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Clinical evaluation of a novel occluder device (Occlutech®) for percutaneous transcatheter closure of patent foramen ovale (PFO)

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■ **Abstract** *Background* We investigated the safety, feasibility and usefulness for closure of PFO with the new nitinol meshwire PFO-occluder device (Occlutech Figulla®-single layer occluder) with an unique braiding technology which allows a 50% reduction of meshwork material on the left atrial side in combination with a greater flexibility as compared to the Amplatzer® occluder device. *Methods* The retention discs of the new PFO Occlutech Figulla® single layer device (23/25 mm) are connected by a 3 mm waist in the centre with only one right atrial side hub. The left atrial disc is a single flat layer covered by an ultrathin polyethylene terephthalate (PET) patch. We investigated the safety, feasibility and usefulness for closure of PFO in a multicenter clinical trial. Indications for closure included cryptogenic stroke with evidence of a patent foramen ovale in transesophageal echocardiography (PFO max. diameter 13 mm according to sizing balloon). The device was implanted in 36 patients (mean age 57, 18–80 years) by means of fluoroscopy and transesophageal echocardiography (TEE) using a 9 French delivery sheath and employing a femoral vein approach. Both acetylsalicylic acid 100 mg/d (6 months) and clopidogrel 75 mg/d (3 months) were administered post interventional. A transthoracic (TTE) and transesophageal echocardiography follow-up examination was performed after 1, 2 and 6 months (TTE day 30 and 180; TEE day 60). *Results* The device was successfully implanted in 36 pts. In one patient PFO implantations was attempted but not crossed with a guide wire. Perioperatively there were no major in-hospital-adverse events or complications thromboembolism, occluder dislodgement, infection or myocardial infarction. One patient had transient atrial fibrillation 2 h after implantation, which terminated medically after 12 h. TEE studies in the remaining 35 pts (one pt was unwilling to further participate) showed a residual shunt in 8.6% (3/35) after 60 days and a left-to-right shunt in 2.6% (1/35) of pts. After 180 days one pt with severe arteriosclerotic heart disease and A.carotic stenosis revealed a stroke without evidence of cardioembolic origin or devices thrombosis. *Conclusions* The novel Occlutech Figulla® PFO N single layer device appears to be safe, feasible and useful for PFO closure despite a 50% reduction of the meshwire, no distal hub and an improved flexibility of the left atrial disc.

■ **Key words** PFO – paradoxical embolism – device

Introduction

The patent foramen ovale (PFO) is an open passage between the superior limb of the septum secundum in right atrium and the septum primum in left atrium. It represents a normal interatrial communication with that is present throughout fetal life.

Functional closure normally occurs postnatal, although in about 27% of humans anatomical fusion does not occur. In the case of a right-to-left shunt, paradoxical embolization may occur with a resulting of transient ischemic attack or a stroke. In 35–44% of pts with ischemic stroke, the origin remains unknown (“cryptogenic”). The prevalence of PFO is higher in cryptogenic stroke groups than in control groups (44–66%) [1, 2, 6, 7].

Transcatheter interventional closure of a PFO has become a routine procedure for adults and children with a low risk of periprocedural complications and good long term findings according to the results in large retrospective studies [3, 4, 9, 17, 19]. Since the implantation of the first device, several different systems have been designed and developed in order to improve feasibility, efficacy and safety.

Nevertheless residual shunts, arrhythmias, recurrent stroke and incomplete adaptation on the interatrial septum may occur. It was our aim to develop a novel occluder to minimize left atrial material, easy to deploy, at every stage retrievable, without nitinol arms that might fracture or penetrate.

The product profile includes complete defect closure, rapid tissue ingrowth, low profile and conformity to variations in septal anatomy.

Methods

■ The occluder device

The occluder device, developed using a unique patented braiding technique, consists of a nitinol wire mesh (0.12 mm) that forms two flexible retention discs (diameter 23/25 mm) allowing a single hub on the right atrial side. The discs are connected by a 3 mm waist in the center. Two polyethylene terephthalate (PET) patches assure complete closure after implantation. (Figs. 1, 2, 3)

The novelty lies in the fact that the left atrial disc consists of only a single layer with no hub thereby minimizing the amount of material on the left atrial side.

The device is characterized by its high flexibility, an ease of handling, the property of self centering in the shunt and its facility of recapture before disconnection from introducer wire.



Fig. 1 The retention disc are forming a very low profile. A screw thread on the proximal disc is connected with an “introducer wire”



Fig. 2 Figulla™-PFO Occluder N single layer without a left atrial hub



Fig. 3 Occlutech Figulla® PFO occluder N single layer in LAO 40° projection

The device was tested in a porcine swine model and both angiographic as well as histopathological examination were performed.

Table 1 Patient demographics (*n* = 37)

Age (years)	mean 57 years
Male	18
Female	17
Defect type	PFO
Defect size mean, mm	7.8 ± 2.5

■ Patients

In an open, prospective, nonrandomized multicenter clinical study, we investigated the usefulness feasibility and safety of the Occlutech Figulla® single layer-PFO occluder N for closure of PFO.

The implantation was successfully performed in 36 pts (mean age 57, 18–80 years), in one pt the wire could not be crossed through the PFO (Table 1).

All pts suffered from cryptogenic stroke and gave written informed consent. The trial was approved by the local ethical committee and the international ethical committee Freiburg.

■ Exclusion criteria

Atrial fibrillation, significant stenosis of the carotid arteries, known thrombophilic disorders, pregnancy, recent myocardial infarction, acute infection and allergic reaction to clopidogrel, aspirin and nickel, age <18 years, PFO diameters >13 mm by balloon sizing were exclusion criteria.

■ Implantation procedure

The right femoral vein was punctured under local anaesthesia and a soft-tipped 0.035" wire was inserted and advanced through the PFO, and finally positioned within a left-sided pulmonary vein. Intravenous heparin (100 IU/kg) was administered. With the help of a compliant 25 mm sizing balloon (NuMED Inc. 2880 Main Street, Hopkinton, NY, 12965 USA), the size and anatomy of the defect was determined. A defect size of over 13 mm was an exclusion criterion. After that a Cook® 9F delivery sheath was advanced to the left atrial side over the guide wire. The PFO-occluder was subsequently loaded in a 9F Cook® delivery sheath and advanced by means of the pusher cable to the left atrial side. After opening the LA disc, the system was retracted until the LA disc was positioned opposite the left interatrial septum. The right atrial disc was deployed thereafter. After correct position was confirmed by means of fluoroscopy and transesophageal echocardiography an initial residual right-to-left-sided shunt was ruled out by contrast injection through the delivery sheath and angiography. The device was disconnected at the end of the procedure. A prophylaxis

for the prevention of endocarditis was recommended for 6 months according to guidelines.

■ Endpoints of the study

The primary endpoint of the study was defined as usefulness and safety of the closure device. That included device failure, left atrial thrombus formation, major periprocedural complications, position of the occluder after 6 months, major adverse events, including peripheral thromboembolism, occluder dislodgement or endocarditis. Secondary end points of the study were defined as efficiency of PFO closure, determined by the investigation of a relevant residual shunt by means of TTE and TEE methods.

■ Follow-up

On the first day after implantation all patients underwent fluoroscopic control, ECG and a laboratory examination. For ninety days after procedure all patients continued taking a daily dose of 75 mg clopidogrel. Aspirin was given at a dose of 100 mg for 180 days post-procedure. Transesophageal echocardiographic (TEE) follow-up examination was performed after 60 days to analyze for thrombus formation and residual shunt, TTE was carried out on days 30 and 180. The quantification of the residual shunt was determined by contrast injection at rest and during the Valsalva maneuver. A "small" shunt volume was defined as 3–20 bubbles and a "large" residual shunt as >20 bubbles. An atrial septal aneurysma was defined as an interatrial septum of abnormal mobility with septal protrusion in the left or right atrium of at least 10 mm beyond baseline [18].

A Data, Safety, and Adverse Events Monitoring Committee (HC Management GmbH, Homburg, Germany) reviewed and evaluated all reported adverse events.

Results

A total of thirty-seven patients were enrolled in the study between May and September 2006. Details of the patient flow through the trial and follow-up data are listed in Table 1. Table 2 shows patient recruitment for the treatment group.

A successful implantation was achieved in 36 patients. In 1 patient PFO guide wire crossing was impossible therefore no device was implanted. There were no periprocedural major complications (Table 2).

There were two short-term post-procedural complications after deployment and implantation. A blood transfusion was needed due to groin bleeding in one patient, and in another case a transient atrial

Table 2 Patient recruitment and outcome

	No.
Total enrollment	37
PFO not crossed	1
Successful implant	36
Completed study (day 1)	36
Completed study (day 30)	36
Discontinuation study after 30 days	1
Completed study (day 60)	35
Lost to follow up from day 60–180	1
Completed study (day 180)	34

fibrillation registered 2 hours after implantation which was treated with an intravenous beta-blocker and digoxin. Finally, conversion to sinus rhythm was documented within 12 h.

One patient suffered from a stroke with a right-sided paresis which was noticed 4 months after implantation. The patient had an aortic stenosis (aortic valve area 1.1–1.2 cm²), coronary artery heart disease, recurrent cerebral ischemic events with right-sided paresis of the arm in the history and a moderate to high graded stenosis of the left arteria cerebri media. Thrombus formation, occluder dislodgement or residual shunt could be ruled out by TEE. The most probable diagnosis was atherosclerosis of the cerebral arteries. One patient refused to participate in follow up examinations after day 30 but is without complaints. Another patient terminated the trial after the 60 days, so 180 days follow-up examinations were available in only 34 pts.

In 8.6% (3/35) of the pts a minimal residual shunt was detected by transesophageal echocardiography after 60 days. Complete closure was achieved in 88.2% ($n = 30/34$) of the cases after 180 days. In one case, a significant left-to-right shunt could be observed ($n = 1/34$). No thrombus formation was seen on the surface. A correct positioning without device dislodgement was achieved in all pts (Table 3).

Table 3 Follow-up results

	Amplatzer® PFO occluder [5]	Figulla® PFO occluder N
Patients, no.	$n = 69$	$n = 34$
Recurrence of thromboembolic Events	1 (0.7%)	0
TIA	0	0
Stroke	0	1
Peripheral embolism	1	0
Not thromboembolic TIA/Stroke	0	1 (2.9%)
Dislodgement/embolization	0	0
Surgical removal	0	0
Complete PFO closure		
1 month	54 (78%)	$n = 32/36$ (88.9%) ^a
6 month	62 (89%)	$n = 30/34$ (88.2%)
Thrombus formation	0	0

^aResidual shunt by angiographic test after procedure $n = 4$

Discussion

It is appreciated that a PFO is a frequent cause of cerebral embolism. To this day there is a continuous debate as to how these pts should be treated [7, 14, 16]. Multiple data point to higher prevalence of PFO in pts with a second cryptogenic stroke and in pts older than 55 years and those with septal aneurysm [11, 18, 19]. An additional risk of stroke recurrence is presented by a large PFO defect diameter [12].

Despite the existence of several different PFO occluder devices with varying designs, we developed a new nitinol meshwork using a unique patented braiding technique and achieved more than 50% reduction of left atrial material in comparison to the Amplatzer® device system and improved flexibility. The innovative concept of the novel device was a single layer left atrial disc with no hub. The reduction of left atrial metal improved flexibility and optimized the adaptation on the interatrial septum. Additionally, for so called “long track” PFO defects we developed a double layer left atrial disc which is characterized by excellent adaptation. The amount of material in the left atrium carries the risk of clot formation so we thought to test the hypothesis that reduction of material needed on the left atrial side could potentially lead to lower incidence of thrombus formation on the occluder surface.

We routinely used the sizing balloon for definition of the defect size which must not be larger than 13 mm in case of the clinical study. Transesophageal echocardiographic (TEE) studies could not exactly determine the defect size. Implantation by monitoring with intracardiac echocardiography (ICE) is an alternative method which was not routinely used. We generally recommended ICE or TEE monitoring during the procedure in the clinical study. For general use both methods are optional. Balloon assessment of PFOs enhances the understanding of their morphology and aids the identification of long tunnels. Detunnelisation using the same balloon facilitates the uncomplicated transcatheter closure of long tunnel PFOs in most patients.

The device was investigated in 10 “Göttinger mini pigs” (mean age 18 months, mean weight 36 kg). The mean implantation time was 138 days. Successful implantation was achieved in all animals. The mean time from intubation to successful device implantation was 138.9 min. The procedure time varied due to the different anatomical features in comparison to human. Clopidogrel and aspirin were administered over 6 months. Two laboratory animals died of respiratory failure caused by pneumonia (after 3 months) and ventricular fibrillation due to air embolism in coronary arteries while implantation procedure. Angiographic studies showed no large

residual shunt. In our histopathological and gross pathological follow up we could not find any thrombus formation on the disc surface. An incomplete adaptation on the left atrial side was caused by the different anatomical features of the septum (interatrial septum thickness up to 11 mm, human 1–2 mm). Metal struts of the nitinol wire mesh and the central hub were smooth without sign of corrosion. The connective and muscular tissue showed no clue of inflammation or malignant cells. Some multinucleated foreign body giant cells were found neighbouring the polyester fibres. Circumscribed mild lymphocytic infiltration were observed with a loose distribution within the implant, but constantly locally related to the polyester fibres. The histology was dominated by connective tissue containing capillaries and small vessels. Mild inflammatory reactions with concentration of foreign giant body cells neighbouring the polyester fibres were seen in the implant. In comparison to other devices these reactions were mild. There were no further complications (i.e. thromboembolism, stroke, myocardial infarction).

The clinical trial showed a good usefulness and feasibility of the investigated device, without major adverse cardiac events after 180 days therefore.

The CE-mark for the device was obtained on March 2007. During the post implantation 6 months follow up period of the PFO-occluder there was no recurrence of thromboembolic events. Only one patient suffered from stroke caused most likely by arteriosclerosis of cerebral arteries after 4 months procedure. Table 4 compares follow up data between the Amplatzer® and the Figulla® device systems. The aim of the clinical multicenter, non randomized trial, was the investigation of safety, efficacy and usefulness of a novel device system. The comparison of data between the Amplatzer® and Occlutech® occluder have representative value. Within the limits of a non-randomized study design, our findings provide information on the procedural, echocardiographic and clinical outcome of percutaneous PFO closure

with the Occlutech® occluder. The two devices differ in design, amount of material needed and flexibility. Manufacturing properties may have an impact on the implantation procedure, long term outcome, and clinical condition of the patient. Transcatheter closure of PFOs with the Amplatzer® PFO device implantation in adult patients has a high success rate and excellent results that have been documented in several studies [19]. It is most widely used device in the world. The Occlutech® PFO occluder N device received CE- certification to close defects up to 15 mm after amendment (up to 13 mm in the clinical study). There will be no learning curve using the Occlutech® device since the implantation technique is similar to the Amplatzer® system.

The first generation of the implanted Occlutech® occluders, which were used in most of the patients, showed a residual shunt in 11.8%. In addition, we modified retraction power of the retention discs by changing wire geometry with the result of optimized adaptation on the IAS.

So the question is what we should do in case of a significant residual shunt. Bleeding complications during an intensified combined anticoagulation and antithrombotic therapy are rare but a potential threat to the patients [5]. We, therefore, do not further recommend an intensified anticoagulation regimen after implantation of a Occlutech® PFO occluder. It should be clarified that the primary end-point of this study was not to evaluate the “optimal” anticoagulation/antiplatelet regimen in case of a residual shunt after implantation; randomized trials comparing different regimens are necessary to answer this question.

Numerous studies have shown that transcatheter closure of PFO is an effective, safe and feasible procedure as could be shown in this trial [8].

Current non randomized trial data suggested PFO closure is associated with a reduced rate of recurrent stroke and TIA events in patients who present with first events [19].

In addition observational data have shown an improved or cured migraine headache after PFO closure for stroke, and a single, small, randomized trial has demonstrated a reduced headache burden in patients without stroke [1, 13, 15]. Large-scale randomized controlled trials are underway to evaluate the efficacy of PFO closure in secondary prevention of cerebrovascular events and also in improving migraines.

Improvement in device design and the availability of data for a more accurate definition of the patients who most benefit from closure of PFO are bringing this forecasts to greater realization [10, 15].

However, the current study is limited by its non-randomized design regarding patient selection. The trial was aimed at demonstrating the usefulness and safety of the device. However, the effectiveness could

Table 4 Comparison Amplatzer® Vs. Figulla® PFO occluder N

No.	Amplatzer PFO occluder <i>n</i> = 69	Figulla PFO occluder <i>n</i> = 36
Implantation success	100%	100%
Periinterventional Complications		1
(a) minor, <i>n</i> %	1 (1.5%)	1 Atrial fibrillation
Trans. ST-elevation	1 (1.5%)	1 Grain bleeding
(b) major, <i>n</i> %	0	0
TIA	0	0
Devicedislodgement	0	0
Pericardial effusion	0	0
Arrosion of aorta	0	0
Death	0	0

not be shown because there is a very low incidence of recurrent thromboembolic events during follow-up [2]. To show effectiveness of PFO closure to prevent recurrent strokes or TIA larger multicenter randomized trials are underway.

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■ **Conflict of interest statement** Dr. Florian Krizanic and Prof. Dr. H.R. Figulla are consultants of Occlutech®. Prof. Dr. H.R. Figulla has shares in Occlutech® Jena. The other authors reported no conflicts of interests.

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