

EXPEDITED REVIEW

Incidence and Clinical Course of Thrombus Formation on Atrial Septal Defect and Patent Foramen Ovale Closure Devices in 1,000 Consecutive Patients

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OBJECTIVES	The purpose of this study was to investigate the incidence, morphology, and clinical course of thrombus formation after catheter closure of intra-atrial shunts.
BACKGROUND	Post-procedure detailed information about thrombotic material on different devices for transcatheter closure is missing.
METHODS	A total of 1,000 consecutive patients were investigated after patent foramen ovale (PFO) (n = 593) or atrial septal defect (ASD) (n = 407) closure. Transesophageal echocardiography (TEE) was scheduled after four weeks and six months. Additional TEEs were performed as clinically indicated.
RESULTS	Thrombus formation in the left atrium (n = 11), right atrium (n = 6), or both (n = 3) was found in 5 of the 407 (1.2%) ASD patients and in 15 of the 593 (2.5%) PFO patients (p = NS). The thrombus was diagnosed in 14 of 20 patients after four weeks and in 6 of 20 patients later on. The incidence was: 7.1% in the CardioSEAL device (NMT Medical, Boston, Massachusetts); 5.7% in the StarFLEX device (NMT Medical); 6.6% in the PFO-Star device (Applied Biometrics Inc., Burnsville, Minnesota); 3.6% in the ASDOS device (Dr. Ing, Osypka Corp., Grenzach-Wyhlen, Germany); 0.8% in the Helex device (W.L. Gore and Associates, Flagstaff, Arizona); and 0% in the Amplatzer device (AGA Medical Corp., Golden Valley, Minnesota). The difference between the Amplatzer device on one hand and the CardioSEAL device, the StarFLEX device, and the PFO-Star device on the other hand was significant (p < 0.05). A pre-thrombotic disorder as a possible cause of the thrombus was found in two PFO patients. Post-procedure atrial fibrillation (n = 4) and persistent atrial septal aneurysm (n = 4) had been found as significant predictors for thrombus formation (p < 0.05). In 17 of the 20 patients, the thrombus resolved under anticoagulation therapy with heparin or warfarin. In three patients, the thrombus was removed surgically.
CONCLUSIONS	The incidence of thrombus formation on closure devices is low. The thrombus usually resolves under anticoagulation therapy. (J Am Coll Cardiol 2004;43:302-9) © 2004 by the American College of Cardiology Foundation

Transcatheter closure of atrial septal defect (ASD) and patent foramen ovale (PFO) has become a less invasive alternative to open heart surgery. The first attempt at transcatheter closure of an ASD was described by King and Mills in 1974 (1,2). Since then, there has been a remarkable

purpose of our study was to determine and analyze the incidence, morphology, possible predictors, and clinical management of thrombus formation on ASD and PFO closure devices in 1,000 consecutive patients.

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evolution of devices with different materials, mechanism of closure, and methods of implantation (3-19). Although excellent results have been reported for transcatheter occlusion with different devices (3-19), concerns have arisen about peri- and/or post-interventional complications (5,20,21). Information about thrombus formation on devices and its clinical outcome is very limited (21-23). The

METHODS

Patient population. Between August 1992 and January 2003, transcatheter closure of a PFO (n = 593) or an ASD (n = 407) was performed in 1,000 consecutive patients (579 females and 421 males) between the age 13 and 90 years (mean age 48 ± 15 years). Nine different devices were used: 1) Rashkind (USCI Bard, Billerica, Massachusetts); 2) Buttoned (Custom Medical Devices, Amarillo, Texas); 3) ASDOS (Dr. Ing, Osypka Corp., Grenzach-Wyhlen, Germany); 4) Angel Wings (Das Angel Wings, Microvena Corp., Vadnais, Minnesota); 5 and 6) CardioSEAL and StarFLEX (NMT Medical, Boston, Massachusetts); 7) Amplatzer (AGA Medical Corp., Golden Valley, Minne-

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Abbreviations and Acronyms

- AF = atrial fibrillation
- ASA = atrial septal aneurysm
- ASD = atrial septal defect
- PFO = patent foramen ovale
- TEE = transesophageal echocardiographic/echocardiography
- TIA = transient ischemic attack
- TTE = transthoracic echocardiographic/echocardiography

sota); 8) Helix (W. L. Gore and Associates, Flagstaff, Arizona); and 9) PFO-Star (Applied Biometrics Inc., Burnsville, Minnesota).

The stretched ASD diameter, measured with a balloon catheter, varied between 6 and 37 mm (mean 20 ± 6 mm) and pulmonary/systemic output ratio from 0.4 to 4.7 (mean 2.0 ± 0.7). Of the ASD patients, 50 (12%) had multiple defects. In 15 (30%) of these 50 patients, two devices were implanted. An atrial septal aneurysm (ASA) defined as an excursion of the septum of more than 10 mm was present in 52 (13%) of the ASD patients. The following concomitant diseases were present in the ASD patients: pulmonary hypertension in 133 (33%) patients, atrial fibrillation (AF) in 56 (14%), coronary artery disease in 34 (8%) patients,

systemic hypertension in 88 (22%) patients, diabetes in 17 (4%) patients, phlebothrombosis in 18 (4%) patients, and embolic events (stroke, transient ischemic attack [TIA], and peripheral embolism) in 65 (16%) patients.

In the PFO patients, an ASA was present in 157 (27%) cases. The stretched diameter of the PFO was also defined by balloon sizing and ranged from 4 to 21 mm (mean 9 ± 3 mm). In these patients, 741 embolic events occurred before PFO closure: 353 strokes, 315 TIAs, 38 prolonged reversible ischemic neurologic deficits, and 35 peripheral embolisms with no other known source. On average, the patients had 1.2 embolic events before the procedure. The annual recurrence rate after the first event was 25%.

Some ASD and PFO patients had coagulation disorders, such as protein C deficiency (ASD: $n = 2$; PFO: $n = 7$; $p = \text{NS}$), protein S deficiency (ASD: $n = 3$, PFO: $n = 5$; $p = \text{NS}$), or activated protein C resistance (ASD: $n = 9$; PFO: $n = 16$; $p = \text{NS}$). Overall, 14 of 221 (6.3%) ASD patients and 28 of 235 (12%) PFO patients had one of these disorders. This difference was not significant. Of the patients with an ASD, 65 had an embolic event before defect closure. In total, 300 patients had an embolic event (235 PFOs and 65 ASDs). In these 300 patients a coagulation disorder was diagnosed in 39 (13%) cases compared with only 3 (19%) cases in those 156 patients without an embolic event ($p < 0.001$).

Table 1. Comparative Summary of Percutaneous ASD and PFO Occlusion Devices

Device	Design and Construction
Rashkind-PDA-Umbrella	Double umbrella (2nd generation Rashkind occluder) made of polyurethane foam, each disc consists of a 4-arm framework. Device sizes: 11 and 17 mm
Buttoned Device (3rd and 4th generation)	1) square occluder button; 2) rhomboid counter occluder. Device sizes: 25 to 50 mm
ASDOS	Two self-opening umbrellas (5-arm nitinol wire skeleton) with polyurethane membranes. Device sizes: 25 to 60 mm
Angel Wings	Two interconnected square (each 4 legs) nitinol wire frames covered with Dacron (polyester) fabric with a central conjoint ring. Device sizes: 18 to 40 mm
CardioSEAL	Non-centering double umbrella device modified from the Clamshell device with a 4-arm metallic framework covered with Dacron. Device sizes: 17 to 40 mm
StarFLEX	Double umbrella device developed from the CardioSEAL device with a 4- or 6-arm metallic framework, Dacron fabric, self-centering mechanism achieved by nitinol microsprings. Device sizes: 23 to 40 mm
Amplatzer	Self-centering double disc with a short connecting waist made from nitinol wire frame filled with polyester fabric. Device sizes (ASD): 4 to 40 mm; device sizes (PFO): 25 to 35 mm
Helix	Single length of nitinol wire with ultrathin expanded polytetrafluoroethylene which is formed into two equal-size opposing discs that bridge the septal defect. Device sizes: 15 to 35 mm
PFO-Star (1st and 2nd generation)	Two Ivalon-square discs, each umbrella is expanded by 4 nitinol arms—1st generation: 2-mm center posts; 2nd generation: 3- and 5-mm center posts. Device sizes: 18 to 30 mm

ASD = atrial septal defect; PFO = patent foramen ovale.

Table 2. Thrombus Formation at 4-Week TEE and 6-Month TEE After Closure

Occluder	n	TEE Due (n)		TEE Performed (%)		Thrombus (% , n)	
		6 Months	4 Weeks	6 Months	4 Weeks	6 Months	
Rashkind	1	1	100%	100%	0%	0%	
Buttoned Device	52	52	67%	69%	0%	0%	
ASDOS	42	42	66%	83%	3.6% (n = 1)	0%	
Angel Wings	30	30	0%	97%	0%	3.3% (n = 1)	
CardioSEAL	27	27	52%	93%	7.1% (n = 1)*	0%	
StarFLEX	142	111	74%	70%	5.7% (n = 6)*	0%	
Amplatzer	418	375	78%	70%	0%*	0.3% (n = 1)	
PFO-Star	127	127	60%	66%	6.6% (n = 5)*	1.5% (n = 1)	
Helix	161	138	76%	80%	0.8% (n = 1)	0%	

*The difference between the Amplatzer occluder against the CardioSEAL occluder, the StarFLEX occluder, and the PFO-Star occluder was significant (p < 0.05).

TEE = transesophageal echocardiography.

Closure devices. Table 1 provides an overview of the devices used in this series. These have been described in detail elsewhere (3–19).

Occlusion procedure. The procedures were performed under local anesthesia unless the patient did not tolerate the transesophageal echocardiographic (TEE) probe. Detailed echocardiographic assessment of the size and morphology of the ASD or PFO and the correct positioning of the device was performed using a multiplane 5-MHz probe. Patients were fully heparinized (10,000 to 20,000 U heparin), and antibiotic prophylaxis was given. Measurements of the defect and occlusion techniques with the different devices have been reported previously (3–19). Until October 2001 (in 817 patients) heparin was antagonized with protamine at the end of the procedure. Therefore, the patients were usually discharged on the same or following day.

Follow-up. A clinical examination, an electrocardiograph, a chest radiograph in two projections, and a transthoracic echocardiograph (TTE) were performed before discharge and repeated after 1, 6, and 12 months. In addition, TEE follow-up has been performed according to different study protocols approved by the local institutional review board. The TEE was scheduled four weeks and six months after closure with the newer devices: StarFLEX, Amplatzer, Helix, and PFO-Star. In older device protocols (CardioSEAL, Angel Wings, ASDOS, Buttoned Device, and Rashkind), control TEE after four weeks was optional, and at six months it was recommended. Cardiac catheterization was performed in patients with moderate and large residual shunts. Fluoroscopy to evaluate the metallic structures of the device was also performed after six months. Thereafter, follow-up was performed by a questionnaire every 6 to 12 months. In the event of a recurrent embolic situation, additional clinical investigations were performed as necessary. In event of a thrombus, repeat TEEs were scheduled until resolution of the thrombus.

Anticoagulation therapy. According to different device protocols, different regimens of anticoagulation and antiplatelet therapy were begun after implantation. Anticoagulation with warfarin (target international normalized ratio 2

to 3 for patients with the Rashkind and ASDOS devices) or anti-aggregation with aspirin (100 mg daily for patients with the Buttoned, Angel Wings, CardioSEAL, StarFLEX, Amplatzer, and Helix devices) was conducted for six months. As for the PFO-Star study protocol, clopidogrel (75 mg daily) was additionally recommended for three months. Since January 2001 (in 264 patients), protocols were changed for all PFO patients to a combination of aspirin and clopidogrel for six months.

Statistical analysis. Data were described as mean ± SD, and percentages were expressed where appropriate. Comparisons of results in patients with and without thrombus formation and between different devices were assessed by chi-square test; this was replaced by the Fisher exact test in cases in which the cell frequency was <5. A multiple regression analysis was performed to determine how variables (predisposing factors) were related to the risk of thrombus formation on ASD and PFO closure devices after implantation. A value of p < 0.05 was considered to be statistically significant.

RESULTS

Implantation of the device was technically successful in all patients. However, two attempts were necessary in 13 patients. During a follow-up period of 1 to 108 months (mean 36 ± 17 months; 1,327 patient-years), a thrombus formation was detected in 20 of 1,000 (2%) patients.

Thrombus formation in the left atrium (n = 11), right atrium (n = 6), or both (n = 3) was found in 5 of the 407 (1.2%) ASD patients and in 15 of the 593 (2.5%) PFO patients (p = NS). The TEE had been performed four weeks after closure in 709 of 1,000 (71%) patients and after six months in 714 of 1,000 (71%) patients. Thrombotic structures were observed by TEE after four weeks in 14 patients (Table 2), after six months in 3 patients (Table 2), after one year in 2 patients, and after five years in 1 patient. None of these thrombi could be detected by TTE, which had also been performed in all patients at the same time. The diameter of the thrombi varied from 5 to 30 mm (mean 11.7 ± 7 mm). The thrombus appeared as pedunculated

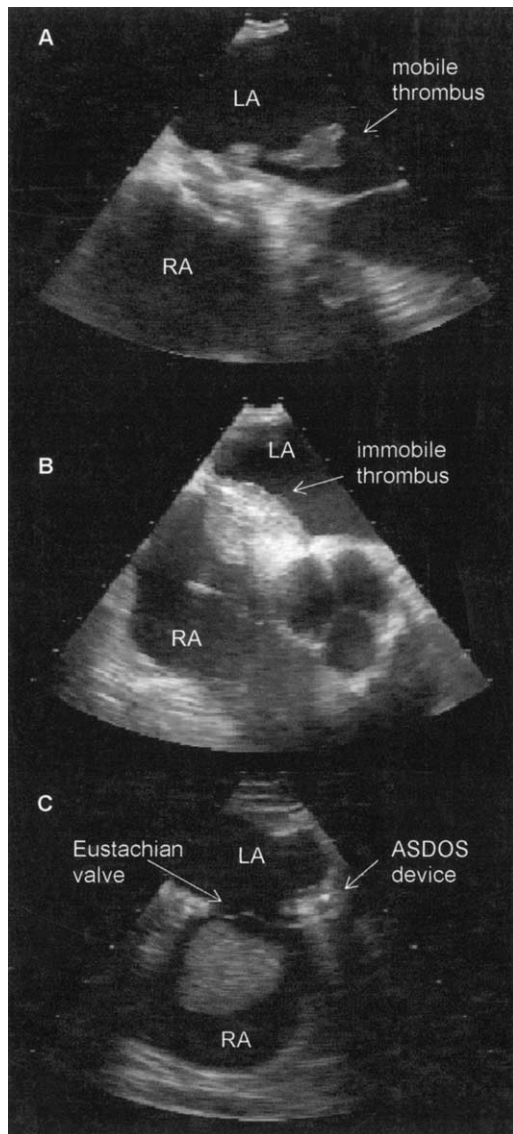


Figure 1. (A) Transesophageal echocardiography four-chamber view: left-sided mobile thrombus attached to a StarFLEX occluder detected four weeks after catheter closure. (B) Transesophageal echocardiography short-axis: right- and left-sided immobile thrombus surrounding an ASDOS occluder detected four weeks after catheter closure. (C) Transesophageal echocardiography short-axis: large mobile thrombus (30 × 18 mm) attached to the right atrial wall (without direct contact to the ASDOS device) detected one year after catheter closure. LA = left atrium; RA = right atrium.

and mobile in 9 (45%) cases (Fig. 1A). Immobile thrombi were detected in 11 (55%) patients (Fig. 1B). In two of these patients, a right atrial thrombus was attached to the lateral atrial wall (Fig. 1C) without direct contact to the occlusion device.

In devices with star-shaped metallic arms (CardioSEAL, StarFLEX, and PFO-Star occluder; n = 14) thrombus formations seemed to be attached either at the center of the right or left atrial disc (n = 5), at the transitional epithelium between device and septum (n = 1), or attached to the expanded nitinol or metal arms (n = 8).

Four weeks after implantation, the TEE revealed a

thrombus formation in 14 of 709 (2%) patients, with an incidence of 0% to 7.1% for different devices (Table 2). The difference between the Amplatzer (0%) versus the CardioSEAL (7.1%), the StarFLEX (5.7%), and the PFO-Star (6.6%) was significant ($p < 0.05$, Fisher exact test) (Table 2). The Amplatzer had the lowest incidence of thrombi against each of those devices. Post-procedure AF (n = 4; $p < 0.05$) and persistent ASA (n = 4; $p < 0.01$) were significant predictors for thrombus formation determined by the Fisher exact test. These and other possible risk factors for thrombus formation are summarized in Table 3. Pre-thrombotic disorders were found in two PFO patients (thrombocytosis in one patient and hyperactivity of factor VIII in one patient). Two minor strokes caused by a left-sided mobile thrombus on a StarFLEX device (one of these patients had a hyperactivity of factor VIII). One minor stroke (patient with a thrombocytosis) and one TIA occurred in two PFO-Star patients. No other pre-thrombotic disorders were found in these 20 thrombi patients. Of the 20 patients, 17 had a good outcome with disappearance of the thrombus following anticoagulation therapy with heparin (n = 1), warfarin (n = 12), or both (n = 4). Repetitive TEE examinations showed that the thrombotic material on the device was completely resolved in 11 of 20 cases after one month and in 6 of 20 cases after a time period of between two and six months. In three patients the thrombus was removed surgically:

Patient 1: A left-sided mobile thrombus on a StarFLEX device was removed together with the device after cerebral embolism and unsuccessful fibrinolysis.

Patient 2: A large right-sided thrombus (30 × 18 mm) attached to the lateral atrial wall did not disappear under long-term warfarin treatment and was removed surgically. The ASDOS occluder was left in place. Only a tip of wire sticking out of the covered device had been cut (Fig. 2).

Patient 3: In this asymptomatic patient diagnosed with AF and four small mobile left-sided thrombi seen on TEE on the StarFLEX occluder, the referring physician decided to send the patient to surgery. During surgery, the left-sided thrombus could not be found anymore, but an 8-mm right-sided thrombus not diagnosed before was detected and removed together with the device (Fig. 3).

DISCUSSION

Atrial thrombi after transcatheter ASD and PFO closure are rare complications (20,24,25). We investigated the incidence of thrombus formation on nine different devices in 1,000 consecutive patients to determine possible predictors. A thrombus formation was found in 5 of the 407 (1.2%) ASD patients and in 15 of the 593 (2.5%) PFO patients ($p = \text{NS}$). La Rosee et al. (23) described thrombus formation in 3 of the 38 (10.5%) ASD patients and in 8 of

Table 3. Potential Risk Factors for Thrombus Formation

Risk Factors After Defect Closure	Patients Without Thrombi	Patients With Thrombi	p Value
Atrial fibrillation	66/980 (6.2%)	4/20 (20%)	< 0.05
Residual shunt immediately after closure	287/980 (29%)	3/20 (15%)	NS
Persistent atrial septal aneurysm	13/980 (1.3%)	4/20 (20%)	< 0.01
Wire fracture	47/980 (4.8%)	3/20 (15%)	NS
Protein S deficiency	8/456 (1.8%)	0/20 (0%)	NS
Protein C deficiency	9/456 (2%)	0/20 (0%)	NS
Resistance to activated protein C	25/456 (5.5%)	0/20 (0%)	NS
Mean age	47 yrs	48 yrs	NS
Gender			
Male	412/980 (42%)	9/20 (45%)	NS
Female	568/980 (58%)	11/20 (55%)	NS
Hypertension	228/980 (23%)	3/20 (15%)	NS
Coronary artery disease	51/980 (5%)	0/20 (0%)	NS
Diabetes	37/980 (4%)	0/20 (0%)	NS
Warfarin	95/980 (10%)	3/20 (15%)	NS
Aspirin	505/980 (52%)	6/20 (30%)	NS
Aspirin + clopidogrel	380/980 (39%)	11/20 (55%)	NS
Protamin	798/980 (81%)	19/20 (95%)	NS

the 60 (13.3%) PFO patients ($p = \text{NS}$). These were diagnosed early, two to three days after implantation. The investigators found a thrombotic structure in 7 of the 40 (17.5%) patients on the ASDOS occluder, in 3 of the 33 (9%) patients on the PFO-Star occluder, and in 1 of the 25 (4%) patients on the Amplatzer occluder ($p = \text{NS}$). In contrast to La Rosee et al. (23), we found atrial thrombi after four weeks only in 1 of the 28 (3.6%) ASDOS devices, 5 of the 76 (6.6%) PFO-Star devices, and 0 of the 328 (0%) Amplatzer devices. Other previous reports revealed a thrombus incidence of 6.5% (9 of 139) in the ASDOS device (17) and 11.1% (3 of 27) in the Buttoned device (26). According to the data of nine different devices implanted in our center, we verified that thrombus formation is not only a clinical event of older devices; newer devices also demonstrate the potential to develop early thrombus formation after four weeks: 1 of 14 (7.1%) CardioSEAL, 6 of 105 (5.7%) StarFLEX, 5 of 76 (6.6%) PFO-Star (1st and 2nd generation), and 1 of 123 (0.8%) Helex.

Furthermore, we found that the difference between the Amplatzer device (0%) on one hand and the CardioSEAL device (7.1%), the StarFLEX device (5.7%), and the PFO-Star device (6.6%) on the other hand was significant ($p <$

0.05). The Amplatzer nitinol wire frame filled with polyester fabric and the Helex nitinol wire covered by an ultra thin membrane of expanded polytetrafluoroethylene seem to be less thrombogenic than the metallic framework and Dacron fabric in the CardioSEAL and StarFLEX devices and the nitinol framework and Ivalon foam in the PFO-Star occluder. Uncoated metal arms in the CardioSEAL and StarFLEX devices and outside nitinol arms in the PFO-Star devices (1st and 2nd generation) may increase the risk for excessive thrombus formation. This has also been affirmed by Braun et al. (19). In their largest PFO-Star device study, adherent thrombus formations could only be detected in generations 1 and 2 when expanded nitinol arms were located on the outer side of the foam. In the 3rd generation, the PFO-Star device nitinol arms were placed from the outer to the inner side of the left atrial foam. After these changes, no further thrombi were noted by TEE.

Possible predictors of thrombi. After the procedure we found paroxysmal AF and persistent ASA to be significant predictors for thrombus formation (Table 3). The prevalence of AF and persistent ASA was higher among patients with thrombus formation than in those without (AF: 20% vs. 6.2%, $p < 0.05$; ASA: 20% vs. 1.3% $p < 0.001$).

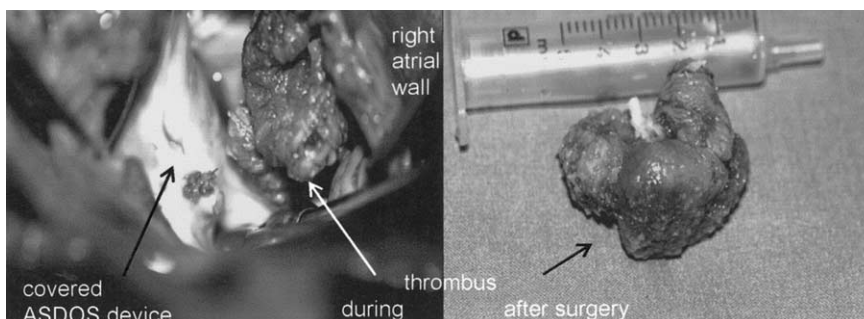


Figure 2. Unsuccessful resolution of a large right-sided thrombus (30 × 18 mm) attached to the lateral atrial wall under long-term warfarin treatment. During surgery the ASDOS occluder was left in place. Only a tip of wire sticking out of the covered device had been cut.

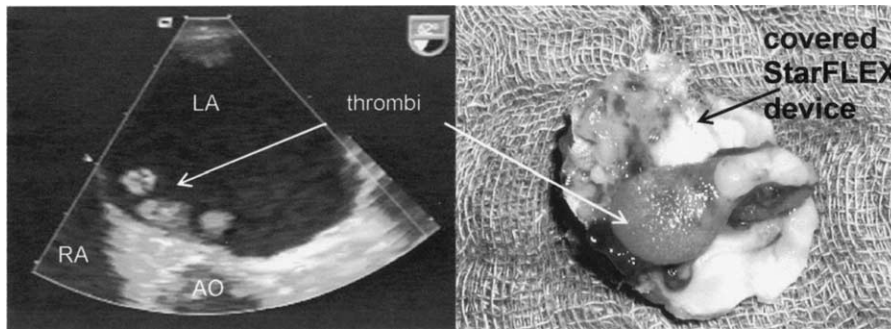


Figure 3. A short transesophageal view of small mobile left-sided thrombi on a StarFLEX occluder. During surgery, the absence of the left-sided thrombi but detection of a right-sided thrombus (8 mm) not diagnosed before was removed together with the device. AO = aorta; LA = left atrium; RA = right atrium.

However, this has to be addressed carefully because of the small number of thrombus formations ($n = 20$) detected in our study. Moreover, there is some evidence that patients with ASA benefit from occlusion in reducing the mobility of the septum. In a previous study (27), the septal excursion had been significantly reduced in 48 of 51 patients six months after closure. A persistent ASA could be found in only 3 of 51 patients. None of them developed an atrial thrombus post-procedure. In our thrombus patients with persistent ASA, no recurrent thromboembolic events occurred. Windecker et al. (28) affirmed that after transcatheter closure the presence of ASA and PFO does not result in a higher recurrence rate of cerebrovascular events; thus, this group of patients would particularly benefit from closure.

No other significant predictors for thrombus formation on several devices could be found. A post-procedural shunt was detected in 3 of the 20 (15%) thrombus patients. A wire device frame fracture was also observed in 3 of 20 (15%) patients: 1 ASDOS, 1 CardioSEAL, and 1 PFO-Star occluder. In all three patients the side of the wire fracture was consistent with the side of the atrial thrombus. These patients all had right-sided atrial thrombi attached to right-sided broken arms or frames. In a study with the Buttoned device, Lambert et al. (26) noted that tilting the occluder created a large residual defect and was associated with left atrial thrombosis. Of the 27 Buttoned devices displaced in that way, 3 (11%) developed thrombus formation. Coagulation disorders such as protein C deficiency, protein S deficiency, and activated protein C resistance did not exist in our thrombus cases; only a hyperactivity of factor VIII and a thrombocytosis could be found in two patients. Gastmann et al. (24) reported a case of a left-sided thrombus formation on an ASDOS device resulting in cerebral thromboembolism. This patient had a deficiency of coagulation factor XII.

Other risk factors for cardiovascular disease, such as diabetes, coronary artery disease, and hypertension may not conduct thrombus formation on implanted devices. Among patients with ($n = 20$) and without ($n = 980$) thrombus formation, no significant differences could be determined in terms of age or gender. According to different study protocols, ASD and PFO patients received different medical

prophylaxes after catheter closure either with antiplatelet agents or with anticoagulants (warfarin: $n = 98$, aspirin: $n = 511$, aspirin + clopidogrel: $n = 391$). Our results do not favor any medical regimen. Patients without thrombi ($n = 980$) were treated with warfarin in 10% of cases ($n = 95$), with aspirin in 52% of cases ($n = 505$), and with aspirin and clopidogrel in 39% of cases ($n = 380$), compared to patients with thrombi ($n = 20$), who received warfarin in 15% of cases ($n = 3$), aspirin in 30% of cases ($n = 6$), and aspirin + clopidogrel in 55% of cases ($n = 11$). However, these differences were not significant.

There are no additional studies comparing these *three* therapeutic regimes relating to the incidence of thrombi formations on devices. In a PFO-Star device study of 276 patients, Braun et al. (19) found that ever since change in the antiplatelet therapy from aspirin alone to a combination of aspirin and clopidogrel, no further thrombotic material occurred. Unfortunately, no statistical evaluation comparing both therapeutic regimes concerning the incidence of device-adherent thrombus was made.

In a smaller Amplatzer device study by Brandt et al. (29), 37 patients (ASD: $n = 21$; PFO: $n = 16$) received clopidogrel and aspirin after transcatheter closure for six months. In an absence of any thrombus at four weeks' and six months' TEE, the investigators concluded that this antiplatelet therapy is safe and effective in preventing thrombus formation on the septal occluder surface. However, they did not have a control group who received aspirin alone. In our study, uncertainty remains regarding the combination of aspirin + clopidogrel because there seemed to be no significant benefit in this particular thrombotic prophylaxis. Of 391 patients with this treatment, 11 (2.8%) developed thrombi after transcatheter closure compared to the patient group, who received only aspirin and detected thrombi in 6 of 511 (1.2%) patients ($p = \text{NS}$). It has to be mentioned that heparin was antagonized with protamine immediately after the procedure in 267 of 391 (68%) patients and 10 of 11 (91%) thrombus cases who received aspirin and clopidogrel. Anti-heparin therapy with protamine in the first hours after implantation might be a disadvantage and thus enhance thrombogenesis. Therefore, we stopped antagonizing heparin in November 2001. Since

then only one thrombus occurred in 183 patients. In all 183 patients a four-week TEE had been performed. However, this has not yet been statistically significant.

In general, resolution of thrombi had been achieved under medical treatment in 17 of 20 patients within four weeks to six months; 12 patients received warfarin, 1 patient received heparin, and 4 patients received a combination of heparin and warfarin. In 11 of 17 patients, the thrombus disappeared after four weeks. Therefore, we currently recommend initial anticoagulation therapy for three months, similar to other studies (19,20) with repetitive TEE examinations depending upon diameter and mobility of device-attached thrombi.

Complications related to thrombus formations. Cardiac surgery was performed in only three patients. One left-sided and one right-sided mobile thrombus attached to a StarFLEX occluder in two patients was removed together with the device, after cerebral embolism and unsuccessful fibrinolysis in one and as decided by the referring physician in the other. In the third patient a large right-sided thrombus—not device-related—attached to the lateral atrial wall did not disappear under long-term warfarin treatment. This thrombus was removed surgically, leaving the ASDOS occluder in place. No further thrombi or other complications occurred in these three patients.

During follow-up, 4 of 20 (20%) patients became symptomatic and suffered from thromboembolic events. Two minor strokes occurred in patients with a StarFLEX occluder, and one minor stroke and one TIA occurred in two PFO-Star device patients. There have been other reports about left-sided thrombus formation on ASDOS (24,25) and Buttoned (26) devices complicated by systemic embolism. In the ASDOS device case, reported by Gastmann et al. (24), the patient had a deficiency of coagulation factor XII that is known to be associated with thrombotic complications. The large left-sided thrombus completely resolved after one month. In two of our four thrombus cases resulting in acute strokes, coagulation disorders were also found (hyperactivity of factor VIII in a patient with an ASD occluded with a StarFLEX and thrombocytosis in a patient with a PFO-Star occluder). All patients fully recovered from these neurological deficits.

If some patients endangered by thromboembolic complications nevertheless undergo transcatheter closure, anticoagulation monitoring requires exceptional attention. Similar to other investigators (20,24), we state that TTE is usually unable to detect thrombus formation on the device. According to our results we recommend that all adult patients, including those with good echocardiographic windows, should have a routine TEE examination after 4 weeks, 6 months, and 12 months. For younger children, follow-up by TTE as an imaging perspective might be sufficient. To shed light on the performed follow-up studies of these 1,000 consecutive patients, a group of them did not return for one of the TEE examinations at four weeks ($n = 291$) and at six months ($n = 286$), factors relating either to different device

protocols or to personal declining. These patients were checked by interviews, clinical examination, electrocardiography, chest X-ray, and TTE at 1, 6, and 12 months following implantation. None of them suffered from a TIA or a stroke.

Thrombus formation and cerebrovascular events after surgical defect closure. There is still an ongoing discussion (30,31) about the gold standard for the best therapeutic approach (catheter closure, medical therapy, or even surgery) in ASD and PFO patients. Surgical closure has also been attempted with mixed results in terms of recurrent embolic events derived by thrombus formation. Most recently, Rodriguez et al. (32) noted an intra-atrial thrombus with a small residual PFO six months after surgical PFO closure. Homma et al. (33) reported in a series of 28 patients, four recurrent neurological events (one stroke and three TIAs) after surgical closure at a mean follow-up of 19 months. In these particular patients (two were treated with aspirin and two received no medical treatment), no intra-cardiac mass or thrombus was seen by TEE, and only a small residual shunt was found in two cases. The recurrence only occurred in the older population (>45 years). Thus, the investigators concluded there must be some undefined causes for their patients' strokes.

In a larger study, Dearani et al. (34) documented eight TIAs during a mean follow-up of two years following surgical closure, one caused by temporal arteritis. Using TEE they also demonstrated that all closures had been intact without thrombotic structures. Having multiple embolic events before PFO closure was the only significant risk factor for recurrence after closure.

In a different study, Konstantinides et al. (35) found AF in six of nine patients who suffered from a recurrent stroke or TIA after surgical ASD closure. Only two of the six patients with AF received anticoagulants at the time of the event, that occurred in the late postoperative phase (>30 days after surgery). Reviewing additional surgical closure data it has to be mentioned that there are surgical studies (36,37) with excellent results and no report of neurological recurrences following patients who were embolic free up to an average of 24 and 41 months. However, prospective and randomized clinical trials are warranted to compare percutaneous closure directly with other treatment strategies such as medical therapy and surgical repair of intra-atrial shunts.

Conclusions. The incidence of thrombus on closure devices is low. We found significant differences between different devices. Atrial fibrillation and persistent ASA after transcatheter closure are significant risk factors for thrombus formation. In most of the patients the thrombus resolved under medical therapy without clinical consequences.

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