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CHAPTER

6

Early Randomized Trials of PFO Closure for Stroke (CLOSURE I, PC and RESPECT)

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OUTLINE

INTRODUCTION

Whereas the prevalence of a patent foramen ovale (PFO) in the adult population is approximately 25%, the frequency of PFO in patients who suffer a cryptogenic stroke is 40%–60% [1,2]. This observation of an increased frequency of PFO in cryptogenic stroke patients and respective case descriptions led to the theory that the passage of a venous clot across a PFO can result in systemic embolic events such as ischemic stroke or transient ischemia attack (Chapters 4–7), myocardial infarction (Chapter 8), or peripheral ischemia (Chapter 9) [3–7]. In addition, the results of the PFO-ASA trial (Clinical and Imaging Findings in Cryptogenic Stroke Patients with and without PFO) led to the development of the hypothesis that PFO closure in patients with ischemic stroke of unknown etiology but associated with a PFO may reduce the risk of recurrent stroke [8]. However, findings from PICSS (Effect of Medical Treatment in Stroke Patients with PFO) [9] and the uncertain effectiveness of PFO closure [10] convinced many neurologists that medical therapy was the preferred treatment.

The PFO-ASA trial was a prospective multicenter study involving 30 European neurology departments that evaluated differences in (cryptogenic) stroke risk factors and patterns among patients, with and without PFO, presenting with an otherwise unexplained ischemic stroke [8]. Of 581 stroke patients enrolled, 267 (46%) had PFO and 314 (54%) had no PFO as determined by transesophageal echocardiography (TEE) with a contrast bubble study performed at rest and during provocative maneuvers (Valsalva maneuver and cough). Patients with PFO were younger (40.1 vs. 44.5 years, $P < .0001$) and less likely to have traditional risk factors, such as hypertension (8.6% vs. 21.3%, $P < .0001$), hypercholesterolemia (10.9% vs. 23.2%, $P < .0001$), tobacco use (43.4% vs. 51.6%, $P = .05$), and alcohol use (13.1% vs.

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21.3%, $P = .01$). These findings suggested that the mechanism of stroke in patients with and without PFO were different, supporting the need for randomized trials to evaluate the efficacy of PFO device closure in patients with PFO-associated stroke.

PICSS, a subset analysis of the Warfarin-Aspirin Recurrent Stroke Study (WARSS) (n = 2206), included any stroke patient from WARSS who underwent TEE for clinical purposes (n = 630), including assessment for a diagnosis of cryptogenic stroke. PICSS was a double-blind 42-center study evaluating the rate of recurrent ischemic stroke or death from any cause in patients with or without PFO who were originally randomized to either warfarin adjusted to international normalized ratio 1.4 to 2.8 or acetylsalicylic acid 325 mg daily [9]. A total of 601 patients were included in the final analysis. Within the cryptogenic stroke cohort (250 of the total 601 subjects), 39% (98/250) had a PFO and 61% (152/250) did not have a PFO by TEE. The primary efficacy endpoint, defined as recurrent ischemic stroke or death from any cause, occurred in 9.5% of the patients in the warfarin group and 17.9% of the patients in the acetylsalicylic acid group (HR 0.52, 95% CI 0.16–1.67, $P = .28$) at a mean follow-up of 13.2 ± 10.5 months. Although this did not reach statistical significance, the risk of recurrent stroke with antiplatelet therapy was nearly twice that of oral anticoagulation and presumably would have become statistically significant with a larger sample size. Nonetheless, PICSS was interpreted as demonstrating that warfarin was no better than acetylsalicylic acid in reducing the risk of a recurrent stroke in cryptogenic stroke patients found to have a PFO. One must be cautious when interpreting the results of some of the early PFO studies because the diagnosis of PFO was often determined by TEE or even just transthoracic echocardiography, techniques which are not as sensitive as transcranial Doppler (Chapter 2) [11–14]. Thus, the presence of a PFO may have been missed in the "non-PFO" group, potentially confounding the results and decreasing the accuracy of the conclusions.

Whether to close a PFO to reduce the risk of recurrent stroke remained a matter of debate. With the advent of catheter-based percutaneous PFO closure, investigators speculated that the benefits of PFO closure may outweigh the procedural risks among individuals with PFO-associated stroke. In parallel to observational studies (Chapter 5), randomized clinical trials were designed to determine if percutaneous PFO closure was superior to medical therapy for secondary prevention of stroke in patients who did not have another identifiable etiology for their stroke other than PFO. The 3 early randomized trials of PFO closure for cryptogenic stroke are summarized in Table 6.1 [15,16,18].

THE CLOSURE I PFO TRIAL

CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO) was the first randomized, multicenter, open-label study to evaluate the efficacy and safety of percutaneous PFO closure plus medical therapy versus medical therapy alone for secondary prevention of stroke or transient ischemic attack (TIA) [15]. A total of 909 patients, aged 18–60 years, with cryptogenic stroke or TIA, who had a TEE-confirmed PFO were included. Patients randomized to the PFO closure group underwent device closure with the STARFlex septal closure system (NMT Medical; Boston, Massachusetts) and subsequently received acetylsalicylic acid 81 or 325 mg for 2 years and clopidogrel 75 mg for 6 months. Individuals randomized to the medical therapy group received either warfarin with a target international normalized ratio of 2.0–3.0, acetylsalicylic acid 325 mg daily, or acetylsalicylic acid 81 mg daily plus warfarin. The cumulative incidence (Kaplan–Meier estimate) of the primary composite endpoint, defined as stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years, occurred in 5.5% (23/447) of patients in the device arm and 6.8% (29/462) of patients in the medical therapy arm (HR 0.78, 95% CI 0.45–1.35, $P = .37$). The rates of recurrent stroke were similar when PFO closure was compared to medical therapy (2.9% vs. 3.1%, $P = .79$). In addition, the rates of recurrent TIA were similar between PFO closure and medical therapy (3.1% vs. 4.1%, $P = .44$). Neither the device arm nor the medical therapy arm had deaths from any cause within the first 30 days or from neurologic causes between 31 days and 2 years. In regard to safety, episodes of device closure demonstrated a significantly higher rate of major vascular complications (3.2% vs. 0%, $P < .001$) and atrial fibrillation (5.7% vs. 0.7%, $P < .001$) at 2 years.

Inconsistencies between CLOSURE I and previous observational studies have been attributed to problems with the STARFlex septal closure device itself. Backed by prior observational studies [19,20], it was postulated that the STARFlex device was likely more prone to thrombus formation, atrial fibrillation, and residual shunting when compared to other PFO-occluding devices, resulting in a higher risk of recurrent stroke or TIA. For example, 14%

TABLE 6.1 Early Clinical Trials Randomizing Cryptogenic Stroke Patients to Percutaneous PFO Closure or Medical Therapy.

Randomized Clinical Trial (Ref #)	Cohort (Number of Patients)	Device Arm (Number of Patients)	Medical Arm (Number of Patients)	Follow-Up	Primary Outcome	Results
CLOSURE I (15)	Cryptogenic stroke or TIA + PFO; age 18−60 yrs (909)	PFO closure with the STARFlex device + acetylsalicylic acid 81 or 325 mg daily for 2 years + clopidogrel 75 mg for 6 months (447)	Acetylsalicylic acid 325 mg daily, warfarin with a target international normalized ratio of 2.0−3.0, or both (462)	2 years	Composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, and death from neurologic causes between 31 days and 2 years	5.5% versus 6.8% (HR 0.78, 95% CI 0.45−1.35, $P = .37$) → PFO closure did not significantly reduce recurrent stroke or TIA compared with medical therapy
PC trial (16)	Cryptogenic stroke, TIA, or peripheral embolism + PFO; age < 60 yrs (414)	PFO closure with the Amplatzer PFO Occluder + acetylsalicylic acid 100−325 mg daily for 5−6 months + either clopidogrel 75−150 mg or ticlopidine 250−500 mg for 1−6 months (204)	At the discretion of the treating physician and could have included either antiplatelet therapy or anticoagulant therapy (210)	Mean of 4.1 years in the closure group and 4.0 years in the medical therapy group	Composite of death, nonfatal stroke, TIA, or peripheral embolism	3.4% versus 5.2% (HR 0.63, 95% CI 0.24−1.62, $P = .34$) → PFO closure did not significantly reduce recurrent embolic event or death compared with medical therapy
RESPECT (extended follow-up) (18)	Cryptogenic stroke + PFO; age 18−60 (980)	PFO closure with the Amplatzer PFO Occluder + acetylsalicylic acid 81−325 mg daily for 6 months + clopidogrel for 1 month followed by antiplatelet therapy at the discretion of the site investigator (499)	4 medical regimens were allowed: acetylsalicylic acid, warfarin, clopidogrel, or acetylsalicylic acid + extended-release dipyridamole (481)	Median of 5.9 years	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.58 events per 100 patient-years versus 1.07 events per 100 patient-years (HR 0.55, 95% CI 0.31−0.999, $P = .046$) → PFO closure significantly reduced recurrent stroke compared with medical therapy

CI, confidence interval; *HR*, hazard ratio; *PFO*, patent foramen ovale; *TIA*, transient ischemic attack.
Adapted with permission from Ref. [47].

of the stroke patients who underwent PFO closure had residual right-to-left shunting on 6-month follow-up TEE. Another possibility was that many index strokes that were adjudicated as cryptogenic during enrollment occurred in patients with a history of vascular risk factors (34% had hypertension, 47% had hypercholesterolemia, and 22% had a history of tobacco abuse), thereby raising the question whether the index stroke was truly due to paradoxical embolism [21]. Subsequent randomized clinical trials have confirmed the low rate of recurrent stroke on medical therapy described in the CLOSURE I trial at about 1% per year.

THE PC TRIAL

PC (Percutaneous Closure of PFO in Cryptogenic Embolism) was a randomized, multicenter, multinational, open-label trial that investigated whether percutaneous PFO closure was superior to medical therapy for secondary prevention of cryptogenic embolism [16]. Eligible individuals were patients aged <60 years, with a TEE-documented PFO, presenting with clinical and/or radiological evidence of ischemic stroke, transient ischemic attack, or an extracranial peripheral thromboembolic event. Patients randomized to PFO closure underwent percutaneous device

closure with the Amplatzer PFO Occluder (Abbott; Chicago, IL, USA) and subsequently received acetylsalicylic acid 100−325 mg/day for at least 5 months plus either clopidogrel (75−150 mg/day) or ticlopidine (250−500 mg/day) for 1−6 months. Individuals assigned to the medical therapy arm received antithrombotic treatment, but the exact regimen of either antiplatelet or oral anticoagulant was left to the treating physician's discretion. The primary endpoint, a composite of death, nonfatal stroke, TIA, or peripheral embolism over a 4-year follow-up, occurred in 3.4% (7/204) of patients in the PFO closure group and 5.2% (11/210) of patients in the medical therapy group (HR 0.63, 95% CI 0.24−1.62, $P = .34$). The rate of serious adverse events (43 in the closure group vs. 37 in the medical therapy group, $P = .37$), including procedural complications (3 in the closure group vs. 0 in the medical therapy group, $P = .12$), major bleeding (1 in the closure group vs. 3 in the medical therapy group, $P = .62$), and atrial fibrillation (6 in the closure group and 2 in the medical therapy group, $P = .17$), did not differ significantly between the PFO closure and medical therapy groups.

One major limitation of the PC trial was that it was statistically underpowered and prone to type II error. The trial was designed to detect a 66% reduction in the primary composite endpoint, from 3% per year in the medical therapy group to 1% per year in the PFO closure group. However, at a mean follow-up of 4 years, the medical therapy group had an event rate of 5.2%, which is less than half of the expected 12% incidence. Consequently, the power of the trial to detect the initial planned reduction of 66% in relative risk was less than 40%, thereby substantially increasing the statistical risk of type II error. Also, inclusion of patients with extracranial systemic embolism made the study group slightly different from the cohorts of most observational studies, which primarily investigated patients with PFO-associated stroke. Moreover, since the clinical presentation of TIA can be similar to the transient neurological deficits experienced in migraine with aura, this may have resulted in inclusion of patients with symptoms unrelated to cerebrovascular ischemia, although positive brain imaging had to be present. Finally, lack of blinding or regular onsite audits may have resulted in undocumented off-label use of PFO-occluding devices in the medical therapy arm [22].

THE RESPECT TRIAL

RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) was a prospective, multicenter, randomized, open-label study that evaluated the efficacy and safety of PFO closure versus standard of care blood thinners for the prevention of recurrent stroke or early death [17,18]. Patients between 18 and 60 years of age who had a cryptogenic stroke and TEE-confirmed PFO were enrolled.

Cryptogenic stroke was defined as an acute focal neurologic deficit with symptoms that lasted >24 hours or an acute focal neurologic deficit with symptoms that lasted <24 hours but was associated with magnetic resonance or computed tomography findings of a new neuroanatomically relevant cerebral infarct. Subjects were randomized in a 1:1 ratio to device closure with the Amplatzer PFO Occluder or medical therapy alone. Participants assigned to the closure arm received acetylsalicylic acid 81−325 mg and clopidogrel for 1 month after device deployment to reduce platelet adhesion to the fresh implant; this was followed by acetylsalicylic acid monotherapy for 5 months, and thereafter at the site or investigator's discretion. One of four permissible medical regimens was assigned to patients in the medical therapy arm: acetylsalicylic acid, warfarin, clopidogrel, or acetylsalicylic acid plus extended-release dipyridamole. The RESPECT trial did not pre-specify a timeframe for stopping the study and performing an analysis; it was designed to assess the results only after the occurrence of 25 events (blinded to investigators by the data monitoring safety committee). The primary efficacy endpoint was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death following randomization (defined as death from any cause within 30 days after device implantation in the PFO closure group and from any cause within 45 days after randomization in the medical therapy group). The early follow-up of RESPECT, which ended when the target of 25 primary endpoint events had occurred, assessed patients for a median of 2.1 years [17]. The long-term follow-up of RESPECT analyzed the same patients for a median of 5.9 years [18].

Early Follow-Up of the RESPECT Trial

By trial design, a total of 25 primary endpoint events occurred, all of which were recurrent nonfatal ischemic strokes. The final results were evaluated using intention-to-treat, per-protocol, and as-treated analyses. In an intention-to-treat analysis, all participants are analyzed in the group to which they were originally randomized,

irrespective of the actual treatment received. In a per-protocol analysis, only participants who adhered to the original protocol are analyzed. This better estimates the efficacy of the intervention but is subject to selection bias due to cross-over and loss of follow-up. In an as-treated analysis, participants are analyzed according to the treatment that they received rather than according to the treatment they were originally assigned to. This analysis is subject to confounding bias but gives a sense of what happens to the subjects who actually received PFO closure versus only medical therapy.

In the intention-to-treat analysis (n = 980), 9 strokes occurred in the closure group (n = 499), compared to 16 strokes in the medical therapy group (n = 481). A raw count analysis of these data was deemed invalid based on the difference between the 2 groups in the number of patient-years of follow-up. Instead, a pre-specified time-to-event analysis was performed. The rate of the primary endpoint was 0.66 events per 100 patient-years in the closure group as compared with 1.38 events per 100 patient-years in the medical therapy group (HR 0.49, 95% CI 0.22−1.11, $P = .08$).

In the per-protocol analysis (n = 944), 6 events occurred in the closure group (n = 471), compared to 14 events in the medical therapy group (n = 473). The rate of the primary endpoint was 0.46 events per 100 patient-years in the closure group as compared with 1.30 events per 100 patient-years in the medical-therapy group (HR 0.37, 95% CI 0.14−0.96, $P = .03$).

In the as-treated analysis (n = 958), 5 events occurred in the closure group (n = 474), compared to 16 events in the medical therapy group (n = 484). The rate of the primary endpoint was 0.39 events per 100 patient-years in the closure group, compared with 1.45 events per 100 patient-years in the medical therapy group (HR 0.27, 95% CI 0.10−0.75, $P = .007$) (Table 6.2).

The rate of serious adverse events, including major bleeding, did not differ significantly when PFO closure was compared to medical therapy (23% vs. 22%, $P = .65$).

The intention-to-treat analysis of RESPECT did not show a statistically significant benefit of PFO closure compared to medical therapy in cryptogenic stroke patients found to have a PFO during the early median follow-up of 2.1 years. However, there was a positive trend, and the per-protocol and as-treated analyses showed a statistically significant benefit of PFO closure over medical therapy in those people who followed the protocol or who actually received the PFO-occluding device. Of the 9 primary events of recurrent ischemic stroke that occurred in the closure group of the intention-to-treat analysis, 3 occurred in patients who did not have a device in place at the time of the recurrent stroke. In one case, the stroke occurred after randomization but before the closure procedure. In the second case, the stroke occurred in a patient who decided not to undergo the procedure. In the last case, the stroke occurred after the patient underwent unanticipated coronary artery bypass surgery during which the PFO was closed with a surgical patch rather than with the assigned device.

TABLE 6.2 Results of the Early Follow-Up of the RESPECT Trial by Cohort Subtype [17].

	Intention-to-Treat Cohort (n = 980)	Per-Protocol Cohort (n = 944)	As-Treated Cohort (n = 958)
PFO Closure Group			
N	499	471	474
# of primary events	9	6	5
Rate of primary endpoint per 100 patient-years	0.66	0.46	0.39
Medical Therapy Group			
N	481	473	484
# of primary events	16	14	16
Rate of primary endpoint per 100 patient-years	1.38	1.30	1.45
PFO Closure Group Versus Medical Therapy Group			
Hazard ratio (95% CI)	0.49 (0.22−1.11)	0.37 (0.14−0.96)	0.27 (0.10−0.75)
P-value by log-rank test	0.08	0.03	0.007

CI, confidence interval; *PFO*, patent foramen ovale.

A hypothesis-generating subgroup analysis in the intention-to-treat cohort demonstrated enhanced efficacy of device closure if the PFO was associated with an atrial septal aneurysm (1.1% vs. 5.3%, HR 0.19, 95% CI 0.04−0.87, $P = .02$) or a large shunt (0.8% vs. 4.3%, HR 0.18, 95% CI 0.04−0.81, $P = .01$). The number needed to treat (NNT) to prevent 1 stroke at a 5-year follow-up was estimated to be 42 [18]; in comparison, a subanalysis of the final RESPECT trial results (median follow-up 5.9 years) showed a very low NNT when PFO closure was performed for stroke patients with an atrial septal aneurysm (NNT = 16) or large shunt (NNT = 20) (p-interaction = .04 for both) (Chapters 7 and 18). This is consistent with a prior epidemiologic study, which showed that an atrial septal aneurysm or a large shunt was associated with an increased likelihood of recurrent stroke [23].

Long-Term Follow-up of the RESPECT Trial

Because the results of the RESPECT trial were close to showing statistical significance in the intention-to-treat analysis and were impressive in the as-treated results, the Food and Drug Administration (FDA) agreed to have the RESPECT trial follow-up extended. Over a median follow-up time of 5.9 years, a total of 46 primary endpoint events occurred, all of which were recurrent nonfatal ischemic strokes. In the intention-to-treat cohort (n = 980), 18 events occurred in the PFO closure group (n = 499), compared to 28 events in the medical therapy group (n = 481), yielding rates of 0.58 events per 100 patient-years and 1.07 events per 100 patient-years, respectively (HR 0.55, 95% CI 0.31−0.999, $P = .046$) [18].

It was assumed that if the RESPECT trial extended follow-up, as subjects aged, there would be recurrent events due to other causes, such as atherosclerosis or atrial fibrillation, in addition to possible recurrent paradoxical embolic events. When the ASCOD phenotyping of ischemic stroke (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: dissection) was applied to classify the 46 recurrent ischemic strokes, 13 of the 46 (28%) strokes were associated with a known mechanism that was determined to be unrelated to PFO and the remaining 33 strokes had an undetermined cause. In the closure group, there were 10 of 33 (30%) strokes of undetermined mechanism, compared to 23 of 33 (70%) strokes in the medical therapy group. This yielded rates of 0.32 events per 100 patient-years and 0.86 events per 100 patient-years, respectively (HR 0.38, 95% CI 0.18−0.79, $P = .007$). Thus, with longer follow-up of these subjects, even with the intention-to-treat analysis, the trial showed a statistically significant difference between device closure of PFO and medical therapy.

The rate of serious adverse events in the long-term follow-up was 40.3% in the PFO closure group and 36% in the medical therapy group ($P = .17$). The 25 serious adverse events in the PFO closure group were adjudicated as being device-related (e.g., ischemic stroke, pulmonary embolism, residual shunt requiring closure) or procedure-related (e.g., cardiac tamponade and bleeding).

One limitation of the RESPECT trial was a difference in the dropout rates between the PFO closure and medical therapy groups. In the long-term follow-up of RESPECT, the dropout rate was 20.8% in the PFO closure group and 33.3% in the medical therapy group. This significant difference in dropout rate between the 2 groups resulted in unequal duration of exposure to the risk of recurrence, thereby complicating interpretation of the results. Loss of patients from the medical therapy group was thought to be due to availability of off-label septal occluder devices that were approved by the FDA for atrial septal defect closure; additionally, the high dropout rate in the medical therapy arm may further be explained by patients' reluctance to remain in a long-term follow-up study when the only therapy received was a blood thinner. Moreover, selection bias could have been present in all trials due to the possibility that high-risk patients were preferentially treated outside the trial with PFO closure. Either patients or referring physicians were less likely to enroll subjects who had large strokes or large shunts and were thought to be at higher risk of recurrent stroke [22].

A COMMON LIMITATION OF ALL THE EARLY RANDOMIZED TRIALS

All of the early randomized clinical trials comparing percutaneous PFO closure to medical therapy overestimated the expected recurrent stroke rate. The estimate of 3% per year was based on the available observational studies reporting a range of 1%−8% [24,25]. They may have overemphasized the risk and raised expectations for the new entity of paradoxical embolism causing cryptogenic stroke. The actual recurrent stroke rate in the early and later randomized controlled trials was consistently about 1% per year in the medically treated group. This led to underpowered trials.

META-ANALYSES OF THE EARLY TRIALS OF PFO CLOSURE FOR STROKE

Several meta-analyses of CLOSURE I, PC, and the early RESPECT trial were conducted in an effort to increase the sample size and reduce the risk of type II error [26–30]. Most of these showed that PFO closure was beneficial as compared to medical therapy in the prevention of recurrent stroke.

Kent et al. performed a pooled analysis of individual participant data from CLOSURE I, PC, and RESPECT to better synthesize data from the 3 randomized clinical trials [26]. An individual participant data–based meta-analysis was chosen over an aggregate data–based meta-analysis to standardize outcome definitions and analyses across the studies, address any missing data, perform covariate adjusted analyses, and assess for the possibility of heterogeneity of treatment effects acrosss subgroups. Consequently, many experts believe this meta-analysis to be the most relevant one. This patient level pooled analysis gave rise to a new database comprising of 2303 randomized patients. Fig. 6.1 depicts Kaplan–Meier curves for the primary composite outcome, defined as ischemic stroke, TIA, or death from any cause. The primary outcome was observed in 1.5% (45/3057) of patients in the device group and 2.3% (63/2792) of patients in the medical therapy group. Unadjusted Cox proportional hazards modeling of this data narrowly missed statistical significance (HR 0.69, 95% CI 0.47–1.01, $P = .053$). However, once these same data were adjusted for age, sex, race, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, index event (stroke vs. TIA), atrial septal aneurysm, and PFO shunt (large vs. small), device closure was statistically favorable (HR 0.68, 95% CI 0.46–1, $P = .049$). Of note, the stated covariates were selected based on the Risk of Paradoxical Embolism (RoPE) score (Chapter 4). The same composite outcome using an as-treated analysis occurred in 1.4% (40/2948) of patients in the PFO closure group and 2.3% (66/2877) of patients in the medical therapy group (HR 0.64, 95% CI 0.43–0.95, $P = .025$). Once these data were adjusted in the same manner as mentioned above, the findings remained statistically significant (HR 0.63, 95% CI 0.43–0.94, $P = .025$). Safety outcomes of interest included atrial fibrillation, which was higher in the device group (1.44% vs. 0.48%, HR 3.22, 95% CI 1.76–5.90, $P = .0002$) and major bleeding episodes, which were balanced (3.7% vs. 3.7%, HR 1.11, 95% CI 0.48–2.56, $P = .81$).

This pooled analysis showed that although patients aged ≤60 years with PFO-associated stroke had a relatively low stroke recurrence rate on medical therapy, the subgroup treated with PFO closure had a significantly lower primary outcome rate compared with standard of care medical therapy in adjusted analyses. This provided support that PFO closure could be a reasonable therapeutic option in certain cases of cryptogenic stroke. The NNT over 2.5 years to avert 1 primary composite outcome event was 50 and to avert 1 ischemic stroke was 67. A benefit of this magnitude may be clinically important to some patients, especially the younger stroke patients with a long life expectancy.

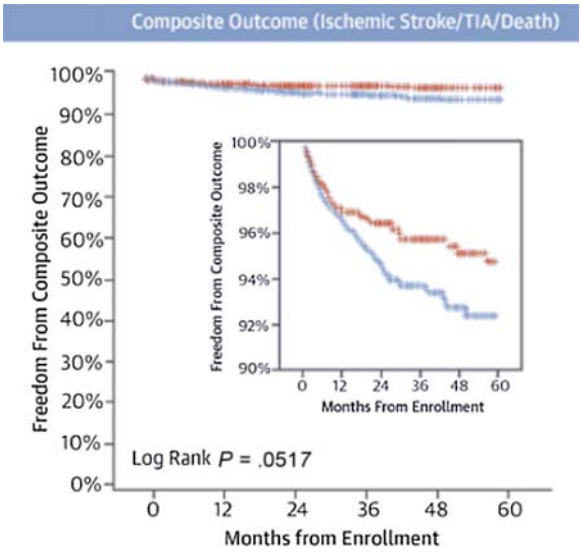

FIGURE 6.1 Kaplan–Meier curve comparing device closure (*red*) versus medical therapy (*blue*) for the primary composite outcome in a patient-level meta-analysis of 3 trials. *Adapted with permission from Ref. [26].*

TABLE 6.3 A Comparison of the Incidence of Atrial Fibrillation in the PFO Closure and Control Arms in the Early PFO Closure in Cryptogenic Stroke and PFO Closure in Migraine Randomized Controlled Trials.

		PFO Device Used	Mean Age (years)		Incidence of Atrial Fibrillation	
			PFO Closure Arm	Control Arm	PFO Closure Arm	Control Arm
PFO Closure in Cryptogenic Stroke Randomized Control Trial	CLOSURE I (15)	STARFlex	46.3 ± 9.6	45.7 ± 9.1	23/447 (5.15%)	3/462 (0.65%)
	PC trial (16)	Amplatzer	44.3 ± 10.2	44.6 ± 10.1	6/204 (2.94%)	2/210 (0.95%)
	Long-term RESPECT (18)	Amplatzer	45.7 ± 9.7	46.2 ± 10.0	6/499 (1.20%)	4/481 (0.83%)
PFO Closure in Migraine Randomized Control Trial	MIST (31)	STARFlex	44.3 ± 10.6	44.6 ± 10.4	2/74 (2.70%)	0/73 (0%)
	PRIMA (32)	Amplatzer	44.1 ± 10.7	42.7 ± 11.0	1/53 (1.89%)	0/54 (0%)
	PREMIUM (33)	Amplatzer	42.8 ± 10.3	43.7 ± 10.2	1/117 (0.85%)	0/103 (0%)

PFO, patent foramen ovale.

One caveat though is that atrial fibrillation was increased with PFO closure (Table 6.3). There were more episodes of atrial fibrillation observed in the PFO closure arm in the early randomized clinical trials looking at the efficacy of PFO closure for cryptogenic stroke as well as for migraine headache. Of note, the migraine population were slightly younger and followed up for a shorter period of time. It was therefore concluded that the PFO closure device itself induced atrial fibrillation by direct irritation and inflammation, which subsequently promoted endocardialization, i.e., encasement of the devices with neo-endocardium. Another observation made was that there were numerically more episodes of late atrial fibrillation in the medically treated cryptogenic stroke patients than for the medically treated migraine patients. Although 0.8% (9/1153) of patients in the combined medical therapy arms of CLOSURE I, PC, and early RESPECT experienced atrial fibrillation, 0% (0/230) of patients in the combined medical therapy arms of MIST [31], PRIMA [32], and PREMIUM [33], the randomized clinical trials investigating the efficacy of PFO closure for migraines (Chapter 11), had atrial fibrillation. This suggests that a few of the cryptogenic stroke subjects may have had atrial fibrillation, instead of a paradoxical embolus, as the index stroke culprit. However, since this difference is not statistically significant ($P = .37$ per Fisher's exact test), it can only be considered to be a hypothesis. Another explanation is that the migraine population was somewhat younger and therefore less subject to developing atrial fibrillation within the relatively short (1 year) follow-up. Nevertheless, this observation raised the issue of meticulously ruling out occult atrial fibrillation as a cause of the index stroke with prolonged monitoring (2–4 weeks) of the cardiac rhythm [34,35]. It has to be kept in mind that in the presence of both atrial fibrillation and a PFO, an ischemic event can result from either condition.

Kent et al. performed a second, individual patient–level meta-analysis to compare the effectiveness of oral anticoagulation to antiplatelet therapy for secondary stroke prevention in medically treated patients with cryptogenic stroke and PFO [36]. The meta-analysis incorporated 12 different studies, 4 of which were PICSS, CLOSURE I, PC, and early RESPECT. Oral anticoagulation included only warfarin. Antiplatelet therapy regimens included acetylsalicylic acid, clopidogrel, ticlopidine, and acetylsalicylic acid plus dipyridamole. A subgroup sensitivity analysis limited to the aforementioned 4 studies did not detect a statistically significant difference in the primary composite outcome of recurrent stroke, TIA, death (HR 0.63, 95% CI 0.23–0.71), or the secondary outcome of stroke alone (HR 0.53, 95% CI 0.14–2.04). Of note, similar results were seen for the main analysis including all 12 studies. The authors concluded that available data from these trials did not provide definitive evidence of whether oral anticoagulation or antiplatelet therapy was better for medically treated patients with cryptogenic stroke and PFO. Interestingly, in the RESPECT trial, 17/499 (3.4%) patients in the device group and 4/481 (0.8%) patients in the medical management group had venous thromboembolic (VTE) events (5 deep vein thrombosis [DVT] and 13 pulmonary embolisms [PE] in the device group vs. 1 DVT and 3 PE in the medical group). Given this imbalance of events, the device cohort was further divided into those without VTE (n = 482) and those with VTE (n = 17), and Fisher's exact test was performed on numerous characteristics to look for differences. The only characteristic to reach a statistical significance was history of DVT: of 482 device patients who did not develop a VTE, 15 (3.11%) had a history of DVT whereas 5 of the 17 (29.41%) device patients who developed a VTE had a history of DVT ($P = .0003$). This finding supports the widely accepted notion that a history of DVT predisposes one to a second VTE. Other characteristics such as atrial septal aneurysm, shunt grade, and hypercoagulable state did not reach statistical significance. A separate analysis of the RESPECT data showed that the imbalance of VTE events in the device and medical arms was primarily driven by

higher warfarin use in the medical arm (512/2671 patient-years [19%] versus 52/3116 patient-years [2%] in the device group). Of note, no patients on warfarin developed a DVT or PE. This is another probable explanation as to why there were more VTE events in the device group compared to the medical management group. A third analysis of the RESPECT data suggested a significantly lower rate of recurrent ischemic stroke with PFO closure than with antiplatelet medical therapy (10/367 [2.7%] versus 23/360 [6.4%], HR 0.38, 95% CI 0.18−0.79, $P = .007$) but not when compared with anticoagulant medical therapy (8/132 [6.1%] versus 5/121 [4.1%], HR 1.32, 95% CI 0.43−4.03, $P = .63$). However, since RESPECT was not originally powered to assess the impact of different medication regimens on secondary stroke prevention, this finding can only be considered as hypothesis generating. Taken together, these observations from the RESPECT trial tell us that in terms of medical therapy for patients with cryptogenic stroke and PFO, if there is a history of DVT, clinicians should consider anticoagulation even after the PFO is closed. Otherwise, an antiplatelet agent such as acetylsalicylic acid might be acceptable with a lower risk of bleeding [18].

FDA APPROVAL OF PERCUTANEOUS PFO CLOSURE FOR STROKE

The FDA approval process of PFO closure for cryptogenic stroke in the United States was a long and challenging journey [37]. Prior to October 2006, PFO closure was performed solely under humanitarian device exemption (HDE) use for patients who had a recurrent cryptogenic stroke from a PFO and failed conventional medical therapy. Devices that had received HDE approval were the Amplatzer PFO Occluder and the CardioSeal Septal Occlusion System (NMT Medical, Boston, Massachusetts). However, in October 2006, the FDA requested that the HDE approvals for both devices be voluntarily withdrawn because the number of patients eligible for PFO closure exceeded the regulatory limit of 4000 patients per year, thus meeting the criteria for requiring a randomized clinical trial.

The landmark RESPECT trial changed this regulatory quagmire. The short-term RESPECT results (median follow-up of 2.1 years) published in 2013 demonstrated a significantly lower rate of recurrent stroke in the PFO closure group as compared to the medical therapy group in the as-treated analysis but not in the intention-to-treat analysis. These findings were submitted to the FDA with the hope of obtaining premarket approval of the Amplatzer PFO Occluder. However, the FDA requested additional information, including supplementary analyses. Over the following 3 years, attempts to satisfy the FDA's requests were made, and even a proposal for limited use was submitted, but no agreement was reached. Finally, in October 2015, the long-term RESPECT results (median follow-up of 5.9 years) became available. As already mentioned earlier in this chapter, the intention-to-treat analysis demonstrated a significant reduction in recurrent ischemic strokes in the PFO closure arm. In May 2016, an FDA advisory panel reviewed the submitted data and voted 15 "yes" to 1 "no" for device safety, 9 "yes" to 7 "no" for effectiveness, and 11 "yes" to 5 "no" for benefits of the device outweighing the risks [38]. As a result, on October 28, 2016, the FDA approved the Amplatzer PFO Occluder for "percutaneous transcatheter closure of a PFO to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to presumed paradoxical embolism, as determined by a neurologist and cardiologist after an evaluation to exclude known causes of ischemic stroke" [39]. The Amplatzer PFO Occluder became the first device commercially available in the United States for use in patients with presumed PFO-mediated stroke. This approval for recurrent stroke prevention capped a 16-year journey in the United States in which several devices were used, some under an HDE and some as part of randomized clinical trials. More recently, the Gore Cardioform Septal Occluder was the second PFO-occluding device that was approved by the FDA in April 2018 for the same indication (Chapter 7) [40].

CONCLUSION

Although CLOSURE I, PC, and the early RESPECT data did not independently show a statistically significant benefit of PFO closure compared to medical therapy in the primary analyses, meta-analyses of these studies and the long-term RESPECT trial results eventually demonstrated superiority of PFO closure over standard of care medical therapy for secondary prevention of stroke. The follow-up time is important because the recurrent stroke rate in these early trials was about 1% per year, less than what was predicted based on the early observational studies (Chapter 5). This explains why the first attempt to get the FDA to approve PFO closure for prevention of recurrent stroke in someone with a PFO-mediated stroke was unsuccessful. It took longer follow-up analysis of the RESPECT

trial data, 3 subsequent randomized trials, and meta-analyses of all trials to demonstrate the efficacy of PFO closure to prevent recurrent stroke in patients with stroke thought to be from paradoxical embolism (Chapter 7) [41–47]. FDA and guideline committees paid no attention to the fact that in all randomized trials, device closure was numerically superior to medical treatment. Noninferiority would have been proved by that in respectively designed trials. Rather than classifying PFO closure as a valuable alternative to lifelong platelet inhibitors or oral anticoagulation with their relentlessly accruing bleeding events, it was discouraged outside of randomized trials. Many physicians intuitively randomized lower-risk PFO patients but closed high-risk PFOs. They did well for these individual patients, as we now know, but they hampered enrollment in the randomized trials.

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