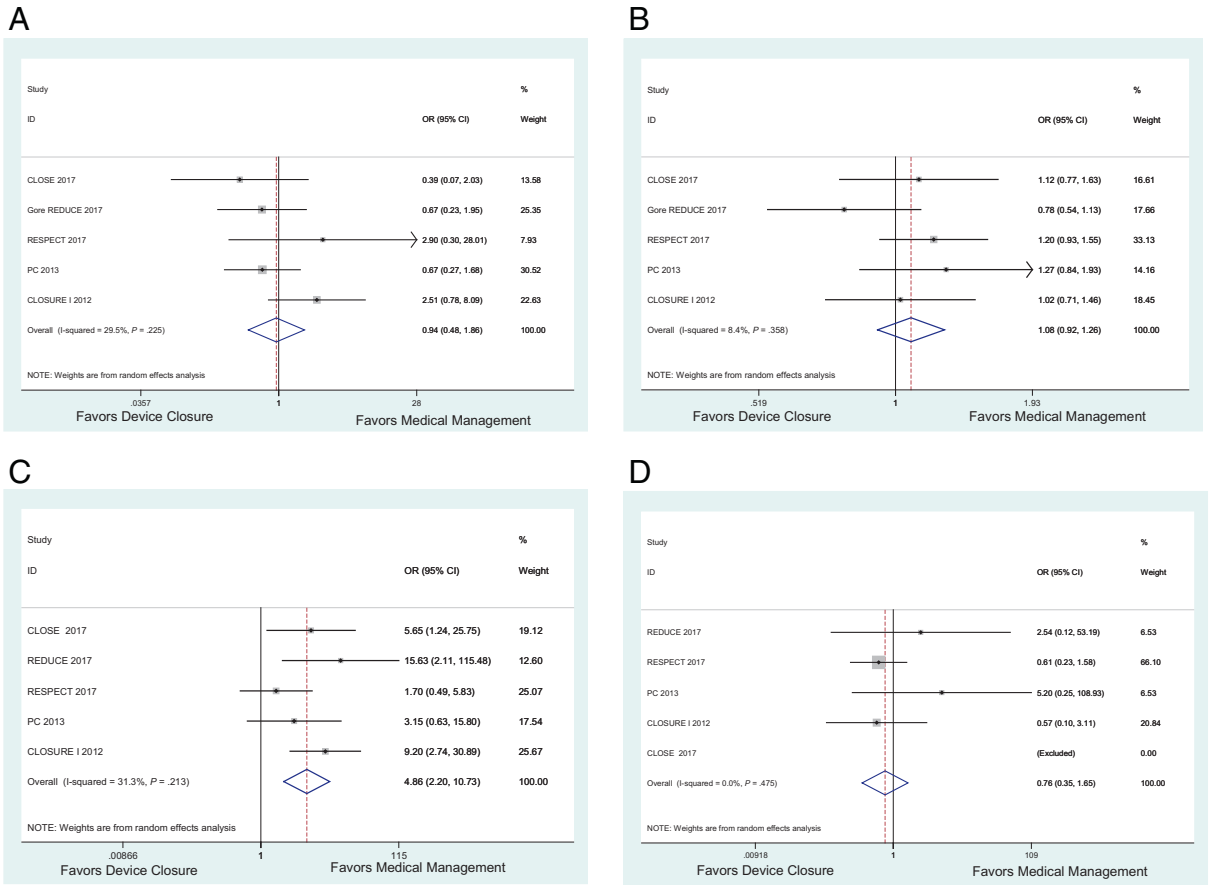

Figure 4. A, Complication of Bleeding. **B**, Any Adverse Event. **C**, Complication of Atrial Tachyarrhythmia. **D**, Mortality.

recurrent neurological symptoms in a patient with a prior stroke. In terms of adverse effects resulting from therapy, atrial arrhythmias occurred significantly more often in the patients undergoing device closure.

Several factors can explain the discrepant results in the historical trials compared with the most recent studies. First, the newer studies used more stringent inclusion criteria. For instance, in the CLOSE trial, patients were enrolled only if they had an atrial septal aneurysm, defined by a septal primum excursion of greater than 10 milimeters present on transesophageal echocardiography, as well as a large shunt, which was defined as the appearance of more than 30 microbubbles in the left atrium within three cardiac cycles of opacification of right atrium. Secondly, the historical trials used a liberal definition criteria for stroke, which may have led to inclusion of the events that were mechanistically distinct from the strokes that occur in patients with PFO (although unclear, the two commonly believed mechanisms are paradoxical embolism traveling via PFO or clot formation within the PFO tract).[14-16] This was illustrated in the CLOSURE I trial, which included patients with lacunar strokes that were unlikely to be explained by PFO.[6] On the other hand, the REDUCE trial used a strict definition of cryptogenic stroke that included an exhaustive work-up to exclude conventional causes of stroke, such as cerebral lacunes, atherosclerotic disease, atheroembolic phenomenon and hypercoagulable disorders.[11] The definition of "cryptogenic" continues to be elusive. The REDUCE trial also excluded patients older than 60 years of age, those with concomitant vascular disease and other factors that could lead to randomizing patients in whom PFO may have simply been an innocent bystander and not mechanistically involved.

After the publication of the first three trials, there were a large number of systematic reviews,[14-29] including 13 systematic reviews and meta-analyses published on the topic of PFO closure between October 2013 and March 2014 alone. Interestingly, 9 of these suggested no beneficial role of PFO closure, whereas 4 suggested that PFO closure was associated with reduced risk of stroke. There could be several reasons for the discordant results of prior analyses. First, studies differed on whether the pooled analysis was based on the intention-to-treat or per-protocol analysis. A careful look reveals that benefit was seen only in per-protocol analysis and not in the intention-to-treat analysis. Secondly, the endpoints used in the analysis were different. Third, statistical techniques varied, for instance fixed-effects versus random-effects modeling.

On the other hand, Startecky and colleagues have suggested that the benefit of PFO closure depends on the type of device used, with the Amplatzer PFO Occluder (Abbott Laboratories, Lake Bluff, Il) demonstrating a significant reduction in stroke compared to other devices.[29] The recent trials used several device types, for instance the Gore Helex and Gore Cardioform Septal Occluders (W.L. Gore & Associates; Flagstaff, AZ) in the REDUCE trial and multiple device types in the CLOSE trial. The statistical reduction in stroke observed in the trials using devices other than the Amplatzer PFO Occluder argues that the benefits observed are dependent on the successful closure of PFO, independent of the device type.

Perhaps the biggest question is how should these trials impact clinical decision making? The latest iteration of the stroke guidelines recommends PFO closure as a class 2B recommendation (suggesting insufficient evidence for benefit).[3] These guidelines were published well before the most recent studies were presented or published and are likely to be revised in the light of the most recent evidence. Interestingly, the US FDA approved the Amplatzer PFO Occluder for use in patients with presumed paradoxical embolic stroke and a patent foramen ovale shortly after guideline publication, suggesting a different interpretation of previously existing data.

It is also important not to extrapolate the findings of these trials to patient populations that are unlikely to benefit from such an intervention. For example, a 78 year old man with a lacunar stroke on MRI, a

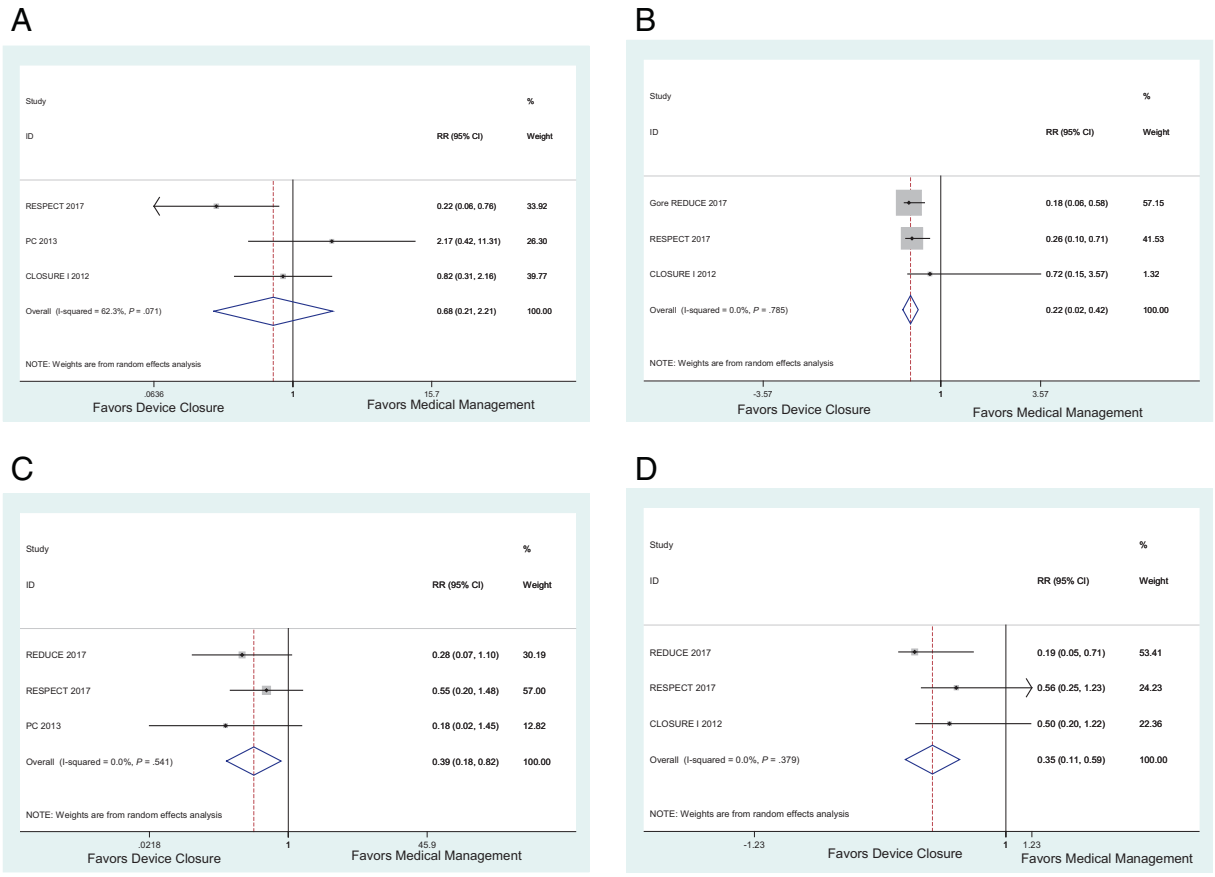

Fig. 5. A, Atrial septal Aneurysm. **B**, Large Shunt Size. **C**, Age Under 45 Years Sub-analysis. **D**, Sub-analysis for Men.

history of paroxysmal atrial fibrillation and an incidental diagnosis of PFO on a transthoracic echocardiogram is unlikely to benefit from PFO closure; whereas a 48 year old patient with stroke and "negative" workup except for the finding of a PFO and a large right to left shunt on echocardiography, is much more likely to benefit. The Risk of Paradoxical Embolism (RoPE) Score can also help guide the decision of which patients benefit from PFO closure.[30] It is also noteworthy that the overall risk of stroke in these clinical trials was quite small. The effect sizes seen in these trials should also be thoroughly discussed with patients in order to help inform decision-making. The CLOSE trial suggested that for every twenty patients treated, one stroke could be prevented compared to antiplatelet therapy alone over a period of 5 years.

Our analysis has several limitations. First, we performed a pooled estimate from individual trials and did not have access to individual patient data. Second, the patient populations appeared heterogenous. Third, the inclusion criteria and the characterization of stroke differed between studies. Despite these limitations, we believe that this analysis represents a timely update of the current evidence that will be very useful to inform decision-making. In conclusion, our study shows that transcatheter closure is associated with a significant reduction in the risk of stroke compared to medical management at the expense of an increased risk of atrial arrhythmias.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.01.008.

Acknowledgements

None

Disclosures

Dr. Krasuski served as an investigator in the CLOSURE I and PFO REDUCE trials, serves as a consultant to Actelion and is participating in research trials with Actelion, Edwards Life Sciences and Abbott.

None of the other authors have any disclosures.

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