Structural Interventions
AMPLATZER™ PFO Occluder

CLINICAL INSIGHTS:

CLINICAL EVIDENCE FOR PFO OCCLUSION FOR RECURRENT STROKE RISK REDUCTION USING THE AMPLATZER™ PFO OCCLUDER

Abbott

Clinical Insights

A PUBLICATION DELIVERING CONCISE CLINICAL DATA

AMPLATZER™ PFO OCCLUDER

CLINICAL EVIDENCE FOR PFO OCCLUSION FOR RECURRENT STROKE RISK REDUCTION USING THE AMPLATZER™ PFO OCCLUDER

INTRODUCTION

Approximately one-third of ischemic strokes cannot be attributed to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite extensive vascular, cardiac, and serologic evaluation[1]. These strokes of undetermined mechanism account for an annual number of approximately 200,000 and 300,000 strokes in the US and the EU, respectively[1,2].

While a patent foramen ovale (PFO) is not considered a risk factor for stroke in general, its presence is commonly reported in patients with a stroke of undetermined mechanism. A meta-analysis of data from 22 studies showed that a PFO is more likely to be associated with such a stroke compared with stroke of determined mechanism (OR: 3.16, 95% CI: 2.30 – 4.35)[3], with a strong association especially in patients younger than 55 years[4]. Paradoxical embolism through a PFO has been suggested as a mechanism leading to a stroke in the absence of established risk factors for ischemic stroke. Factors that may influence the risk for stroke in the setting of a PFO include the size of the PFO and the significance of shunting[5,6], the coexistence of an atrial septal aneurysm (ASA)[3] and venous thrombosis[7].

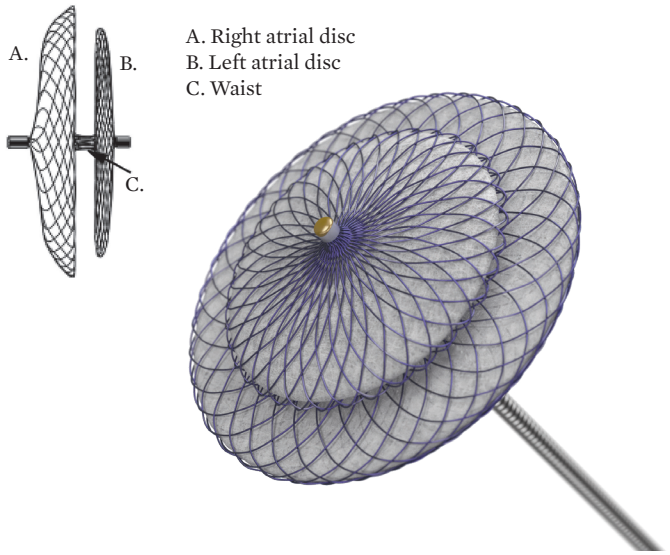
Given the mechanism of paradoxical embolism, PFO closure has been suggested as a secondary stroke prevention treatment in patients who suffered a stroke of undetermined mechanism. As younger patients are less likely to have established stroke risk factors, randomized trials on prevention of recurrent stroke by PFO closure have consistently enrolled patients younger than 60 years.

AMPLATZER PFO OCCLUDER

The AMPLATZER PFO Occluder was first implanted in September 1997 by Dr Kurt Amplatz and Dr Bernie Meier. The design of the device builds on extensive technological and clinical experience with the AMPLATZER portfolio of occlusion devices.

The AMPLATZER PFO Occluder consists of two self-expanding discs from nitinol mesh, connected by a short waist (see Figure 1). The waist connecting the right atrial disc and the smaller left atrial disc allows free motion of each disc and is designed to centralize the device within the PFO. The discs are designed to be introduced in the heart in a collapsed configuration, and will self-deploy at specific steps during the implantation procedure. To increase its closing ability, the device is filled with polyester fabric that is securely sewn to each disc by a polyester thread. Radiopaque marker bands are on the distal and proximal ends of the device. An end screw on the proximal end facilitates connection with the delivery cable during implantation.

FIGURE 1



RECENT CLINICAL EVIDENCE

Results from 3 large, randomized controlled trials using the AMPLATZER PFO Occluder and/or competitive devices have recently been reported (Table 1).

Among these trials, the RESPECT trial[8] is the most extensive study with regard to the number of patients as well as follow-up duration. Medical therapy in the control group involved antiplatelets only (REDUCE and CLOSE trials[9,10]) or antiplatelets or warfarin therapy (RESPECT trial[8]). Regarding patient inclusion, the CLOSE trial[10] required the presence of an ASA or a significant right-to-left shunt, which constituted additional requirements compared with the other 2 trials. Although this trial did not report results separately per device, the outcomes were dominated by the AMPLATZER PFO occluder, which was used in 51% of the procedures.

SAFETY

Key safety outcomes reported from the 3 trials are summarized in Table 2. Although the studies found variable numerical results regarding serious adverse event rates, none of the trials detected a significant difference between patients randomized to PFO closure or medical therapy.

The lowest incidence of new-onset atrial fibrillation (AF) was reported from the RESPECT trial. The incidence of AF outside of the periprocedural period was not significantly different between the PFO and control arms. Even when accounting for the separately reported 7 cases of periprocedural AF, the

TABLE 1: LARGE RANDOMIZED CONTROLLED TRIALS ON PFO CLOSURE WITH RECENTLY REPORTED RESULTS

	RESPECT[8]	REDUCE[9]	CLOSE[10]
Study description	Multicenter randomized controlled trial of PFO closure versus medical treatment	Multicenter randomized controlled trial of PFO closure versus medical treatment	Multicenter randomized controlled trial of PFO closure versus medical treatment
Key inclusion criteria	Echocardiographic evidence of PFO, age ≤60 years	Echocardiographic evidence of PFO, age ≤60 years	PFO associated with ASA or large right-to-left atrial shunt, age ≤60 years
PFO closure therapy: **Number of patients** **Mean age (years)** **Therapy**	 499 45.7 ± 9.7 AMPLATZER PFO occluder, APT for 6 months followed by antithrombotic therapy at the discretion of the site investigator	 441 45.5 ± 9.3 Gore PFO occluders, APT	 238 42.9 ± 10.1 CE-marked PFO occluders, DAPT for 3 months followed by single antiplatelet therapy for the remainder of the trial
Control: **Number of patients** **Mean age (years)** **Therapy**	 481 46.2 ± 10.0 APT or warfarin therapy	 223 44.8 ± 9.6 APT	 235 (see note) 43.8 ± 10.5 APT
Follow-up (years) **Total follow-up (patient years)**	Median: 5.9 3141 (PFO) 2669 (control)	Median: 3.2 1529 (PFO) 703 (control)	Mean: 5.4 (PFO) / 5.2 (control) NR

(D)APT: (dual) antiplatelet therapy; ASA: atrial septal aneurysm; NR: not reported
NOTE: The CLOSE trial also compared APT with anticoagulation therapy (not included in this document).

overall incidence of AF associated with the AMPLATZER device appears to be lower than with the GORE devices used in the REDUCE trial or the mix of devices used in the CLOSE trial. Similar observations, favoring the AMPLATZER PFO Occluder, were made from a meta-analysis including results of the CLOSURE I study (StarFlex Septal Closure System) and the PC trial and early results of the RESPECT trial (AMPLATZER PFO Occluder). Based on outcomes from all 3 trials, the risk of AF was significantly higher among patients treated with PFO closure compared with medical therapy (hazard ratio (HR): 3.22; p=0.0002)[11]. With the analysis restricted to the AMPLATZER PFO Occluder, the difference in AF incidence was no longer significant (HR: 1.85; p=0.12)[11]. Both analyses (i.e. including data from all 3 trials, as well as data from AMPLATZER devices only) did not show a significant difference in bleeding rates between PFO closure and medical therapy[11].

Long-term follow-up of the RESPECT study showed a higher incidence of venous thromboembolism in the PFO group than in the medical therapy group. This difference was specifically prominent in patients with a history of deep venous thrombosis and may be explained by the lower usage of oral anticoagulants in the PFO closure group compared with medical therapy (3.4% vs. 21.8% of the follow-up time).

CLINICAL OUTCOME

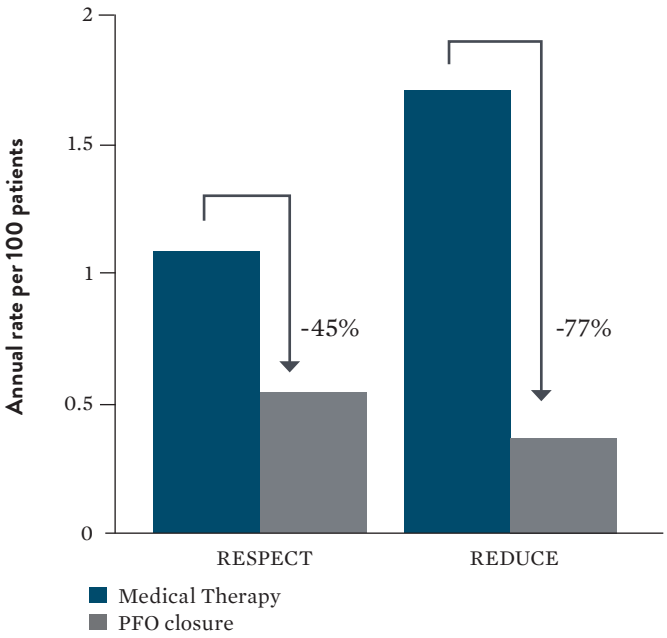
Both the RESPECT[8] and REDUCE[9] trials reported a marked reduction in the rate of all ischemic strokes after PFO closure, compared with medical therapy (see Figure 2). The difference in outcomes between these trials may be related to the different antithrombotic regimens (APT only in REDUCE versus APT or anticoagulants in RESPECT) and the different follow-up periods. Despite these differences, both trials underline the

	RESPECT[8]		REDUCE[9]		CLOSE[10]	
	PFO	Control	PFO	Control	PFO	Control
SAE rate throughout the follow-up period (%)	40.3	36.0	23.1	27.8	35.7	33.2
	P = 0.17		*P* = 0.22		*P* = 0.56	
Procedure-related SAE (%)	2.4		2.5		5.9 (note)	
Device-related SAE n (event per 100 pt-yr rate)	13 (0.4)		6 (0.4*)			
All-Cause Death (%)	1.4	2.3	0.5	0	0	0
	P - value NR		*P* = 0.55		-	
Serious Atrial fibrillation / flutter % (n, n per 100 pt-yr rate)	1.4% (7, 0.22 per 100 pt-yr)	0.6% (3, 0.11 per 100 pt-yr)	2.3% (10, 0.65 per 100 pt-yr*)	0.4% (1, 0.14 per 100 pt-yr*)	4.6% (NR†)	0.9% (NR†)
Any AF/Flutter % (n, n per 100 pt-yr rate)	4.8% (24, 0.76 per 100 pt-yr)	1.9% (9, 0.34 per 100 pt-yr)	6.6% (29, 1.90 per 100 pt-yr*)	0.4% (1, 0.14 per 100 pt-yr*)	NR	NR
DVT / PE n of patients (%)	20 (4.0)	4 (0.8)	3 (0.7)	2 (0.9)	NR	
Serious bleeding (%)	NR		1.8	2.7	0.8	2.1
			P = 0.57		*P* = 0.28	

SAE: serious adverse event; DVT: deep-vein thrombosis; PE: pulmonary embolism; NR: not reported
Note: The CLOSE trial reported procedure- or device-related complications together and did not report patient years.

*Rates calculated based on data in final publication.
†Follow-up patient-years was not reported for CLOSE Trial.

FIGURE 2: COMPARISON OF STROKE RATES ACHIEVED BY PFO CLOSURE VERSUS MEDICAL THERAPY, REPORTED FROM THE RESPECT TRIAL (USING THE AMPLATZER PFO OCCLUDER)[8] AND THE REDUCE TRIAL (USING GORE OCCLUDERS)[9].



potential of PFO closure to reduce the risk of recurrent ischemic stroke in patients who experienced a stroke of undetermined mechanism. This potential was further demonstrated by a meta-analysis of results reported from the CLOSURE I study, the PC trial and early results of the RESPECT trial. This analysis showed that PFO closure achieved a significant reduction in stroke rate compared with medical therapy, when including data from all 3 trials (42% reduction) and data obtained with the AMPLATZER PFO Occluder alone (59% reduction)[11]. Of further note, in an editorial related to this meta-analysis it was estimated that approximately 8 to 11 patients need to be treated to prevent one stroke over a 15 to 20 year time frame[12]. This period is considered reasonable, given the relatively young age (~45 years) of patients enrolled in the analyzed trials. The editorial concluded that currently available scientific data support PFO closure combined with medical therapy as a more effective treatment than medical therapy alone.

In the RESPECT trial, PFO closure and medical therapy were associated with similar rates of recurrent stroke of a determined mechanism (0.25 and 0.19 events per 100 patient-years, respectively; p=0.60)[8]. However, recurrent strokes of undetermined mechanism, presumably mediated by a PFO, were significantly less common in patients treated with PFO closure than in patients on medical therapy alone (0.32 vs. 0.86 events per 100 patient-years, respectively; p=0.007; relative risk reduction: 62%). Further analysis suggested that patients with an atrial septal aneurysm and those with a substantial right-to-left shunt might have an even greater relative benefit of PFO closure.

In the CLOSE study[10], with AMPLATZER PFO Occluders being implanted in 51% of the procedures, PFO closure achieved a relative risk reduction for recurrent ischemic stroke of 97%, compared with antiplatelet therapy (no strokes in the PFO closure group vs. 14 in the APT group). This high risk reduction should be interpreted in view of the risk profile of patients enrolled for this trial (i.e. presence of an atrial septal aneurysm or significant shunt). For instance, of the 14 recurrent strokes in the APT group, 9 occurred in the 74 patients with an atrial septal aneurysm.

CONCLUSIONS

- Clinical evidence from 3 recently published randomized controlled trials as well as results from a recent meta-analysis show that PFO closure using the AMPLATZER PFO Occluder or other competitive devices is a generally safe and effective therapy for prevention of recurrent ischemic stroke in patients younger than 60 years who had a stroke of undetermined mechanism.

- Clinical data indicates that the safety of the therapy depends on the type of device, which may be inherent to their design features and materials. In the PFO closure arms of RESPECT and REDUCE, the overall observed rate of AF/Flutter was lower in RESPECT using the AMPLATZER PFO device versus in REDUCE using the GORE devices. In RESPECT, the rate of serious and non-serious atrial fibrillation events beyond the periprocedural period did not differ significantly between the PFO closure group and the medical therapy group.

REFERENCES

1. Truelsen T, Piechowski-Jozwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. Eur J Neurol. 2006;13:581-598.
2. Mozaffarian D, Benjamin E, Go A, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133:e38-e360.
3. Overell J, Bone I, Lees K. Interatrial septal abnormalities and stroke - A meta-analysis of case-control studies. Neurology. 2000;55:1172-1179.
4. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med. 2007;357:2262-8.
5. Steiner M, Di Tullio M, Rundek T, et al. Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. Stroke. 1998;29:944-948.
6. Stone D, Godard J, Corretti M, et al. Patent foramen ovale: association between the degree of shunt by contrast transesophageal echocardiography and the risk of future ischemic neurologic events. Am Heart J. 1996;131:158-61.
7. Cramer S, Rordorf G, Maki J, et al. Increased pelvic vein thrombi in cryptogenic stroke: results of the Paradoxical Emboli from Large Veins in Ischemic Stroke (PELVIS) study. Stroke. 2004;35:46-50.
8. Saver J, Carroll J, Thaler D, et al. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. New Engl J Med. 2017;377:1022-1032.
9. Søndergaard L, Kasner S, Rhodes J, et al. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. New Engl J Med. 2017;377:1033-1042.
10. Mas J, Derumeaux G, Guillon E, et al. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. New Engl J Med. 2017;377:1011-1021.
11. Kent D, Dahabreh I, Ruthazer R, et al. Device Closure of Patent Foramen Ovale After Stroke - Pooled Analysis of Completed Randomized Trials. J Am Coll Cardiol. 2016;67:907-917.
12. Love B, Diener H. PFO - "Please Figure Out," or Now "Potentially Figured Out?" J Am Coll Cardiol. 2016;67:918-920.

Abbott Vascular International BVBA, Park Lane, Culliganlaan 2B, 1831 Diegem, BELGIUM