

## Research Article

# Patent Foramen Ovale Closure and Medical Therapy for Cryptogenic Stroke: Evidence from Randomized Controlled Trials and Beyond

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**Received:** 08 May 2020; **Accepted:** 24 May 2020; **Published:** 29 May 2020

**Citation:** Razi Khan. Patent Foramen Ovale Closure and Medical Therapy for Cryptogenic Stroke: Evidence from Randomized Controlled Trials and Beyond. *Cardiology and Cardiovascular Medicine* 4 (2020): 203-217.

## Abstract

There has been substantial investigation recently into the role of patent foramen ovale (PFO) closure for treatment of patients with cryptogenic stroke (CS). In this review, the background, results and limitations of 6 randomized controlled trials (RCTs) comparing PFO closure with medical therapy (MT) for CS are summarized. Methodologic and treatment-related differences between older and newer trials are outlined and serve as potential sources for discrepancy in results obtained. In particular, the selection of patients with “high-risk” anatomic features of PFO and continued use of antiplatelet therapy were important reasons for the benefit of PFO closure demonstrated in newer RCTs. The review also examines the association of PFO with CS in older patients, as well as discussing the role for PFO closure in these patients who were largely excluded from large RCTs. Thus far, direct

comparisons of PFO closure and MT in older patient cohorts are lacking, with results from small, non-randomized studies demonstrating inconsistent conclusions about differences in recurrent embolic event rates between older and younger patients after device implantation. Finally, this review discusses limitations in the evidence for use of oral anticoagulation compared with antiplatelet therapy in patients with CS and PFO not undergoing PFO closure.

## Abbreviations:

ASA – Atrial Septal Aneurysm

CI - Confidence Interval

CS – Cryptogenic Stroke

ESUS – Embolic Stroke of Unknown Source

HR – Hazard Ratio

OR – Odds Ratio

PFO – Patent Foramen Ovale

MT – Medical Therapy

RCT – Randomized Controlled Trials

TIA – Transient Ischemic Attack

**Keywords:** Cryptogenic Stroke; PFO Closure; Oral Anticoagulants; Antiplatelets

## Introduction

Cryptogenic stroke (CS) is a subset of ischemic stroke where the etiology of disease remains unidentified. CS accounts for 10-40% of all patients with ischemic stroke, and therefore approximately 150,000-250,000 cases of CS are estimated to occur annually in North America [1, 2]. Variation of CS frequency is dependent on patient age, the use of specific diagnostic criteria for evaluation and the extent of peri-stroke investigations performed [3]. In patients <60 years, the frequency of CS noted in studies varies markedly ranging from as little as 10% to up to 60% [4-7]. The term embolic stroke of undetermined source (ESUS) was created recently to lessen the heterogeneity associated with CS by creating strict standardized criteria necessary for diagnosis [8]. However, regardless of the terminology used, annualized rate of stroke amongst patients who have had CS or ESUS has been estimated to be between 1.9-4.5% [8, 9], suggesting the need for additional therapies targeting disease.

Patent foramen ovale (PFO) is thought to be involved in the pathophysiology of CS by acting as a channel for passage of paradoxical emboli from the venous to the arterial system, leading to the occlusion of branches of the cerebral artery tree. De novo thrombus formation at the septum and in the right atrium has also been postulated as an alternative source for thromboembolism for CS in patients with PFO, particularly in the presence of atrial septal aneurysm

(ASA). Based on both necropsy and imaging-based studies, the prevalence of PFO in the overall population ranges between 20-25% [10, 11]. In contrast, PFOs have been noted in >40% of patients with CS [12]. There have been a number of observational studies that have subsequently noted an association between PFO and CS [13-16]. In contrast, large population-based cohort studies have not consistently found such associations [17, 18], while others have noted that certain anatomical features, such as the presence of ASA or a large degree of interatrial shunting, were required with PFO to increase the risk of recurrent stroke after initial CS [9]. When examining treatment of CS, there has been suggested benefit for PFO closure in preventing recurrent stroke from non-randomized studies and accompanying meta-analysis [19-23]. However, until this last decade, randomized data was lacking.

This review summarizes older and more recent randomized controlled trials (RCTs) comparing PFO closure with medical therapy (MT) for CS. It also outlines the risk and potential benefit for PFO closure in older patients with CS that were not included in large RCTs. Finally, it examines the evidence for use oral anticoagulation compared with antiplatelet therapy for CS patients with PFO that may not be suitable for PFO closure.

## PFO Closure RCTs in CS

### OLDER Trials

#### Closure Trial

The CLOSURE trial was the first published RCT comparing PFO closure with MT [24]. The trial examined patients between 18-60 years of age with a history of recent (<6 months) CS or transient ischemic attack (TIA) who were followed for 2 years (Table 1).

Transesophageal echocardiography was used to confirm PFO in all patients. The primary end-point, a composite of recurrent stroke/TIA or death at 2-years, occurred in 5.5% and 6.8% of the PFO closure and MT group, respectively ( $p=0.37$ ) (Table 2). There were no differences in individualized endpoints of TIAs (PFO closure 3.1% vs. MT 4.1%,  $p=0.44$ ) and recurrent stroke (PFO closure 2.9% vs. MT 3.1%,  $p=0.79$ ). Rates of atrial fibrillation were almost 20-fold higher in the closure group at 2-year follow-up (PFO closure 5.7% vs. MT 0.3%,  $p<0.001$ ).

A major criticism of the study pertained to the use of STARFlex® (NMT, Boston, MA) device for PFO closure. The rate of successful closure, defined by the absence of more than trace residual shunting, was low (86%) at 6-month follow-up with transesophageal echocardiography. A second limitation of the trial related to the fact that alternative identifiable etiologies were noted for recurrent TIA/stroke outcomes in 3/4 patients in the PFO closure and MT groups, respectively. Etiologies for recurrent events included atrial fibrillation, lacunar infarction and left atrial clot, suggesting that the index event for initial patient selection may not have been truly cryptogenic in nature.

### PC Trial

The PC trial was the first PFO closure study to start recruitment, with enrollment being initiated 13 years prior to publication in 2000 [25]. Patients included in the RCT were those <60 years of age with PFO and recent TIA, stroke or peripheral thromboembolic event (Table 1). Transesophageal echocardiography was used to diagnose PFO. Mean follow-up was 4.1 and 4.0 years in the PFO closure and MT groups, respectively.

Results of the RCT suggested that PFO closure compared with MT was not associated with a statistically significant reduction in the primary outcome composite of death, nonfatal stroke TIA or peripheral embolism (PFO closure 3.4% vs. MT 5.2%,  $p=0.32$ ) (Table 2). Similarly, no differences were noted between treatment groups when examining the single outcome of non-fatal stroke (PFO closure 0.5% vs. MT 2.4%,  $p=0.14$ ). Rates of atrial fibrillation were almost 3-times higher in the closure group when compared with MT, although this was not statistically significant (PFO closure 2.9% vs. MT 1%,  $p=0.16$ ).

Trial	Refs	Trial Size (N)	Sites	Entry Criteria	PFO Diagnosis	Devices	Follow-up	PFO Group Medications	MT Medications
CLOSURE	[24]	909	United States and Canada	CS/TIA	TEE with bubble study	STARFlex Septal Occluder	2yrs <sup>†</sup>	DAPT <sub>X</sub> 6M, then ASA	Warfarin, Aspirin Warfarin/ASA
PC	[25]	414	Europe, Canada, Brazil and Australia	CS/TIA/Peripheral Embolic Event	TEE with bubble study or Doppler flow or positional maneuvers	Amplatzer Septal Occluder	4.0-4.1yrs	AspirinX5-6M/Ticlopidine or Clopidogrel 1-6M	Aspirin, Clopidogrel or Ticlopidine, Warfarin
RESPECT (Early)	[26]	980	United States and Canada	CS	TEE with bubble study	Amplatzer Septal Occluder	2.6yrs	DAPT <sub>X</sub> 1M, then AspirinX5M	Aspirin, DAPT, Aspirin/Dipyramidole, Warfarin
RESPECT (Late)	[27]						5.9yrs		
CLOSE	[28]	663 <sup>^</sup>	France and Germany	1) CS and 2) "High-Risk" PFO <sup>*</sup>	TTE/TEE with bubble study	Multiple	5.3yrs	DAPT <sub>X</sub> 3M, then Aspirin, Aspirin/Dipyramidole, Clopidogrel	Aspirin, Aspirin/Dipyramidole, Plavix
REDUCE	[29]	664	United States, Canada, Denmark, Finland, Norway, Sweden and United Kingdom	CS	TEE with bubble study	GORE HELEX/Cardioform Septal Occluder	3.2yrs	Clopidogrel X3days then Aspirin, Aspirin/Dipyramidole, Clopidogrel	Aspirin, Aspirin/Dipyramidole, Clopidogrel
DEFENSE-PFO	[30]	120	South Korea	1) CS and 2) "High-Risk" PFO <sup>#</sup>	TEE with bubble study	Amplatzer Septal Occluder	2yrs	DAPT <sub>X</sub> 6M	Aspirin, Clopidogrel, Cilostazol, Warfarin

ASA – Atrial septal aneurysm, CS- Cryptogenic Stroke DAPT - Dual antiplatelet therapy, M – Months, MI - Myocardial infarction, MT – Medical therapy, PFO - Patent foramen ovale, Refs – References, TEE – Transesophageal echocardiography, TTE - Transthoracic Echocardiography, TIA - Transient ischemic attack

<sup>^</sup> 190 patients randomized to oral anticoagulants not included in PFO closure analysis

<sup>†</sup> Median follow-up 2.8yrs, but outcomes provided for 2yr follow-up

<sup>\*</sup> "High-Risk" PFO - PFO with ASA or Large Shunt

<sup>#</sup> "High-Risk" PFO - PFO with large size, ASA or hypermobile septum

**Table 1:** Baseline Data of Randomized Controlled Trials Comparing PFO Closure and Medical Therapy

A major limitation of the PC trial was the very high rate of attrition noted. In the trial, there were a total 55 (13.2%) of patients lost to follow-up across both trials arms. Additionally, antiplatelet therapy was not mandated in the PFO closure group after 6 months. The use of antiplatelet therapy likely serves to reduce the risk of both CS and non-CS ischemic stroke even after PFO closure. Finally, PC trial investigators had expected primary composite outcome rates of 3%/yr in

the MT arm rather than the true rate of 1.3%/yr noted at trials end, making benefit with PFO closure difficult to detect.

**Respect (Early) Trial**

The RESPECT trial examined PFO closure in patients who had recent CS (≤270 days) between the ages of 18-60 (Table 1) [26]. Median follow-up for the trial was 2.1 years. When compared to the 2 preceding PFO

closure RCTs, the index event for study inclusion was limited to CS rather than TIA or peripheral embolism. PFO was identified by transesophageal echocardiography. At trials end, there was a non-significant trend toward reduced recurrent stroke with PFO closure based on the intention-to-treat analysis (p=0.08) (Table 2). The 2-year recurrent stroke event-rate point was estimated to be 1.6% in the PFO closure

group and 3.0% in the MT group. In per-protocol analysis, a significant reduction in primary outcome event rates was evident with PFO closure (p=0.03). Rates of atrial fibrillation were 2-fold greater in the PFO closure arm (3.0% vs 1.5%, p=0.13), but this difference was not statistically significant. A trend toward a higher rate of venous thromboembolism was noted in the PFO closure group.

Trial	Refs	Primary End-Point	Age (PFO Closure vs. MT)	Primary End-point (PFO Closure vs. MT)	Recurrent Stroke (PFO Closure vs. MT)	Atrial Fibrillation
CLOSURE	[24]	Stroke/TIA/Early Death/Neurologic Death	46.3yrs vs. 45.7yrs	5.5% vs. 6.8% (HR 0.78, 95% CI 0.45-1.35)	2.9% vs. 3.1% (HR 0.90, 95% CI 0.41-1.98)	5.7% vs. 0.3%
PC	[25]	Death/MI/Stroke/Peripheral Embolism	44.3yrs vs. 44.6yrs	3.4% vs. 5.2% (HR 0.63, 95% CI 0.24-1.62)	0.5% vs. 2.4% (HR 0.63, 95% CI 0.24-1.62)	2.9% vs. 1.0%
RESPECT (Early)	[26]	Fatal/Non-fatal Stroke/Early Death	45.7yrs vs. 46.2yrs	1.8% vs. 3.3% (HR 0.49, 95% CI 0.22-1.11)		3.0 vs. 1.5%
RESPECT (Late)	[27]			3.6% vs. 5.8% (HR 0.55, 95% CI 0.31-0.99)		
CLOSE	[28]	Stroke	42.9yrs vs. 43.8yrs	0% vs. 4.9% (HR 0.03, 95% CI 0-0.26)		4.6% vs. 0.9%
REDUCE	[29]	1a) New Brain Infarction, 1b) Recurrent Stroke	45.4yrs vs. 44.8yrs	5.7% vs. 11.3% (RR 0.51, 95% CI 0.29-0.91)	1.4% vs. 5.4% (HR 0.23, 95% CI 0.09-0.62)	6.6% vs. 0.4%
DEFENSE-PFO	[30]	Stroke/Vascular Death/Major Bleeding	49.0yrs vs. 54.0yrs	0% vs. 12.9% (p=0.013, HR NS)		0% vs. 10.5% (p=0.023, HR NS)

**Table 2:** Outcomes in Randomized Controlled Trials Comparing PFO Closure and Optical Medical Therapy

CI – Confidence interval, HR – Hazard ratio, MT – Medical therapy, NS – Not specified, PFO - Patent foramen ovale, Refs – References, TIA - Transient ischemic attack

## Respect (Late) Trial

The promising results from the RESPECT study prompted investigators to extended follow-up for a median of 5.9 years (Table 1) [27]. Here, PFO closure was associated with a significant reduction in recurrent stroke, with event rates being noted at 0.58/100 patient-years (3.6%) and 1.07/100 patient-years (5.8%) in the PFO closure and MT groups, respectively ( $p=0.04$ ) (Table 2). There was also a significant reduction in the secondary outcome of recurrent CS with PFO closure (PFO closure 2.0% vs. MT 4.8%,  $p=0.007$ ). In long-term follow-up, there was no difference in the rates of atrial fibrillation between both arms of the study (PFO closure 0.2% vs. MT 0.1%,  $p=0.36$ ).

Much like in the PC trial, a major limitation to the RESPECT trial was the very high dropout rate documented. Over the close to 6-year extended follow-up, the dropout rate was 33.3% in the MT group and 20.8% in the PFO closure group. Disparity between the dropout rates in the MT and PFO closure groups resulted in differences in treatment exposure in the 2 trial arms, potentially affecting the final results of the trial. Finally, again as in the PC trial, antiplatelet therapy was continued for only 6 months after device implantation. Therefore, the secondary prevention stroke benefit provided by aspirin was absent in the PFO closure group after 6 months.

## Newer Trials

### Close Trial

The CLOSE trial was a uniquely designed RCT. In addition to a direct comparison of PFO closure with antiplatelet therapy, a third arm where patients received oral anticoagulation was also included [28]. Patients between the ages of 16-60 years were randomized in 1:1:1 distribution and followed for a mean duration of

5.3 years (Table 1). A total of 663 patients with recent CS ( $\leq 6$  months) and PFO, diagnosed by transthoracic or transesophageal echocardiography, were enrolled in the study. However, unlike older PFO closure RCTs, only patients with “high-risk” PFO, defined by the presence of an ASA and/or a large right-to-left interatrial shunt, were included. Trial results indicated that PFO closure was associated with a significant reduction in the primary outcome of recurrent stroke when compared with antiplatelet therapy (PFO closure 0% vs. MT 6.0%,  $p<0.001$ ) (Table 2), with no recurrent strokes being noted in the PFO closure group at study completion. Additionally, there was a >2-fold reduction in the secondary composite outcome of stroke, TIA or systemic embolism with PFO closure (PFO closure 3.4% vs. MT 8.9%,  $p=0.01$ ). Atrial fibrillation was >5-fold more common in the PFO closure group, with over 90% of episodes resolving within one month of device implantation (PFO closure 4.6% vs. MT 0.9%,  $p=0.02$ ).

The inclusion of patients with “high-risk” PFO likely selected those with PFO presumably involved in the pathogenesis of CS rather than being incidental in nature. The absence of recurrent stroke noted after >5-year follow-up within the PFO Closure group highlights this careful selection of patients in the trial. Also, in the PFO closure arm, patients received dual antiplatelet therapy for 3 months, followed by single antiplatelet therapy until trial completion, rather than stopping therapy at 6 months as had been practiced in older trials.

### Reduce Trial

Publication of the REDUCE trial coincided with that of the CLOSE trial [29]. A total of 664 patients with recent CS and PFO were enrolled in a 2:1 distribution to PFO closure and MT, and subsequently followed for

a median of 3.2 years (Table 1). PFO was diagnosed on transesophageal echocardiography. At trial completion, PFO closure was associated with a >3-fold reduction in the rate of recurrent ischemic stroke compared with antiplatelet therapy (PFO closure 1.4% vs. MT 5.4%,  $p=0.002$ ) (Table 2). There was a similar almost 2-fold reduction in the co-primary endpoint of combined clinical/subclinical stroke with PFO closure (PFO closure 5.7% vs. MT 11.3%,  $p=0.04$ ). Rates of atrial fibrillation were substantially higher in the PFO group (PFO closure 6.6% vs. MT 0.4%,  $P<0.001$ ), but the majority of these episodes resolved within 2 weeks of onset.

As in the CLOSE trial, antiplatelet therapy was continued in both treatment arms until trial termination. Although identification of high-risk PFO was not necessary for inclusion in the trial, over 80% of patients had at least moderate-large right-to-left shunting, suggesting again that PFO in patients selected likely contributed to index CS pathology.

### Defense-PFO Trial

The DEFENSE-PFO study was the last RCT published comparing PFO closure and MT for CS, with all centres based solely out of South Korea [30]. After a lengthy enrollment period, only 120 patients with both CS and PFO were randomized equally amongst both treatment groups, and then followed for a median of 2.8 years (Table 1). As with the CLOSE RCT, only those with “high-risk” PFO, as defined by the presence of an ASA, a hypermobile septum (septal excursion in either atria >10mm) or a large-tunnel PFO ( $\geq 2$ mm separation between septum primum and secundum) documented on transesophageal echocardiography, were included. The results of the study suggested that PFO closure was associated with a significant reduction in recurrent

stroke (PFO closure 0% vs. MT 10.5%,  $p=0.023$ ) (Table 2). Atrial fibrillation was noted in 2/60 patients in the PFO closure arm, while rates were not specified in the MT arm.

There were a number of limitations associated with the DEFENSE-PFO RCT. The trial was much smaller than previous PFO closure RCTs. It consisted of only 2 sites which is likely why patient enrollment was difficult and prolonged. Finally, the MT group in the study had a recurrent stroke rate (>5% annually) that was 3-4-fold higher than had been noted in the MT groups of comparable PFO closure RCTs. In contrast, a major strength of the trial was the inclusion of only “high-risk” PFO patients, which is likely a significant reason for the lack of recurrent strokes noted in follow-up after PFO closure.

### PFO and CS in Older Patients

Little is known about the potential utility of PFO closure in older patients with CS, as the RCTs discussed have not included patients >60yrs old. However, evidence for the association between CS and PFO is still present in older patients. “High-risk” features of PFO, thought to be involved in increasing risk for CS, have also been noted in older population cohorts. Additionally, both the risk and risk factors for developing deep vein thrombosis, involved in embolic events leading to CS, progressively increase with age. Thus far, few PFO closure studies have attempted to compare outcome benefit between older and younger CS patients.

The association between the increased prevalence of PFO and CS appears to be consistent in both older and younger patient populations. In patients  $\geq 55$  years of age, Di Tullio et al noted that PFO was >4-fold more common with CS when compared to those with stroke

of known cause [16]. In a landmark paper examining 503 patients with ischemic stroke, the presence of PFO was independently associated with CS [31]. Amongst individuals  $\geq 55$  yrs of age in this study, the adjusted odds ratio (OR) for the presence PFO was 3.0 in patients with CS when compared to those with stroke of known cause. The frequency of PFO in patients with CS appeared to be similar when comparing those older and younger than 55 years of age [32]. In older patients with CS, risk of recurrent neurological events has been noted to increase with the presence of PFO. In the PICSS trial, CS patients  $\geq 65$  yrs with PFO had a  $\geq 3$ -fold risk of adverse events at 2-year follow-up when compared with CS patients without PFO [33]. Of note, amongst patients with PFO in this study, the rate of recurrent neurological event-rate was 31% in older ( $\geq 55$  yrs) CS patients compared with 12.2% noted in younger ( $< 55$  yrs) CS patients.

In patients with PFO, risk of recurrent cerebral events after CS is increased with the presence of ASA [9, 15, 34], right-to-left shunting [13, 35], and larger PFO diameter [36, 37]. In patients  $\geq 55$  years of age, the combination of PFO and ASA was  $> 3.5$  more common in CS patients compared to those with stroke of known cause [31]. Amongst a population of patients  $\geq 55$  years of age with ischemic stroke undergoing transesophageal echocardiography, there was no association between the isolated presence of PFO or ASA and CS, but the coexistence of PFO and ASA was  $> 7$ -fold more common in patients with CS compared with those who had stroke of known cause [38]. Right-to-left shunting noted on bubble transcranial Doppler studies was significantly more common in older patients ( $> 60$  years) with CS when compared to those with stroke of known cause (OR 2.06); this association was absent in younger patients ( $\leq 60$  years) [39]. In this

population-based study, the majority (61%) of CS patients with large right-to-left shunting were  $> 60$  years of age. Finally, the diameter of PFO has been noted to increase with age, potentially allowing for easier passage of paradoxical emboli from the venous to arterial systems [10, 40].

The risk of deep vein thrombosis, the most common suspected source for paradoxical embolism leading to CS, also increases with age. In particular, the incidence of deep vein thrombosis increases markedly after age  $\geq 55$  years [41]. This is likely attributable to a higher co-morbidity burden and/or reduced mobility noted with ageing [42, 43]. Additionally, age-associated alterations in both endothelial and platelet function in older patients may serve as additional cause for increased risk of deep vein thrombosis [44, 45].

Data from RCTs regarding the use of PFO closure in older CS patient populations is lacking. Therefore, evidence for procedural efficacy and safety in older CS patients is derived from a small number of observational studies that have compared outcomes after device implantation in both older and younger patients (Table 3). In the first study published, Kiblawi et al. noted that the risk of neurological events was similar between older ( $\geq 55$  yrs) and younger ( $< 55$  yrs) patients assessed approximately 18 months after PFO closure [46]. Although the burden of atrial arrhythmias was comparable between both age groups, the risk of atrial fibrillation after PFO closure was higher in older patients. Oddly 5/7 recurrent neurological events occurred within one month of device implantation, while a 6<sup>th</sup> event arose in a patient with PFO malposition, suggesting that these outcomes may have been in part procedure-related. In a similar but larger comparative study, Spies et al. noted estimated annual



recurrent neurological event rates of 1.3% in older ( $\geq 55$  yrs) and 1.8% in younger ( $\leq 55$  yrs) patients after PFO closure for cryptogenic thromboembolism [47]. Examining 475 consecutive patients with cryptogenic thromboembolism and PFO, Wintzer-Wehekind found that there was a trend toward greater risk of recurrent stroke after PFO closure in older patients, but this did not persist after controlling for traditional cardiovascular risk factors [48]. Mortality rates were higher amongst older patients receiving PFO closure, but these differences were predominantly attributable to noncardiovascular causes of death. In fact, older patients undergoing PFO closure had a mortality rate that was similar to the estimated rate for individuals  $\geq 65$  years of age in the general population based on provincial (Quebec, Canada) databases. Frequency of atrial fibrillation was similar between older and

younger patients in multivariate analysis. In contrast, Scacciatella et al. found that there was an increase in the risk of recurrent neurological events in older ( $\geq 55$  yrs) compared with younger patients [49]. Mean time for recurrent events was  $>3$  yrs from the time of procedure suggesting that events were unlikely to be related to device implantation. Age remained the only predictor of recurrent neurological events even after adjusting for other cardiovascular risk factors (hazard ratio (HR) 8.38, 1.5-83.2).

Study	Refs	Devices	Older Subgroup	Follow-up	Older (n)	Younger (n)	Mortality Rates (PFO Closure vs. MT)	Recurrent Stroke Rates (PFO Closure vs. MT)	Recurrent Thromboembolic Event Rates (PFO Closure vs. MT)	Atrial Fibrillation Rates (PFO Closure vs. MT)
Kiblawi et al.	[46]	CardioSEAL	$\geq 55$ yrs	17.8 months	184	272	0.5% vs. 0% (p=NS)	0.5% vs. 0.7% (p=NS)	1.6% vs. 1.5% (p=NS)	21.7% vs. 17.3% (p=NS)
Spies et al.	[47]	Amplatzer PFO, ASD, Cardia, Cardioseal, Intrasept	$>55$ yrs	18 months	423	632		1.4% vs. 1.4%	4.0% vs. 2.8% (p=0.329)	NS
Winter-Wehekind et al.	[48]	Amplatzer PFO, ASD, Cribiform, Premere, Cardia	$>60$ yrs	8 yrs	90	385	7.8% vs. 2.6% (HR 4.12, 95% CI 1.56-10.89)	2.2% vs. 0.5% (HR 5.08, CI 0.71-36.2)	5.5% vs. 2.6% (HR 2.62, CI 0.89-7.75)	5.5% vs. 1.8% (HR 4.09, CI 1.28-13.16)
Scacciatella et al.	[49]	Amplatzer PFO, Cribiform	$\geq 55$ yrs	3.1 yrs	151	307	0.7% vs. 0.7% (p=0.48)	1.4% vs. 0% (p=0.04)	4.0% vs. 0.3% (p=0.002)	3.3% vs. 2.0% (p=0.37)

CI – Confidence interval, HR – Hazard ratio, MT – Medical therapy, NS – Not specified, PFO – Patent foramen ovale,

Refs – References

**Table 3:** Studies Comparing Baseline Characteristics and Outcomes in Older and Younger Patients Undergoing PFO Closure

Thus far, there have been no studies directly comparing PFO closure with MT in CS patients older than 60 years of age, despite the fact that contemporary stroke registries have suggested that close to 50% of ischemic strokes may be labelled as CS in this patient population [39]. Although, the presence of PFO and associated “high-risk” PFO features are not uncommon in older patients, evidence for PFO closure remains poor and is derived predominantly from small studies comparing older and younger patients undergoing device implantation. Heterogeneity in the different patient cohorts included in these studies has led to considerable discrepancy in the rates of recurrent neurological events and atrial fibrillation noted after PFO closure in older patients. RCTs examining PFO closure for older CS patients would help offer insights into prognosis and provide direction of care for treatment in these individuals.

### Medical Management for CS Patients with PFO

For CS patients with PFO who are not candidates for PFO closure or for those who fall outside the inclusion parameters of PFO closure RCTs, MT has been advocated [50, 51]. However, to date, there remains a question of what ideal or optimal MT entails for patients with CS and PFO. Given the presumptive role of paradoxical embolism in CS pathology, anticoagulation has been suggested as a potential treatment for disease. Comparisons between oral anticoagulation and antiplatelet therapy for treatment of CS in patients with PFO have been restricted to observational studies, subgroup analysis of large CS/ESUS-related RCTs and examination of non-PFO closure groups in the CLOSE trial.

Two meta-analysis published prior to recent PFO closure RCTs have provided conflicting evidence for use of oral anticoagulation in CS patients with PFO. In the first meta-analysis, involving 8 observational studies, there was a suggested reduction in recurrent neurological events by >50% with oral anticoagulation compared with antiplatelet therapy in CS patients with PFO [52]. However, the analysis did not control for confounding factors and bias within these non-randomized studies. A subsequent meta-analysis included patients from observational studies and the MT arms of 3 PFO closure RCTs, with investigators using individual patient data and propensity scoring to help control for confounding. The study noted no significant difference between oral anticoagulation and antiplatelet therapy for the composite outcome of recurrent stroke/TIA/death [adjusted HR 0.76, 95% confidence interval (CI) 0.52–1.12] or for recurrent stroke alone (adjusted HR 0.75, 95% CI 0.44–1.27) [53]. There was also no benefit with oral anticoagulation treatment in patients with high-risk features of PFO, such as the presence of ASA or large shunt on transesophageal echocardiography.

Several subgroup analysis of larger RCTs have assessed the efficacy of oral anticoagulation for treatment of CS in patients with PFO. The first study termed the PICSS trial, a substudy of the WARSS RCT, compared use of warfarin (INR target 1.4-2.8) with aspirin (325mg) in patients with both recent ischemic stroke ( $\leq 30$  days) and PFO [33]. Only ~40% of stroke patients included had underlying CS. Amongst patients with both CS and PFO, there was no difference in the 2-year rate of recurrent ischemic stroke or death between warfarin and aspirin groups (9.5% vs. 17.9%,  $p=0.28$ ).

More contemporary data derived from subgroup analysis of the NAVIGATE ESUS trial assessed use of a direct oral anticoagulant, rivaroxaban (15mg daily), with aspirin (100mg daily) for treatment of ESUS patients with PFO [54]. Patients with PFO analysed represented 7.4% (n=534) of all patients from the initial trial. The study found that there was a numerical but not statistical reduction in the risk of recurrent ischemic stroke with rivaroxaban when compared with aspirin (2.6 events/100 patient-years vs. 4.8 events/100 patient-years, HR 0.54 95% CI 0.22-1.36). Due to the relatively few events noted at trial termination, the impact of shunt size or ASA on treatment could not be evaluated. Risk of major bleeding also trended to being higher with rivaroxaban in patients with PFO (HR 2.05; 95% CI 0.51-8.18), which was similar to the findings noted in the overall trial population. Within the same manuscript, the authors performed a meta-analysis comparing oral anticoagulation with antiplatelet therapies for CS patients with PFO, with inclusion of the NAVIGATE ESUS substudy, as well as data from the CLOSE and PICCS trials. The combined data suggested that oral anticoagulation was associated a significant reduction in recurrent stroke when compared to antiplatelet therapy for CS/ESUS patients with PFO (OR 0.48, 95% CI 0.26-0.96). Relatively wide confidence intervals noted were likely due to the small cumulative number of patients analysed (n=838) despite the inclusion of 3 different trial cohorts.

The CLOSE trial was the only RCT examining CS patients with PFO that included separate trial arms comparing oral anticoagulation and antiplatelet treatments amongst those with contraindications to PFO closure [28]. Patients in the oral anticoagulation group were placed on direct oral anticoagulants (7%) or vitamin k antagonists (93%), while those in the

antiplatelet therapy group received clopidogrel (10.8%), aspirin (86.7%), aspirin with extended-release dipyridole (1.3%) or the combination of aspirin and clopidogrel (1.3%). In the intention-to-treat analysis, the 5-year estimate for recurrent stroke was 1.5% and 3.8% in the oral anticoagulation and antiplatelet group, respectively (HR 0.44, 95% CI 0.11-1.48). The study was not powered to assess statistical significance, although there were no marked numerical differences in the frequency of stroke or bleeding events between groups.

Currently, optimal MT for CS patients unable or contraindicated to PFO closure remains unclear. Results from studies underpowered for major clinical outcomes make conclusions about the potential risks and benefits of oral anticoagulation treatment in CS patients with PFO difficult to extrapolate into real world practice. There is a need for large RCTs directly comparing anticoagulation and antiplatelet therapies for patients with PFO and CS that cannot undergo PFO closure.

## Conclusion

In patients with CS under 60 years of age, PFO closure offers reduction in recurrent stroke risk when compared with antiplatelet therapy. New RCTs have shown the importance of selecting patients with “high-risk” PFO, as well as the need for continued antiplatelet therapy after procedure. For CS patients greater than 60 years of age, data for PFO closure is limited, with smaller, non-randomized studies having suggested variable outcomes when comparing older and younger patient cohorts after device implantation. Amongst CS patients with PFO that are not candidates for PFO closure, there is currently inadequate evidence to recommend use of

oral anticoagulation over antiplatelet therapy, with greater study being required to define optimal MT in this patient population.

### Acknowledgements

I would like to thank Natasha Kohli for her patience and thoughtfulness during this manuscript preparation.

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