Structural Interventions
AMPLATZER PFO Occluder

CURRENT NEWS: 3 POSITIVE STUDIES REGARDING PFO CLOSURE

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A PUBLICATION DELIVERING CONCISE CLINICAL DATA

AMPLATZER™ PFO OCCLUDER

THE MOST IMPORTANT FACTS AT A GLANCE

TAKING A CLOSER LOOK: PATENT FORAMEN OVALE (PFO)

In up to every fourth adult the foramen ovale does not close after birth, resulting in a Patent Foramen Ovale (PFO). The following article describes potential clinical consequences of a PFO including the diagnosis and treatment.

WHEN PRENATAL RIGHT-TO-LEFT SHUNTS STAY OPEN

An open or persistent foramen ovale (PFO) is a gate opening in the interatrial septum. In the fetal circulation the PFO acts as a physiological connection, which enables oxygenated blood from the maternal circulation to flow from the right into the left atrium. After birth the increase of pressure in the left atrium leads to the functional closure of the PFO. Later on the opening closes completely because the left-atrial septum primum and the right-atrial septum secundum grow together. If the foramen ovale persists, there is the possibility that in the case of a right-atrial pressure increase, the right-left-shunt causes embolic material to pass over from the venous circulation, e.g. from the deep leg and pelvic veins. As a result, the embolic material can then end up in the brain (paradoxical embolism).

A PFO can be detected in about 15-25% of the adult population and is associated with an increased risk for ischemic stroke[1]. The prevalence of PFO is 2.5 times higher for younger patients (age 55 and younger) with cryptogenic stroke than for patients with a stroke of known cause, and 5 times higher than for people without a stroke[2]. Furthermore, there is evidence that a concomitant atrial septal aneurysm (ASA) further increases the stroke risk of PFO patients.[1] Moreover, patients with PFO and prior cryptogenic stroke have a higher risk for further cerebrovascular events.[1]

DIAGNOSTIC ASSESSMENT OF PFO: BUBBLE TEST AND MORE

A right-to-left shunt can be detected by transesophageal echocardiography (preferably with contrast medium under Valsalva maneuver) or by a contrast-enhanced transcranial Doppler sonography[3,4]. In both cases, the intravenously injected contrast medium contains tiny gas bubbles; if they enter the arterial circulation, this signal is then registered. Therefore, the method of detecting a PFO is called a “bubble test”. ECG & long-term ECG in order to exclude atrial fibrillation, Doppler & duplex sonography of the carotid arteries and a detailed coagulation analysis complete the diagnostic assessment of PFO.[4]

Indicators for a paradoxical embolism as a consequence of a PFO are:[4]

- sonographic or phlebological evidence for vein thrombosis
- an embolic stroke pattern in CAT scan or MRI
- carried-out pressing maneuver before the insult
- increased pulmonary arterial pressures e.g. after pulmonary embolism

PFO THERAPY: OLD GUIDELINE RECOMMENDATIONS AND NEW DATA

In order to prevent a stroke, the same general procedures are recommended whether or not a PFO is present. These procedures include eliminating risk factors such as smoking, exercises for the legs after extended sitting and wearing compression stockings. In order to reduce the risk of a stroke and recurrent stroke in patients at risk, antiplatelet therapy with acetylsalicylic acid or oral anticoagulation is recommended.[1,4]

Furthermore, the PFO can be closed either surgically or via transcatheter intervention. The authors of the US AHA/ASA Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack (updated in 2016) for example recommend transcatheter PFO occlusion only with reservations, because of insufficient evidence for its benefit[1]. With the results of the recently published CLOSE[5], REDUCE[6] and RESPECT[7] studies, this assessment now seems obsolete.

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CHANGE FROM CONTROVERSIAL TO EFFECTIVE PROPHYLAXIS

PFO CLOSURE IN "CRYPTOGENIC" STROKE: THREE STUDIES BRING THE CHANGE

The long-lasting debate about whether or not the closure of an open foramen ovale in patients with "cryptogenic" stroke prevents recurrent ischemic stroke seems to have been decided. Three recently published studies demonstrate such a benefit for closure of the PFO in select patients.

Until recently it was controversial whether PFO closure is more effective than medical therapy in reducing the risk of recurrent ischemic stroke in patients with cryptogenic stroke. In three studies published in 2012 and 2013 (CLOSURE I, PC study, RESPECT Primary Endpoint Results), a relevant benefit for percutaneous PFO closure could not be conclusively demonstrated when compared to pharmacotherapy (ASA or oral anticoagulation).

The recently published results of three studies (REDUCE, CLOSE, RESPECT Extended Follow Up) in the New England Journal of Medicine (NEJM) make the pendulum now swing clearly towards a benefit for interventional occluder therapy.

How can this be explained? At first sight it is noticeable that the follow-up period in the three recently published studies was longer than in the three initial studies. But this alone would probably not be enough to sufficiently explain the change to positive data. More important could have been the stricter criteria for study participant inclusion.

CLOSE: NOT A SINGLE STROKE AFTER PFO CLOSURE

The CLOSE study enrolled only patients with high risk PFO characteristics; a PFO with a large interatrial shunt or a PFO with a small to large shunt and an atrial septal aneurysm (ASA). In this study, PFO closure led to a significant reduction of recurrent ischemic stroke compared to antiplatelet therapy alone (hazard ratio: 0.03, $p < 0.001$). While 14 events occurred in the antiplatelet treatment arm, not a single stroke was documented after percutaneous occluder implantation. Most strokes – namely nine – occurred in patients that had a PFO as well as an atrial septal aneurysm.

In the oral anticoagulation group, the rate for recurrent stroke was about half as high as with antiplatelet prophylaxis (3 vs. 7 events; HR 0.43). Concerning this comparison, the study does not allow reliable conclusions to be drawn due to the low number of participants in the compared groups.

In connection with PFO closure, an increase in predominantly periprocedural atrial fibrillation was observed.

GORE REDUCE: RISK REDUCTION OF 77%

In the GORE-REDUCE study, PFO closure was also the winner in the comparison with a prophylaxis based on antiplatelet therapy alone. 664 patients (mean age: 45 years) with PFO and cryptogenic stroke took part in this study. About 80% had a PFO with a moderate to large shunt and about 20% an atrial septal aneurysm.

The participants were randomly assigned in a 2:1 ratio to two groups, in which the treatment consisted of either the implantation of a septal occluder plus antiplatelet therapy or of antiplatelet therapy alone. The median duration of follow-up was 3.2 years.

During this time, recurrent ischemic stroke was noted in six patients (1.4%) in the PFO closure group and in 12 patients (5.4%) in the group on antiplatelet therapy alone – which corresponds to a significant reduction in relative risk of 77% (HR 0.23, p=0.002).

The incidence of new brain infarctions – this "co-primary" endpoint included clinically manifest as well as clinically silent brain lesions that could only be objectively evaluated by imaging – decreased by 49% (incidence: 5.7% vs. 11.3%; relative risk: 0.51, p=0.04). The analysis of exclusively silent infarctions did not yield a significant difference (4.4% vs. 4.5%). Also in the GORE REDUCE study, the risk of newly occurring atrial fibrillation was significantly increased in the periprocedural phase.
28 patients had to be treated with the septal occluder in order to prevent an event within two years (number needed to treat NNT: 28 over the course of two years). In the CLOSE study, a NNT of 20 was determined to prevent one stroke in five years.

RESPECT: PATIENCE IS REWARDED

The primary analysis results of the RESPECT Trial, which began in 2003, were first published in 2012. In the case of this study, in which 980 patients with PFO and cryptogenic stroke were involved, the primary analysis (intention-to-treat) after a median follow-up period of 2.1 years showed point estimates in favor of PFO closure for reducing the risk of recurrent ischemic stroke, but did not reach statistical significance.

However, this result did not remain unchanged, as the study was continued (extended follow-up period). The data obtained from an “exploratory“ analysis performed after a median follow-up time of 5.9 years and published in September 2017 in the NEJM, show a significant relative risk reduction in favor of PFO closure for reducing recurrent ischemic stroke. The risk for any recurrent ischemic stroke was relatively reduced by 45% (18 vs. 28 events; HR 0.55, p=0.046). In absolute terms, ten events therefore make the difference.

62% LESS “CRYPTOGENIC“ RECURRENT EVENTS

If only such recurrent strokes were taken into account that were considered “cryptogenic“, the relative risk reduction was 62% (10 vs. 23 events; HR 0.38, p=0.007). Here, over close to six years, the reduction amounts to 13 events. Recurrent stroke with identifiable causes such as atrial fibrillation that were considered “non-cryptogenic“ and therefore not influenceable by PFO occlusion, were excluded from this analysis.

A difference to the disadvantage of occluder therapy was observed regarding venous thromboembolisms: pulmonary embolisms (HR 3.48, p=0.04) and deep vein thrombosis (HR 4.44, p=0.14) were more commonly recorded in this group than in the pharmacologically treated comparison group.

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CLOSE STUDY

100% STROKE-FREE AFTER OCCLUDER IMPLANTATION

With the CLOSE Study, the investigators led by Dr. Jean-Louis Mas from the Parisian Sainte-Anne hospital wanted to assess whether (1) PFO closure with device plus (chronic) antiplatelet therapy on one hand, and (2) oral anticoagulants on the other hand, are superior to antiplatelet therapy, to prevent stroke recurrence in patients 16 to 60 years old with cryptogenic stroke and PFO with atrial septal aneurysm or PFO with large shunt.

NOT A SINGLE CASE OF RECURRENT STROKE AFTER PFO CLOSURE

The primary endpoint of the CLOSE study was the number of patients with recurrent stroke during the follow-up period. In the comparison between PFO occluder plus long-term antiplatelet therapy and antiplatelet therapy alone, the interventional PFO closure was clearly superior: while not a single stroke occurred in the occluder group, 14 patients experienced a stroke in the antiplatelet group. This corresponds to a relative risk reduction of 97% (hazard ratio 0.03;95 % confidence interval 0–0.26, p<0.001; fig. 1).[1] The majority of strokes in the antiplatelet group occurred in patients that had a PFO as well as an atrial septal aneurysm (rate of stroke 12.2% vs. 3.1%).[1] The fact that an atrial septal aneurysm is associated with an increased risk of stroke had already been observed in other studies.[2,3,4]

In the comparison between antiplatelet therapy and oral anticoagulation the situation was less clear: Although here, too, stroke occurred in more patients in the antiplatelet group than in the anticoagulation group (7 vs. 3 patients), the group sizes were too small to analyze the statistical significance of these results.[1]

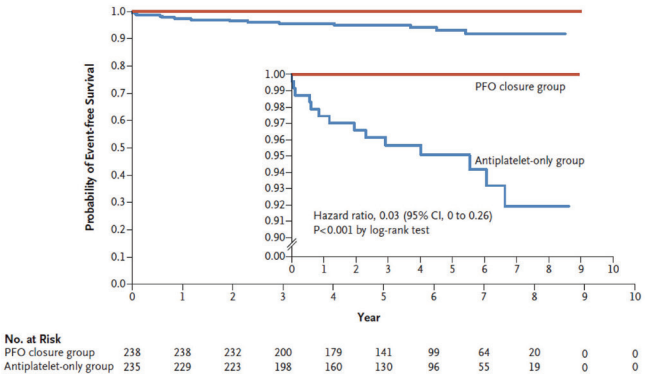

FIGURE 1: KAPLAN-MEIER ESTIMATE FOR THE RATE OF STROKE IN THE PFO CLOSURE GROUP COMPARED TO THE ANTIPLATELET GROUP (MODIFIED ACCORDING TO MAS ET AL., 2017). THE ANALYSIS WAS PERFORMED IN THE INTENTION-TO-TREAT COHORT. CI (CONFIDENCE INTERVAL) PFO (PATENT FORAMEN OVALE).

IMPORTANT FACTS ABOUT THE CLOSE STUDY

- **Number of patients:** 663 (32 sites in France, 2 in Germany)
- **Age:** 16–60 years (mean: 44 years)
- **Treatment arms**:
  - PFO closure + long-term antiplatelet therapy
  - antiplatelet therapy only
  - oral anticoagulation
- **Device for PFO closure:** multiple; investigator could choose any approved PFO closure device (11 devices used; 51% were AMPLATZER PFO Occluder)
- **Mean duration of follow-up:** 5.3 ± 2,0 years
- **Rate of stroke (intention-to-treat):**
  - PFO closure: 0% (0 of 238 patients)
  - antiplatelet therapy: 5.1% (21 of 409 patients)
  - oral anticoagulation: 1.6% (3 of 187 patients)

MAJORITY OF PFO PATIENTS WITH PRONOUNCED RIGHT-TO-LEFT SHUNT

The majority of the participants of the CLOSE study had a large right-to-left shunt (> 30 microbubbles in the left atrium within three cardiac cycles after opacification of the right atrium, measured via transthoracic or transesophageal echocardiography). About a third of the participants additionally had an atrial septal aneurysm, defined as an excursion of the septum primum > 10 mm in the

transesophageal echo. Furthermore, a relatively young patient population was studied: The mean age of participants was 44 years, and all had had a cryptogenic ischemic stroke within the previous 6 months before joining the study.[1]

NO INCREASE IN SERIOUS ADVERSE EVENTS

The implantation of the PFO occluder did not lead to an increase in the frequency of serious adverse events compared to the antiplatelet group (35.7% vs. 33.2%, p=0.56). However, in the PFO closure group atrial fibrillation occurred more often than with antiplatelet therapy alone (4.6% vs. 0.9%, p=0.02). The majority of atrial fibrillation (AF) cases was detected within 30 days after the implantation, suggesting a connection between the occurrence of atrial fibrillation and the intervention.[1]

EFFECTIVE PFO CLOSURE WITH LOW COMPLICATION RATES

The rate for effective PFO closure, defined as no or only minimal residual shunt in follow-up echocardiography, was 93.0% in the CLOSE study. 14 patients (5.9%) from the PFO closure group experienced major procedural or device-related complications.[1] Similar rates for PFO closure and complications had already been observed in previous studies.[5,6,7]

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REDUCE STUDY

INTERVENTIONAL PFO CLOSURE PREVENTS RECURRENT STROKE BETTER THAN ANTIPLATELET THERAPY ALONE

The main objective of the REDUCE study was to study the safety and efficacy of PFO closure compared to platelet inhibition alone in PFO patients with prior cryptogenic stroke. The focus was on freedom from recurrent stroke or transient ischemic attack, but because the incidence of all new brain infarctions was a co-primary endpoint, in addition to the occurrence of clinically manifest brain lesions also silent lesions that were only detected via imaging played a role.

PFO CLOSURE REDUCES STROKE RISK BY 77%

Concerning the first primary endpoint, namely the number of patients with a clinically manifest recurrent ischemic stroke, PFO occlusion performed significantly better than antiplatelet therapy alone: while 6 of 441 patients (1.4%) in the PFO occlusion group suffered another stroke, this happened to 12 of 223 patients (5.4%) in the group that received antiplatelet therapy alone. This corresponds to a relative risk reduction of 77% (hazard ratio 0.23; 95% confidence interval [CI] 0.09–0.62, p=0.002; fig. 1).[1]

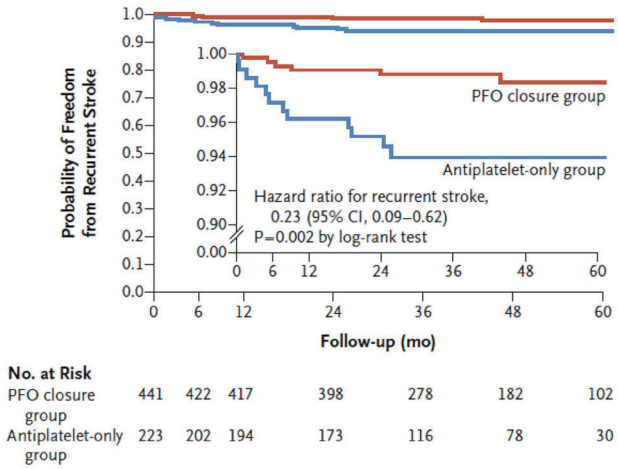

FIGURE 1: KAPLAN-MEIER ESTIMATE FOR THE PROBABILITY OF FREEDOM FROM RECURRENT ISCHEMIC STROKE IN THE PFO CLOSURE GROUP COMPARED TO THE ANTIPLATELET GROUP (MODIFIED ACCORDING TO SØNDERGAARD ET AL., 2017);
THE ANALYSIS WAS PERFORMED IN THE INTENTION-TO-TREAT COHORT;
CI (CONFIDENCE INTERVAL) PFO (PATENT FORAMEN OVALE)

IMPORTANT FACTS ABOUT THE REDUCE STUDY

- **Number of patients:** 664 (63 sites in Canada, Denmark, Finland, Norway, Sweden, the United Kingdom and the USA)
- **Age:** 18–59 years (mean: 45.2 years)
- **Treatment arms:**
  - PFO closure + antiplatelet therapy
  - Antiplatelet therapy only
- **Device for PFO closure:** GORE™ HELEX™ Septal Occuder or GORE™ CARDIOFORM Septal Occluder (both by W. L. Gore & Associates)
- **Mean duration of follow-up:** 3.2 years (interquartile range 2.2–4.8 years)
- **Rate of stroke (intention-to-treat):**
  - PFO closure: 1.4% (6 of 441 patients)
  - Antiplatelet therapy: 5.4% (12 of 223 patients)

PFO closure also excelled in regard to the second, co-primary endpoint by significantly reducing the number of new brain infarctions, which included cases of clinically manifest stroke as well as silent lesions: While 22 (5.7%) patients in the PFO group had a new stroke, the corresponding number in the antiplatelet group was 20 patients (11.3%), which amounts to a reduction in relative risk of 49% (effect size 0.51, 95% CI 0.29–0.91, p=0.04).[1]

However, the incidence of silent infarctions only did not differ between the treatment arms (p=0.97), therefore the difference in the co-primary endpoint is attributable to the lower incidence of recurrent clinically manifest stroke. The authors do point out that the absence of a difference in the rate of silent lesions could be due to insufficiently sensitive imaging: Since establishing the criteria used for the study, the diagnostic evaluation of stroke has evolved, enabling a more sensitive measurement of silent lesions.[15]

MOSTLY PATIENTS WITH MODERATE AND LARGE SHUNT

The patients enrolled in the study had a mean age of 45 years and had suffered a cryptogenic ischemic stroke within the last 180 days before randomization. 18.7% of patients had a small PFO shunt (1 to 5 microbubbles in the left atrium during three cardiac cycles after detection of the contrast agent in the right atrium, assessed via transesophageal echocardiography), 40.6% had a moderate PFO shunt (6 to 25 microbubbles) and 40.7% a large PFO shunt (> 25 microbubbles). The presence of a concomitant atrial septal aneurysm (ASA) was only determined at the time of occluder implantation, therefore data concerning ASA is only available for the PFO closure group. In this patient collective the prevalence of ASA was 20.4%.[1]

SUCCESSFUL IMPLANTATION & CONVINCING SAFETY PROFILE

The intervention via PFO occluder led to a complete closure of the PFO in 75.6% of the cases at 12 months; an effective closure defined as freedom from large shunt was achieved in 94.5% of patients. Procedural or device-related serious complications occurred only infrequently (1.4 and 2.5 %, respectively).[1]

There was no significant difference between both groups in regard to the frequency of serious adverse events (23.1% in the PFO group vs. 27.8% in the antiplatelet group, p=0.22). However, atrial fibrillation was reported more often after PFO closure (6.6% vs. 0.4%, p<0.001); in 83% of the cases, atrial fibrillation occurred within 45 days after implantation. The majority of cases (59%) was transient and subsided within 2 weeks after the first occurrence.[1]

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RESPECT: THE STUDY WITH THE MOST EXTENSIVE FOLLOW-UP

AMPLATZER PFO OCCLUDER DEMONSTRATES LONG-TERM SAFETY AND EFFICACY

The RESPECT study examined whether the percutanous closure of a patent foramen ovale (PFO) with the AMPLATZER PFO occluder can prevent recurrent embolic stroke better than medical therapy alone.

45% LESS RECURRENT STROKES IN THE PFO CLOSURE GROUP

In the medical therapy group, 28 patients suffered recurrent stroke. In the PFO closure group, 18 patients suffered recurrent stroke. This means that closure with the AMPLATZER PFO occluder reduced the relative risk for recurrent ischemic stroke by 45% (hazard ratio [HR] 0.55; 95% confidence interval [CI] 0.31–0.999, p=0.046; fig. 1).[1]
If only looking at the number of recurrent ischemic strokes of undetermined cause, the relative risk in the PFO closure group was reduced by 62% (10 vs. 23 patients; HR 0.38; 95% CI 0.18–0.79, p=0.007).[1]

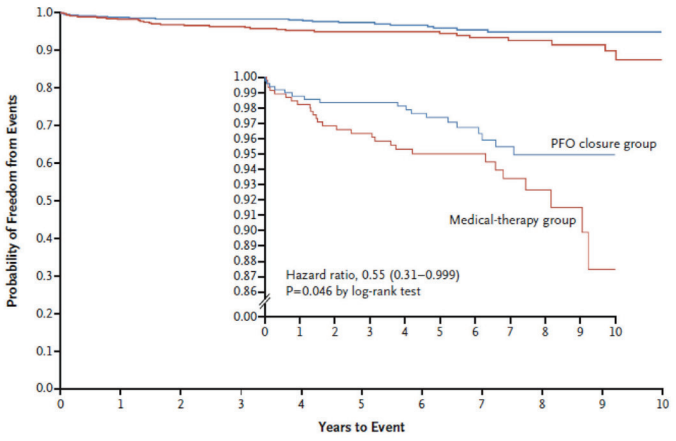

FIGURE 1: KAPLAN-MEIER ESTIMATE OF THE PROBABILITY OF FREEDOM FROM EVENT IN THE PFO CLOSURE GROUP COMPARED TO THE MEDICAL THERAPY GROUP (MODIFIED ACCORDING TO SAVER ET AL., 2017);
THE ANALYSIS WAS PERFORMED IN THE INTENTION-TO-TREAT COHORT;
AN EVENT WAS DEFINED AS RECURRENT NON-FATAL OR FATAL ISCHEMIC STROKE AS WELL AS EARLY DEATH AFTER RANDOMIZATION;
ALL 46 REGISTERED EVENTS WERE RECURRENT NON-FATAL ISCHEMIC STROKES;
CI (CONFIDENCE INTERVAL) PFO (PATENT FORAMEN OVALE)

IMPORTANT FACTS ABOUT THE RESPECT STUDY

- **Number of patients:** 980 (69 sites in the USA and Canada)
- **Age:** 18–60 years (mean: 45.9 years)
- **Treatment arms:**
  - PFO closure
  - Medical therapy (ASA, warfarin, clopidogrel, ASA+dipyridamole)
- **Device for PFO closure:** AMPLATZER PFO Occluder (Abbott)
- **Mean duration of follow-up:** 5.9 years (interquartile range 4.2–8.0 years)
- **Rate of stroke (intention-to-treat):**
  - PFO closure: 3.6% (18 of 499 patients)
  - Medical therapy: 5.8 % (28 of 481 Patients)

SUBGROUP ANALYSIS: HIGHEST RISK REDUCTION IN PATIENTS WITH ATRIAL SEPTAL ANEURYSM AND SUBSTANTIAL SHUNT

The subgroup analysis demonstrated that two patient groups particularly benefit from PFO closure: in patients with a substantial right-to-left shunt, the relative risk reduction was 74% (HR 0.26, 95% CI 0.10–0.71, p=0.005), and 80% in patients with an atrial septal aneurysm (HR 0.20, 95% CI 0.06–0.70, p=0.005).[1]

These two subgroups comprised a major part of the study population: in approximately half of the patients (48.8%) the PFO caused a substantial right-to-left shunt of grade 3 (> 20 microbubbles in the left atrium within three heart cycles after appearance of the contrast agent in the right atrium, determined via transesophageal echocardiography). In addition to the PFO, 35.7% of all study participants also had an atrial septal aneurysm, defined as an excursion of the septum primum of 10 mm or more.[1]

ANTIPLATELET THERAPY VERSUS ANTICOAGULATION

After occluder implantation, patients in the PFO closure group first received acetylsalicylic acid (ASA) plus clopidogrel for one month and thereafter ASA monotherapy for 5 months. Whether and how antithrombotic therapy was continued, was at the discretion of the site investigator. The participants in the medical therapy study arm also received a number of different drugs (ASA, warfarin, clopidogrel, ASA+dipyridamole).[1]

The subgroup analysis showed that the type of medical therapy does affect stroke risk: Although recurrent stroke occurred equally often with anticoagulation as with antiplatelet therapy (5.1% vs. 4.5%), most stroke cases happened with antiplatelet therapy in the pharmacotherapy group (2.7 vs. 6.4%, HR 0.38; 95% CI 0.18–0.79, p=0.007).[1]

HIGH PROCEDURAL SUCCESS AND SIMILAR RATES FOR SERIOUS ADVERSE EVENTS

Implantation of the AMPLATZER PFO Occluder resulted in high rates of technical (99.1%) and procedural success (96.1%). Effective PFO closure (≤ 9 microbubbles after 6 months) was achieved in 93.5% of patients; in 72.7% of cases the occluder implantation led to a complete closure of the PFO.[2]

Also part of the extended follow-up phase of the RESPECT study was the analysis of the safety profile in both treatment arms. Here, the total rate for serious adverse events (SAE) was 40.3% in the PFO closure group and 36% in the medical therapy group (p=0.17). Likewise, the risk for atrial fibrillation did not differ significantly between both groups (0.48 per 100 patient years vs. 0.34 per 100 patient years; HR 1.47; 95% CI 0.64–3.37, p=0.36). In contrast, pulmonary embolism (HR 3.48; 95% CI 0.98–12.34, p=0.04) and deep vein thrombosis (HR 4.44; 95% CI 0.52–38.05, p=0.14) occurred more often in the PFO closure group. Venous thromboembolic events were more common among patients with a history of clinically manifest deep vein thrombosis: While these patients comprised only 4% of the participants in the PFO closure group, they incurred 25% of the venous thromboembolic events.[1]

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CONCLUSIONS FOR DAILY PRACTICE

INTERVIEW WITH PROFESSOR HORST SIEVERT: Q & A CONCERNING INTERVENTIONAL PFO CLOSURE

The three studies CLOSE, REDUCE and RESPECT have recently provided new data on the safety and efficacy of interventional PFO closure. We talked about this with Professor Horst Sievert, MD, from the CardioVasculäres Centrum Frankfurt (CVC), Germany. Here he explains what impact the study results have on physicians' daily practice.

PROFESSOR SIEVERT, WHAT DO YOU THINK ARE THE MOST IMPORTANT RESULTS OF THE THREE STUDIES?

These studies were finally able to show without a doubt – after this has essentially already been known for 150 years – that a PFO can be the cause of paradoxical embolism and that it should be closed in afflicted patients. The recently published data is therefore important, but unsurprising to me. The results match what we have achieved for 25 years with this intervention in non-randomized studies.

WHICH PATIENTS CAN ESPECIALLY BENEFIT FROM A PFO OCCLUDER?

Interventional PFO closure is especially suitable for patients after a stroke that was caused by paradoxical embolism due to a PFO. In such cases it is of course important to exactly determine the cause of the stroke, because the more possible causes for the stroke there are, the less likely it is that it is precisely the PFO that caused the stroke.

WHERE THERE IS LIGHT, THERE IS SELDOM NO SHADOW: WHAT COMPLICATIONS CAN HAPPEN WITH OCCLUDER THERAPY AND HOW OFTEN DO THESE OCCUR?

Among the possible adverse events are among others transient atrial fibrillation, occluder embolization, air embolism and the formation of a thrombus on the occluder. However, these complications occur very rarely: overall, such adverse events occur in less than two percent of the patients, and they virtually never cause permanent damage.

PROF. HORST SIEVERT, MD

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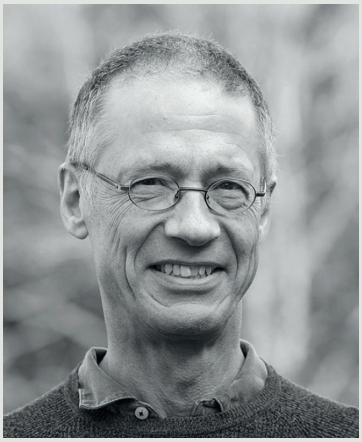
Focus of clinical and scientific activities: interventional cardiology and interventional angiology



THANK YOU VERY MUCH FOR THE INTERVIEW, PROFESSOR SIEVERT!

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CAUTION: Device depicted may not be available in all countries. Check with your Abbott representative for product availability in your country. Investigational use only in U.S.

BRIEF SUMMARY: Prior to using these devices, please review the Instructions for Use for a complete listingof indications, contraindications, warnings, precautions, potential adverse events and directions for use.

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