

Cryptogenic Stroke: To Close a Patent Foramen Ovale or Not to Close?

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Journal of Central Nervous System Disease
Volume 10: 1–9
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DOI: 10.1177/1179573518819476



ABSTRACT: A patent foramen ovale (PFO) has been shown to be highly prevalent in patients diagnosed with strokes of unknown cause, which are also called cryptogenic strokes (CSs). It has been a long-running controversy as to whether a PFO should be closed or not to prevent recurrent strokes in patients diagnosed with CS. A paradoxical embolism that is produced through a PFO is hypothesized to be a leading cause of CS, especially in younger patients with low risk factors for stroke. It remains controversial as to which anticoagulation therapy, defined as antithrombin or antiplatelet therapy, is better for patients with CS and a PFO. In addition, surgical and transcatheter closure of a PFO has been proposed for the secondary prevention of stroke in patients with CS with PFO. Several randomized controlled trials have been conducted in recent years to test whether a PFO closure gives a significant benefit in the management of CS. Three earlier randomized controlled trials failed to show a statistically significant benefit for a PFO closure; thus, many investigators believed that a PFO was an incidental bystander in patients with CS. However, meta-analyses and more recent specific trials have eliminated several confounding factors and possible biases and have also emphasized the use of a shunt closure over medical therapy in patients with CS. Therefore, these latest studies (the CLOSE and REDUCE trials) can possibly change the treatment paradigm in the near future.

KEYWORDS: Cryptogenic stroke, paradoxical embolism, patent foramen ovale, atrial septal aneurysm, transcatheter closure

RECEIVED: May 30, 2018. **ACCEPTED:** November 19, 2018.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Strokes account for approximately 1 of every 20 deaths in the United States. They are the fifth leading cause of death and a major cause of disability in adults. Every 40 seconds, someone in the United States has a stroke, and among those individuals, almost 87% of strokes are ischemic. On average, every 4 minutes, someone dies of a stroke.¹ Despite recent advances in diagnosis and treatment, approximately one-fifth of stroke survivors require institutional care 3 months after the index event, and 15% to 30% of these survivors are permanently disabled.² With approximately 795 000 stroke events occurring each year, approximately 185 000 are recurrent attacks. The highest number of recurrent attacks recorded at 4 years after the index event, accounted for almost 18.4% compared with only 1.8% in the first year, as evidenced in a cohort of 10 399 patients who were discharged with a stroke in the state of South Carolina in 2002. Despite the use of antithrombotic agents, children who have experienced an arterial ischemic stroke remain at a high risk for recurrent events.¹

There are numerous causes of ischemic stroke. Most of these causes can be categorized into 3 groups: atherosclerotic, cardioembolic, and lacunar (a small vessel occlusion). Approximately, 25% to 39% of ischemic strokes do not have an identifiable cause and are termed as a stroke of unknown cause or a cryptogenic stroke (CS).³ The most commonly used classification for strokes is the TOAST (trial of ORG 10172 in acute stroke treatment) classification, and it defines a CS as a brain infarction that is not attributable to definite cardioembolism, large artery atherosclerosis, or small artery disease, despite

extensive vascular, cardiac, and serologic evaluations. However, it is obvious that no human disease is without a cause; hence, stroke classification depends on how extensive and rapid the diagnostic workup is performed.⁴ A CS is more common in younger patients (<55 years of age), and the frequently considered causes are a cardiac embolism, followed by vasculopathy and coagulopathy. One of the most frequent causes of cardiac embolism in CS is a paradoxical embolus, which might originate from a venous source, such as a deep venous thrombosis (DVT), through an unidentified patent foramen ovale (PFO), either with or without an atrial septal aneurysm (ASA).

A PFO has been shown to be more prevalent in patients with a CS than in the general population.⁵ However, the condition by itself has not been shown to increase the risk of an ischemic stroke. The true prevalence of a paradoxical embolus remains unknown because of the difficulty in the diagnosis of this phenomenon.⁶ It has been a topic of debate as to whether the prevalence of a PFO, or any other such shunt in patients with CS, represents a cause-effect relationship. Numerous studies have displayed a strong relationship between shunts and development of a CS. Some studies suggest that a PFO could be the major contributor of strokes in younger patients and those with a lower degree of atherosclerotic risk factors.⁵ There is strong evidence that documents a physiological gradient that results in an increased risk of a paradoxical embolism, which is related to both the shunt size and the presence of an additional ASA.⁷ Therefore, the issue of whether or not to close a PFO in patients with a CS is of great interest in both the neurology and cardiology communities.



To evaluate the effects of a PFO closure, several newer percutaneous device techniques were introduced. The Amplatzer PFO Occluder was approved by the Food and Drug Administration (FDA) on October 28, 2016. This device is indicated for the percutaneous transcatheter closure of a PFO, to reduce the risk of a recurrent stroke in patients who have been determined by a neurologist and a cardiologist as having a CS via a paradoxical embolus. In the past 5 years, several trials have been conducted, to evaluate the benefit of a PFO closure.⁸ Through the analysis of the results of these studies, we can gain a better understanding of this cause-effect relationship.

PFO as a culprit for a paradoxical embolism that causes CS

A paradoxical embolism refers to the mechanism in which an embolus, originating from the venous system, traverses to the systemic circulation via an intracardiac or pulmonary shunt. An intracardiac embolus via a PFO is hypothesized to be one of the possible mechanisms that leads to a CS. A PFO is a remnant of the fetal circulation and is by far the most common intracardiac shunt. During an autopsy, it has been identified in almost 27% of patients with normal hearts. It is formed by the left-sided interatrial septum primum and the right-sided interatrial septum secundum. The prevalence of a PFO appears to decrease with increasing age, with an incidence of 34% during the first 3 decades and an incidence of 25% in the third to seventh decades.^{2,6}

Under normal physiologic conditions, the mean left atrial pressure exceeds the right atrial pressure creating a pressure gradient that facilitates passive closure of the PFO. However, a transient increase in the right atrial pressure can occur during Valsalva maneuver, such as coughing, sneezing, squatting, defecation, or micturition, resulting in a right to left shunt and passage of particulate matter like thrombi into the systemic circulation. It was demonstrated in the SPARC study⁹ that the prevalence of right-to-left shunting increases from 14% to 23% with the performance of these maneuvers, whereas a permanent increase in the right cardiac pressure can occur in pathologic conditions, such as a pulmonary embolism or an increase in pulmonary artery pressure. These can result in a paradoxical embolus in the systemic circulation, which can then cause end organ damage, such as a stroke, transient ischemic attack (TIA), or peripheral thromboembolism. The estimated risk of a paradoxical embolism in patients with an acute pulmonary embolism is approximately 60%.¹⁰ The important factors that determine the significance of a PFO are its size and the degree of a right-to-left shunt. Those patients with a PFO size of >4mm are at a greater risk of a paradoxical embolism. It has also been noted that, in patients with CS, the PFOs are larger, have long tunnels, and are frequently associated with an ASA.

It is extremely difficult to establish the presence of a venous thrombus and/or a thrombus in transit through the PFO in

most of the cases. Therefore, without a visualization of an entrapped thrombus in the defect, it can only be assumed that the cause could be a paradoxical embolus. In addition, clots that are less than 2 mm in size are beyond the resolution of the transesophageal echocardiography (TEE) transducers, and there is a higher chance of not detecting them. Thus, efforts to establish a cause-effect relationship between a PFO and a paradoxical embolism would be confounded by these multiple factors.¹¹ To overcome these drawbacks and to identify whether the PFO was related to a stroke or an incidental event, an index scoring system was proposed in the Risk of Paradoxical Embolism (RoPE) study.¹² The RoPE score was developed in patients of all ages, and it ranges from 0 to 10. A higher score indicates a greater probability that the stroke is secondary to a PFO. The score is higher for younger patients, with a score of up to 5 points for those patients who are less than 30 years old and a score of 1 point each for the absence of hypertension, diabetes, smoking, a history of a stroke or a TIA, and the presence of a cortical infarct on imaging.^{13,14} This scoring system can guide clinicians and researchers in avoiding patients with incidental PFOs who are to be enrolled in clinical trials while also testing for the effectiveness of PFO closures on a CS. Furthermore, it can be used for selecting appropriate candidates for a closure to prevent a CS.

Anatomic variations of PFO

The PFO can have several anatomic variations, including a eustachian valve, a Chiari network, an ASA, or an atrial septal defect (ASD).

A prominent, residual eustachian valve can coexist with the PFO in almost 70% of cases and can frequently be a common finding in patients with a presumed paradoxical embolism. It is a tenuous, valve-like ledge that is formed as the embryonic remnant of the right valve of the sinus venosus, which directs the oxygenated blood from the inferior vena cava to the fossa ovalis during fetal life. After birth, it usually disappears gradually in most of the population. If it does not disappear, it can remain as a PFO and lead to the passage of a clot from the right to the left side of the atrium, thus leading to a paradoxical embolism.⁶

A Chiari network is generally seen in almost 2% to 4% of the general population and is another embryonic remnant of the right valve of the sinus venosus. It is formed by a reticulated complex of threads and fibers in the right atrium that results from the incomplete resorption of the sinus venosus during embryonic heart development. Although the Chiari network is usually an incidental finding on an echocardiography, it is frequently associated with a PFO (83%), a significant right-to-left shunt (55%), or an ASA (24%), which can all facilitate a paradoxical embolism.

An ASA is a localized, "saccular" deformity that is generally found in the central region over the undulating portion of the

septum primum, where it overlaps the septum secundum, which can protrude to the right or the left atrium or on both sides. It is usually an incidental finding during a routine echocardiogram or during the workup of a stroke. It is defined as an atrial, septal excursion that is ≥ 10 mm, with a base diameter of ≥ 15 mm, that can involve the region of the fossa ovalis or the entire septum. It can either be secondary to a difference in the interatrial pressure differences or can also be present as a primary malformation. Rarely, an ASA can be seen as an isolated abnormality, but it is most often associated with a PFO. It is estimated that, if an ASA is associated with a PFO, it can act as a large PFO, as it can easily open with every heartbeat, which then increases the risk of a paradoxical embolus.^{6,15}

The nonclosure of a PFO can also result in one of the most common congenital heart defects called an ASD. An ASD is an open communication between the atria that persists after septation and accounts for one-third of the CHDs in the adult population. Depending on their location, ASDs are classified into 3 types: an ostium primum, an ostium secundum, and a sinus venosus, otherwise known as coronary sinus defects. Most of these defects are type II, or secundum-type ASDs, which constitute almost 77% of all ASDs and are located at the site of the fossa ovalis. Depending on the size of the defect, patients can present with several clinical symptoms, such as dyspnea on exertion, fatigue, or even tachyarrhythmia. The incidence of paradoxical embolisms in patients with ASDs is reported to be as high as 14% and is frequently referred for a closure.^{6,16}

Diagnostic modalities of PFO

The preferred imaging modality used for the diagnosis of PFO is the TEE. Transesophageal echocardiography is considered superior to transthoracic echocardiography to better describe the morphologic characteristics of the lesion and can aid in better diagnosis. The presence of bubbles within the left atrium may suggest a PFO or an intrapulmonary shunt. The appearance should occur within several cardiac beats. To assess the degree of right to left shunt across the PFO, agitated saline contrast is used. While asking the patient to perform the Valsalva maneuver, the saline contrast medium is injected into the peripheral vein and visualization of the atrial septum is performed at a 90° angle to a more vertical plane. To standardize and quantify the PFO, the number of contrast bubbles appearing in the left atrium is measured.

In the French PFO-ASA study, appearance of 3 contrast bubbles was considered positive for the presence of a PFO. If 3 to 9 bubbles appeared, the shunt was considered small and moderate if 10 to 30 bubbles present. The defect is considered large only if more than 30 bubbles were observed left atrium.¹⁷

But according to the PFO in CS study (PICSS), a PFO was considered to be present if at least 1 or more contrast bubbles were noted in the left atrium. The defect was considered large if more than 10 bubbles were seen. Using this protocol, a PFO

was identified by TEE in 33.8% of all patients enrolled in the PICSS with an age range of 30 to 85 years. Among them, around 39.2% were patients with CS with PFO and 29.9% of patients had a known cause of stroke ($P < .02$).^{2,17}

A similar cutoff point was also used for all the latest studies conducted for the evaluation of the effectiveness of PFO closure. When 30 microbubbles were needed in the CLOSE trial to render them as large defects, REDUCE trial divided it into 3 categories and those with more than 25 microbubbles were considered large and those with 6 to 25 bubbles observed in the left atrium were considered moderate. On the contrary, in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial, the shunt size of PFOs was graded on a standard scale, considering the presence of 10 to 20 microbubbles as grade 2 and the ones with more than 30 microbubbles to be defined as grade 3.

Medical therapy vs PFO closure for CS

Antiplatelet therapy, along with a stroke risk factor modification, remains the mainstay of treatment in most patients who are diagnosed with a CS, with or without evidence of a PFO. Even though there is a growing interest in the use of anticoagulation therapies, there are insufficient data to establish whether oral anticoagulation (OAC) is equivalent to, or superior to, aspirin as a secondary prevention of a CS. In most cases, current practices are individualized according to patient risk factors and physician preferences. However, the identification of atrial fibrillation (AF) in patients with CS makes OAC the preferred therapy over antiplatelet therapy.^{2,18}

The major study to correlate the efficacy of anticoagulation therapy with antiplatelet therapy in patients with CS was derived from post hoc analyses of the Warfarin-Aspirin Recurrent Stroke Study (WARSS) trial,¹⁸ which included 2206 patients with stroke who were evaluated over a period of 24 months for recurrent stroke or death, while receiving either aspirin or warfarin. Even when the primary analysis of WARSS did not show any significant benefit of warfarin over aspirin in the secondary prevention of noncardioembolic strokes, the use of warfarin was shown to be associated with one-third fewer recurrent strokes than the use of aspirin in patients with CS, compared with the use of aspirin with an embolic cause of stroke. However, the association did not reach a statistical significance.^{18–20}

When Cujec et al reported that warfarin may be more effective than an antiplatelet therapy for a secondary stroke prevention in the PICSS, the primary end point for patients with CS with a PFO treated with warfarin did not show a statistically significant benefit over those who used aspirin (hazard ratio [HR]=0.52; 95% confidence interval [CI]: 0.16–1.67; $P = .28$). However, the study was not adequately powered for this specific comparison. The PICSS was performed in collaboration

with the WARSS, to evaluate the efficacy of an antithrombotic therapy in a PFO-induced CS.¹⁸ A total of 630 patients with stroke were randomly assigned to either warfarin or aspirin and evaluated for the presence of a PFO using TEE. Overall, 203 patients were found to have a PFO, which accounted for 33.8% of the population. However, no significant difference in the time to reach the primary end point was detected in those with or without a PFO. It should be noted that the primary end points included several subtypes of strokes, and among them, the lacunar infarcts accounted for approximately 244 (38.7%) of cases. It was shown in the PICSS that a larger PFO was associated with a CS. However, the rates of recurrence of a stroke or TIA in patients with or without a PFO were shown to be similar to medical therapies with either aspirin or warfarin. In the study, it was concluded that the presence or absence of a PFO does not affect outcomes over a period of 2 years regarding medical therapy. Therefore, it was necessary to identify the best treatment modality for preventing recurrent strokes in patients with a PFO. Aside from the traditional medical therapies with antiplatelet therapy and an OAC, a surgical closure and a percutaneous device closure attracted interest. Due to the risk of undergoing a major surgery for an uncertain cause, a percutaneous PFO closure gained in popularity.^{20–23}

A percutaneous PFO closure is a catheter-based technique that uses atrial septal occlusion devices. It was initially recommended for the prevention of recurrent strokes in 1992. The safety and viability of these devices have been assessed in several studies.^{24–27} These devices have also been safely used in the closure of ASDs in several patients. The device-related complications that might occur are classified as major vascular complications and major adverse device events. The major vascular complications that could be associated with the closure devices include the following: a hematoma at the access site that is >5 cm, false aneurysm, an arteriovenous fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, procedure-related transfusion, or a need for a vascular surgical repair. However, none of these complications were significant enough to cause a long-term morbidity in any of the patients, as evidenced in the trials.

To define the therapeutic efficacy of this modality, 6 randomized, controlled trials have been conducted during the past 5 to 10 years (see Table 1). The results and analyses of each of these trials are given in detail in the *New England Journal of Medicine* (NEJM). Although 3 of these recently performed trials showed a statistically significant benefit of PFO closures in preventing CSs, the 3 previous trials failed to do so. Therefore, a question still remains regarding the benefit of a PFO closure over medical therapy in patients with a CS. There were signals supporting this claim in 2 of those studies, with an HR favoring a closure. However, the *P* value did not meet statistical significance. Even when the 3 randomized trials individually did not show a significantly lower risk of a recurrent stroke with a

PFO closure than with medical therapy alone, in the pooled individual patient meta-analysis and a study-level network meta-analysis of randomized trials, the closure of the PFO with the Amplatzer PFO Occluder was found to result in a lower risk of recurrence of an ischemic stroke than with the use of medical therapy.^{28,29} Most recently, the Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) trial and the Reduction in the Use of Corticosteroids in Exacerbated Chronic Obstructive Pulmonary Disease (REDUCE) trial were presented at the 3rd European Stroke Organization Conference in 2017. While the CLOSE trial showed results favoring a PFO closure, with an absolute risk reduction for a recurrent stroke of 4.9% in the patients undergoing a PFO closure (with one stroke avoided at 5 years for every 20 patients who were treated), the REDUCE trial showed a 77% relative reduction in recurrent strokes with a PFO closure, with the number of patients needing to be treated to prevent one new stroke being 28 in 2 years.³⁰ In this review, we shall analyze the positive and negative aspects of each of these trials, to help better develop therapeutic interventions.

CLOSURE I trial

One of the earliest trials was the Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale (CLOSURE I) study²³ in 2012, wherein candidates who had a CS or TIA within 6 months and in whom a PFO was detected using TEE with a bubble study were selected from an age range of 18 to 60 years old. The closure was performed using the STARFlex septal closure system, which was sponsored by NMT Medical. It was a prospective, multicenter, randomized, open-label, 2-group superiority trial which included 909 patients. The primary efficacy end points were a stroke or TIA within 2 years of a follow-up, death from any cause in the first 30 days, or death from a neurologic cause within 31 days to 2 years. An antithrombotic therapy was given to the closure group using 75 mg clopidogrel and either 81 or 325 mg aspirin once daily. In the medical therapy group, warfarin was given, to maintain the international normalized ratio (INR) at 2 to 3, along with 325 mg aspirin or no aspirin. However, after 2 years of follow-up, there were no significant benefits with a closure in preventing a stroke or a TIA, compared with a medical therapy. The respective rates were 2.9% and 3.1% for stroke (*P* = .79) and 3.1% and 4.1% for TIA (*P* = .44). The HR was 0.78, with only a 1.3% reduction in the primary end points, with a *P* value of .37, thus making it statistically nonsignificant.²³

Being the oldest of the studies on a PFO closure, several drawbacks are evident in this study, especially when we compare it with the newer studies. The compelling differences can be seen with respect to the study design, the population included in the study, the follow-up period, and the device that was tested. The STARFlex device was associated with a lower

Table 1. Trials on Medical therapy vs PFO closure in Cryptogenic stroke.

TRIAL NAME	DEVICE USED	NO. OF PATIENTS	YEARS OF FOLLOW-UP	COMPARATOR	PRIMARY OUTCOME END POINT	HR	P VALUE	PUBLICATION YEAR
CLOSURE I	STARFlex septal closure	909	2	APT, OAC or both	Composite of stroke or TIA at 2 y, death by neurologic cause by 31 d to 2 y or death from any cause within 30 d	0.78	0.37	2012
PC	Amplatzer PFO Occluder	414	4	APT or OAC	Composite of death, stroke, TIA, peripheral embolism	0.63	0.34	2013
RESPECT	Amplatzer PFO Occluder	980	2.1	APT or warfarin	Composite of recurrent nonfatal or fatal ischemic stroke or early death	0.49	0.08	2013
RESPECT extended f/u			5.9			0.55	0.046	2017
REDUCE	GORE HELEX Septal Occluder	664	3.2	APT	Ischemic stroke and new brain infarction on imaging	0.23	0.002	2017
CLOSE	Any approved device	663	5.3	APT or OAC	Occurrence of stroke	0.03	<0.001	2017

Abbreviations: APT, antiplatelet therapy; OAC, oral anticoagulants; TIA, transient ischemic attack.

effective closure rate, with more provocative events of device thrombosis and AF, compared with the newer Amplatzer PFO Occluder. Although the intention-to-treat analyses of both the RESPECT trial and the CLOSURE I trial did not show any superiority of a closure over a medical therapy, a secondary analysis of the RESPECT trial was able to show a significant benefit of a closure.

The follow-up period was longer in the RESPECT trial, as well as in the newer CLOSE and REDUCE trials, compared with the follow-up period in the CLOSURE I trial, which only had a fixed 2-year observation period. Furthermore, by enrolling patients with a TIA and by not excluding patients with a lacunar stroke or another large artery atherosclerotic disease, the study outcome was considered to be substantially weak.

PC trial

Another trial was performed in 2013 and was known as the Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism (PC) trial, which included 414 patients. This trial included candidates who were less than 60 years old and who had a PFO, a history of an ischemic stroke, a TIA, or a peripheral thromboembolism. The Amplatzer PFO Occluder was used for closures in 204 subjects who also had an antithrombotic therapy through the use of aspirin, along with either ticlopidine or clopidogrel, and 210 subjects in the medical therapy group, who were treated with the discretion of the attending physician using an antiplatelet or an anticoagulant therapy. During the 4-year follow-up period, approximately 28

patients from the medical therapy group were later crossed over to the closure group, mostly due to patient preference. In addition, during this follow-up period, 55 patients were lost to follow-up from either group, and approximately 18 patients withdrew from the study.³¹

The primary end point occurred in 7 and 11 patients in the closure and medical therapy groups, respectively, with a 1.8% reduction in events in the closure group, with an HR of 0.63 and a *P* value of .34. Thus, even when a slight benefit with a closure over the medical therapy was evident, it did not meet statistical significance. However, the lack of a significant effect can be attributed to the attrition bias that was present in the study, due to poor patient retention. It also had other limitations, such as the fact that a TIA was included as the primary end point, which resulted in an increased event rate and a dilution of effects, which is evident by the discrepancy in the HRs of a stroke (0.20) and TIA (0.71). In addition, the trial had a long recruitment period of the selected patient population, which limited the generalizability of the findings. Aside from that, only 5.2% of events were detected from the estimated 12% event rate in the medical therapy group. This finding reduced the power of the trial in detecting a planned reduction in 66% to that of less than 40%, which raised the possibility that a clinically relevant benefit of the closure might exist that was unable to be detected, thus leading to a type II error.³¹

RESPECT trial

The RESPECT trial is the only trial in which the results were contradicted over 2 different periods of time. The trial

outcomes were measured on both a short-term basis and a long-term basis, each of which provided a different set of outcomes. When the results could not demonstrate a statistically significant effect of a PFO closure over a medical therapy in the short-term trial, the long-term follow-up showed a significant benefit of a PFO closure on a CS. This trial had the highest participation with 980 patients, and the initial results were published in 2013, with 499 patients in the PFO closure group and 481 patients in the medical therapy group. The trial used the Amplatzer PFO Occluder as the closure device, which claims to have advantageous safety features as a device. The patients were aged 18 to 60 years old with a mean age of 45.9 years. It was a prospective, multicenter, randomized, event-driven trial, with primary end points of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death. The PFO was identified using TEE and was graded according to the number of microbubbles that appeared in the left atrium, with the largest being grade 3 with more than 20 bubbles, grade 2 with 10 to 20 microbubbles, and grade 1 which had only 1 to 9 microbubbles. An ASA was also identified, with an extrusion of the septum primum of 10 mm or more.³²

The primary results were analyzed with the occurrence of 25 primary end point events. Of the 980 patients, 9 cases were in the PFO closure group and 16 cases were in the medical therapy group, with an HR of 0.49 (95% CI: 0.22-1.11; $P = .08$). Only 851 patients (86.8%) were retained at the end of the 2-year follow-up period of the study, as almost 17.2% of patients in the medical therapy group and 9.2% of patients in the PFO closure group were dropped out of the study. Thus, even when the results favored the PFO closure group, they could not show statistical significance due to a wide CI and a higher P value.

When the primary analysis was conducted on an intention to treat the population, the protocol prespecified that if the dropout rates between the 2 groups differed significantly, an exposure-stratified comparison would be estimated using the survival functions for the time-to-end point event for each treatment. Thus, 2 additional populations were prespecified for the analysis. The per-protocol cohort and the as-treated cohort outcomes were calculated according to the actual treatment received by each cohort. The results of the prespecified analysis were able to show a statistically significant difference, with an HR of 0.37, a 95% CI of 0.14 to 0.96, and a P value of 0.03, with only 6 events for the closure group, compared with 14 events for the medical therapy group, in the per-protocol cohort; and 5 events for the closure group, compared with 16 events for the medical therapy group, in the as-treated cohort, which resulted in an HR of 0.27, a 95% CI of 0.10 to 0.75, and $P = .007$.³²

The major drawbacks in this trial were that the medical therapy group was allowed to use 4 types of treatment options, which were the use of aspirin alone, the use of warfarin alone, the use of clopidogrel alone, or the combined use of aspirin with dipyridamole. The combined use of aspirin with

clopidogrel was also initially used but was later removed. In addition, when patients in the PFO closure group were initially placed on antithrombotic therapy, it was later discontinued after 5 months in most cases, which increased the risk of stroke from other causes. The other important limitation was the unequal duration of exposure due to the differences in the dropout rates. In addition, entry and retention biases could also have been introduced by the possibility that high-risk patients were preferentially treated outside of the trial.

To overcome some of these limitations and to increase the power of the study, a long-term follow-up was done for the RESPECT trial.³³ The patients were followed for a median of 5.9 years. There was a higher dropout rate in the medical therapy group, thus resulting in an unequal treatment exposure among the 2 groups (3141 patient-years in the closure group vs 2669 patient-years in the medical therapy group). Despite that, a statistically significant benefit was noted in the closure group, compared with the medical therapy group, in the intention-to-treat population during the long-term follow-up.

Two types of classification systems were used for the analysis of the end point results. Recurrent stroke events were adjudicated as determined or undetermined based on the Comprehensive Phenotypic Ischemic Stroke Classification (ASCOD) classification system, and strokes were classified as cryptogenic or noncryptogenic based on the TOAST classification. There were a total of 46 primary end point events, all of which were recurrent nonfatal ischemic strokes. Although 28 cases were in the medical therapy group, only 18 cases occurred in the PFO closure group. When the ASCOD classification was applied to the observed cases, 13 of the 46 cases were estimated to be caused by a mechanism that is unrelated to the PFO, and only 33 cases were projected to have an undetermined cause. Among them, only 10 cases were observed in the PFO closure group, and only 23 cases were observed in the medical therapy group (HR=0.38; 95% CI: 0.18-0.79; $P = .007$). On the basis of the TOAST classification, only 12 cases were considered to be cryptogenic in nature, of which only 1 event was noted in the PFO closure group, compared with the 11 events in the medical therapy group (HR=0.08; 95% CI: 0.34-1.20; $P = .16$).³³

By analyzing the results of the trial, the number needed to treat (NNT) with a PFO closure over a medical therapy in preventing one stroke over a period of 5 years was estimated to be 42. The association of a PFO closure with lower rates of recurrent ischemic stroke was apparent, both when events of recurrent stroke were adjudicated as having an undetermined cause on the basis of the ASCOD classification and when events were adjudicated with the TOAST classification. It was also determined that the benefit of the PFO closure was more apparent among patients with an ASA, compared with those patients with a higher grade 3 right-to-left shunt and in those who were only on antiplatelet therapy compared with those who were on anticoagulants.

When evaluating the safety profile of the procedure, a total of 25 serious adverse events were observed in the PFO closure group and were either device related or procedure related. Even when AF was observed in 7 cases, all of them were resolved before discharge from the hospital, and the rate of serious or nonserious events of AF did not differ significantly between the PFO closure and medical therapy groups. Furthermore, an occult AF is an uncommon cause of CS in this age group. In addition, PFO closure was associated with a higher rate of venous thromboembolism (pulmonary embolism and DVT) compared with a medical therapy during the long-term follow-up.³³

CLOSE trial

The most advanced and recent study, known as the CLOSE trial,³⁰ evaluated patients with only a large PFO or an ASA and compared the use of a PFO closure and antiplatelet therapy with the use of antiplatelet therapy alone. They also compared OAC therapy with antiplatelet therapy alone. The study only included patients within the age range of 16 to 60 years, and the outcome was measured over a period of 5 years. It was shown that the risk of a stroke was 4.9% lower in patients who underwent a PFO closure plus antiplatelet therapy, compared with the risk of a stroke in patients who received antiplatelet therapy alone. The NNT to avoid one stroke was calculated as 20 (95% CI: 17–25). Compared with the patients in the antiplatelet group, most patients who developed recurrent strokes had both a PFO and an ASA.

The major advantage of the CLOSE study is that it provides a platform to compare antiplatelet therapy with both PFO closure and OAC therapy. Even when the sample size in the OAC group was comparatively lower and thus underpowered, the study was the result of prompt investigators who wished to perform a follow-up of the PICSS and WARSS studies.

The CLOSE trial is the only trial that actually separately compared a PFO closure with anticoagulation and antiplatelet therapy in a separate 1:1:1 ratio. They used 663 patients from 16 to 60 years of age who had recent strokes that were associated with an ASA or a large interatrial shunt. They were randomized into 3 different groups: the presence of a contraindication to a PFO closure, the absence of a contraindication to a PFO closure, or an anticoagulant therapy. Patients were also randomized based on the type of septal anomaly they possessed (an ASA vs a large shunt). The risk of a paradoxical embolism was also evaluated using the RoPE score.^{13,14} Of the 129 patients with contraindications to anticoagulant therapy, 64 patients were given only antiplatelets, and PFO closure was done in 65 patients.

The primary outcome end point was the occurrence of fatal or nonfatal stroke. The secondary outcomes mainly included ischemic stroke, TIA, systemic embolism, or death

from any cause. All patients were followed for an average of 5.3 years, and the amazing fact was that no strokes occurred among the 238 patients in the PFO closure group, whereas 14 of 235 patients had a recurrence of stroke in the antiplatelet therapy-only group (HR=1.03; 95% CI: 0–0.26; $P<.001$). In addition, it was noted that among patients in the antiplatelet therapy group, recurrent strokes occurred in those with both PFO and ASA. The anticoagulant vs antiplatelet comparison in the current trial also favored the anticoagulant group, with only 3 of 187 patients in the oral anticoagulant group having stroke compared with 7 of 174 patients in the antiplatelet group having recurrent stroke. However, the comparison was underpowered, as the HR had a highly variable CI (HR=0.44; 95% CI: 0.11–1.48; $P<.001$). The secondary outcome end points of TIA or systemic embolism were also significantly lower in the PFO group, compared with the antiplatelet group (HR=0.39; 95% CI: 0.16–0.82; $P=.01$).³⁴

In the PFO closure group, a single antiplatelet therapy was used throughout the trial, after an initial 3 months of aspirin use along with clopidogrel use. The antiplatelet group was allowed to use a single-drug agent that was similar to aspirin, clopidogrel, or aspirin, combined with dipyridamole. The oral anticoagulant group had the freedom to choose from either a vitamin K antagonist, for an INR of 2 to 3, or a direct oral anticoagulant.

The study was also able to determine the major adverse effects with the PFO closure. A new-onset AF was shown to be much higher in the PFO closure group, with most AFs detected within the first initial month of the procedure, which denoted that the procedure itself induced an AF. However, the new-onset AF has not been shown to be significant enough to be a risk factor for further strokes; rather, it can be present as a short-term effect. The AF was also not shown to recur in those candidates over the 5-year follow-up period. Even when it is taken into account, the rate of recurrent stroke was still lower or even absent in the PFO closure group.

REDUCE trial

The REDUCE trial³⁵ investigated the effect of PFO closure plus antiplatelet therapy with antiplatelet therapy alone on recurrent strokes and new brain infarcts. The major difference between the REDUCE trial and the CLOSE trial was the presence of 2 coprimary end points due to the addition of the end point of new brain infarcts. The new brain infarcts included a clinically silent infarction, which is often associated with a subtle neurologic deficit and mainly with cognitive impairment. The Gore REDUCE trial showed a 77% relative reduction in recurrent strokes with PFO closure, with a NNT to prevent one new stroke of just 28 at 2 years. It also showed a 49% relative reduction in new brain infarctions on magnetic resonance imaging (MRI).

Enrollment for the REDUCE trial was performed in a 2:1 ratio, with 664 patients who were randomly assigned to receive either PFO closure plus antiplatelet therapy (the PFO closure group) or antiplatelet therapy alone (the antiplatelet-only group). Moderate-to-large PFO shunts were present in almost 81% of the patients. The coprimary end point of an ischemic stroke was defined as an acute functional neurological disorder (FND) that was due to an ischemia, with the FND causing clinical symptoms lasting for more than 24 hours and with evidence of relevant infarcts on an MRI or a computed tomographic (CT) scan. To exclude potential cases of a large artery atherosclerotic disease, imaging of the intracranial, cervical arteries, and aorta was done using either CT or MR angiography, with an exclusion of patients with more than 50% occlusion. Patients with small deep infarcts less than 1.5 cm in diameter, with a clinical picture of the lacunar syndromes, were also excluded from the study. Patients with uncontrolled comorbid illnesses were also excluded. The PFO was defined as being moderate if 6 to 25 bubbles were visible on the left atrium and as being large if more than 25 bubbles were visible using TEE after an intravenous saline contrast infusion while on the Valsalva maneuver. The presence of an ASA was evaluated only in the PFO closure group during the occlusion procedure and was not assessed in the antiplatelet-only group.

After a median follow-up of 3.2 years, the number of ischemic strokes was significantly lower in the closure group, with an incidence of only 1.4%, compared with the antiplatelet-only group, with an incidence of 5.4% (HR=0.23; 95% CI: 0.09-0.62; $P=.002$). A similarly significant benefit was also seen in the occurrence of new brain infarctions, with only 5.7% of patients in the closure group experiencing infarctions, compared with 11.3% of patients in the antiplatelet group (HR=0.51; 95% CI: 0.29-0.91; $P=.04$). No significant difference was observed in the occurrence of silent brain infarctions in both population groups. However, the adverse effects of AFs were higher in the PFO closure group, along with other device complications.

Although previous trials allowed the use of anticoagulants or antiplatelets in the medical therapy groups at the discretion of treating or trial physicians, the REDUCE trial³⁵ followed a definite guideline for drug agents used in the medical therapy. It required that only antiplatelet agents be used in accordance with established guidelines and current practices, and it was not based on the treating physician's discretion, which has subsequently helped to substantially decrease the confounding bias in this group of patients.

Conclusions

It is evident from all the above studies that PFO closure would be superior to antiplatelet therapy for the prevention of recurrent strokes in patients with a PFO and a CS. However, due to the high prevalence of PFOs in the general population, a comprehensive, clinical history for the exclusion of other possible

causes of stroke is necessary to select candidates for closure. The presence of a large defect, a sizable interatrial shunt, and an associated ASA might be considered an indication for the closure of a PFO. The RoPE scoring system would be beneficial in selecting ideal candidates. A PFO closure may be considered as the initial therapy for those with a PFO, as well as those on aspirin and with a high RoPE score.


Studies also suggest that anticoagulant therapy could have a significant benefit in the management of a CS compared with antiplatelet therapy alone and that anticoagulant therapy might be nearly or equally as effective as a PFO closure. However, due to limited head-to-head studies, the use of either anticoagulation or antiplatelet therapy might be considered based on individual factors. Again, the adherence to anticoagulant therapy and the bleeding complications associated with it favors PFO closure, especially in younger patients with lower risk factors. A PFO closure would also be a reasonable alternative for those with contraindications to oral anticoagulants.

The major complication associated with a PFO closure is an AF. However, as evidenced by the studies, the procedure-induced AF was noted to be of a short duration; hence, it would not be significant enough to cause a cardioembolism. For those patients who are not an ideal candidate for a PFO closure, anticoagulant therapy may be advised. Further large randomized studies are needed to compare antiplatelet therapy with anticoagulant therapy, as well as to compare the closure of a PFO with the optimal anticoagulant therapy to have a better idea about their relationships.

Author Contributions

SJK contributed to the acquisition, analysis and interpretation of the data and drafted the manuscript. RRA made substantial contribution to the concept and design of the study, by critical reading of the article with critical revision and approved the version to be published.

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