INNOVATION IN INTERVENTION:
New Devices in Interventional Cardiology

Ben Van den Branden

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New Devices in Interventional Cardiology

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(met een samenvatting in het Nederlands)

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Hij zocht het geluk, het grote “het”
Hij zocht maar vond het niet
Enkele malen stond hij met een kluitje in het riet
Hij zocht het geluk in het riet
Hij zocht het geluk in het dal, aan de top
Maar werd het zoeken moe
Pas toen hij zei: ik geef het op
Toen kwam het naar hem toe
(Toon Hermans)

Aan Yvette, Evy en Mirte

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Part four: Transcatheter mitral valve repair using the edge-to-edge clip technique

Part five: General discussion

Part one

General introduction

1

General introduction and outline of the thesis

Percutaneous techniques for the treatment of structural heart disease have emerged rapidly over the past few years. Although percutaneous closure of interatrial defects with different devices has become routine practice, modifications in device structure and implantation technique should contribute to the overall safety and efficacy of this procedure.
The desire for less invasive approaches, especially in patients with a high-surgical risk, has driven the field of transcatheter interventions for valvular heart disease.

Patent foramen ovale

Anatomy and pathophysiology

The foramen ovale is a tunnel-like space between the overlying septum secundum and septum primum (Figure 1). The septum primum is thin (about 0.5-1.0 mm) and consists of a layer of cardiac muscle lined on the inferior side with a layer of collagen and elastin. The septum secundum has a similar structure, but the cardiac muscle layer is much thicker.[1] In utero, the foramen ovale is necessary for blood flow across the fetal atrial septum. Oxygenated blood from the placenta crosses the foramen ovale and enters the systemic circulation. After birth, pulmonary vascular resistance decreases and right atrial (RA) pressure drops below left atrial (LA) pressure, resulting in a functional closure of the foramen ovale. In about 75% of the general population, fusion of both septa occurs over time, resulting in anatomical closure. Autopsy studies indicate that in about 27% of the cases, an interatrial communication persists into adulthood, referred to as a patent foramen ovale (PFO).[2]
PFO occurs with equal frequency in men and women and tends to decrease in prevalence with increasing age, although some data suggest that PFOs may recanalize over time.[3, 4] Dynamically, the PFO acts like a valve that closes on the LA side due to the relatively higher left-sided pressure. In case of pressure-rise on the RA side, for example during sneezing, coughing, or lifting a weight, a right-to-left shunt (RLS) through the PFO can be accomplished. In most cases, the presence of a PFO is asymptomatic. However, in 1877 Cohnheim already postulated that a venous thrombus may traverse a PFO, bypasses the pulmonary capillary filter, and give rise to a systemic embolism.[5] Since that time, PFOs have been associated with various

disease processes including paradoxical embolism manifesting as cryptogenic stroke/ TIA, platypnea-orthodeoxia syndrome, decompression sickness in divers, migraine headache, and obstructive sleep-apnea syndrome.[3, 6-10] The most important clinical issue regarding PFOs remains cryptogenic stroke, or stroke of undefined cause, which accounts for up to 40% of all ischaemic strokes.[11] Approximately 50% of patients aged < 55 years with cryptogenic stroke are found to have a PFO.[2] Furthermore, there has been intense speculation on the association of risk factors of stroke in these patients, including the size of the PFO, the degree of RLS, and the presence of an atrial septal aneurysm (ASA).[12-15] In addition, a PFO is more common in patients with ASA and the combination is associated with an increased risk of stroke recurrence.[16]
Important to note, other potential sources for embolic events like carotid atherosclerosis, neurovascular abnormalities, atrial fibrillation, and prothrombotic state (e.g., proteine C or S deficiency, antithrombin III, or lupus anticoagulans) should be excluded for the diagnosis of cryptogenic stroke.

Diagnosis

A PFO is usually detected by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) or transcranial Doppler (TCD). TEE combined with contrast administration is the most sensitive test and therefore considered the method of choice. An advantage of this technique is that the site of the shunt and other anatomic abnormalities can be visualized.[17, 18] Otherwise, TEE is time-consuming and considered semi-invasive. The efficacy of the different imaging techniques has been evaluated in a number of comparative studies.[19, 20] Recently, Maffe et al. postulated that contrast TTE with second harmonic imaging seems to be a very good alternative for TEE as a first-line exam for the detection of PFO.[21] An essential part in the screening for cardiac shunts remains the implementation of an accurate "bubble-test" with a good Valsalva manoeuvre.[22] The patient is asked to press against the closed glottis for at least 10 seconds, until septal shifting to the left is observed. Then, contrast (agitated saline) is injected as a rapid bolus in the antecubital vein which should result in complete opacification of the RA. At that time point, the patient is asked to release pressure. If microbubbles are detected in the left-sided cardiac chambers within three cardiac cycles, a PFO is judged to be present.

Treatment options

Controversy exists regarding the best method for prevention of recurrent events in patients who have experienced a cryptogenic stroke. The choice for medical treatment or percutaneous closure has to be weighed in the context of the respective risks and benefits in any individual patient. Available data support anticoagulation for patients with PFO and ASA and at least antiplatelet therapy for patients with PFO but without ASA.[15, 16, 23] Disadvantages of medical therapy are the increased bleeding risk and the lack of compliance.[24] Moreover, observational studies reported a risk of stroke recurrence ranging from 3.4% to 12% during the first year.[23, 25, 26] Since Bridges et al. proposed in 1992 that percutaneous PFO closure with an umbrella device (Figure 1) would reduce the incidence of recurrent strokes, this technique has shown safety and feasibility with a reported success rate varying between 90 and 100% and a complication rate between 0 and 10%.[27-33] Reported recurrence rates of TIA/stroke varies between 0% and 3.4%.[34-36] However, results from the first randomized trial, comparing percutaneous closure and optimal medical therapy (CLOSURE I) did not show differences in the recurrence of stroke or TIA at 2 years.[37] A higher incidence of atrial fibrillation and vascular complications was also observed in the device group. The current guidelines for secondary stroke prevention state that “insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO” and that “PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical treatment” (class IIB, level of evidence C).[38]

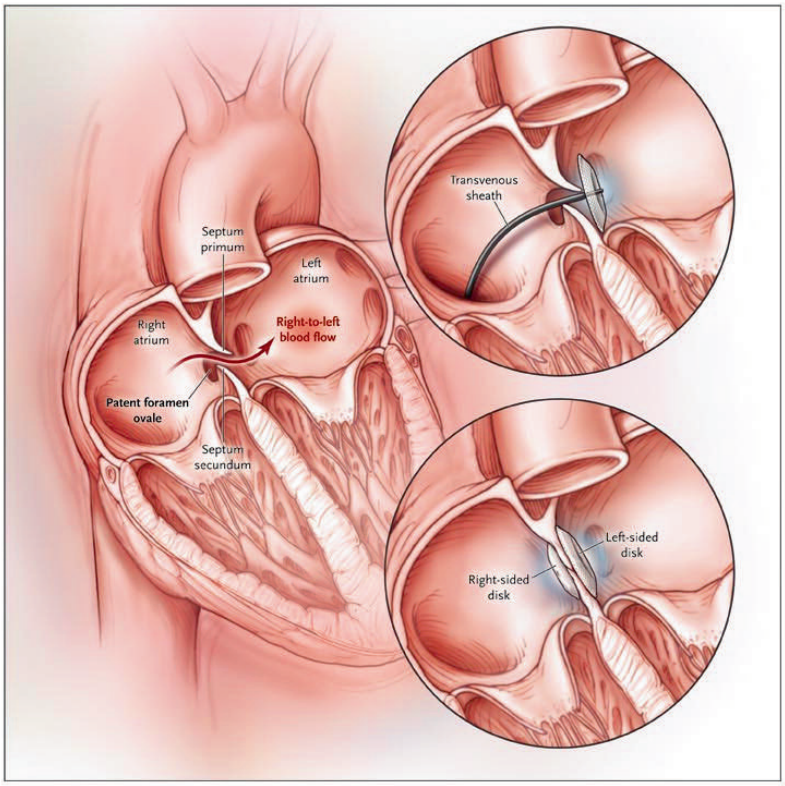

Figure 1. A PFO is a tunnel-like defect in the interatrial septum, prone for RLS of blood and paradoxical embolization. Percutaneous closure can be accomplished by an umbrella-device containing a right- and left-sided disk.[39] (With permission of the Massachusetts Medical Society)

Atrial septal defect

Anatomy and pathophysiology

In distinction to a PFO, an atrial septal defect (ASD) occurs when there is absence of a portion if the interatrial septum and accounts for about one third of all congenital heart defects in adults.[40] Incomplete caudal growth of the septum secundum or excessive resorption of the septum primum give rise to a secundum or type II ASD,

which is located at the center of the septum, involving the fossa ovalis (Figure 2). If the septum primum fails to reach the endocardial cushions, then a primum or type I ASD occurs in the lower part of the septum. A sinus venosus ASD occurs when there is abnormal resorption of atrial septal tissue adjacent to the caval-atrial junction, near the entry of the superior vena cava.

An ASD is characterized by a predominant left-to-right shunt (LRS) because the right ventricle (RV) and pulmonary circuit offer lower resistance to the flow.[41] However, RLS may occur during Valsalva manoeuvre or exercise.[42] The LRS results in diastolic RV volume overloading and an increased pulmonary blood flow, which may be as high as five times the systemic flow. Usually, patients with a large defect remain asymptomatic during their childhood but most of them develop symptoms related to atrial arrhythmias, pulmonary arterial hypertension, paradoxical embolization or heart failure.[40, 42]

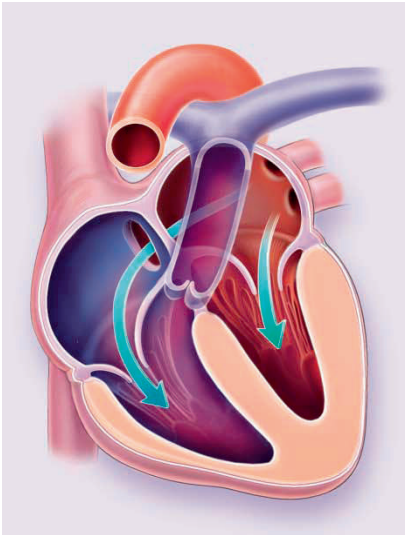

Figure 2. The secundum ASD is associated with a LRS.[41] (With permission of the Massachusetts Medical Society)

Diagnosis

Cardiac auscultation reveals a fixed split of the second heart sound without respiratory variation, a loud pulmonic component of the second heart sound, and a pulmonary outflow tract murmer. A definite diagnosis of an ASD is usually made by echocardiography. Typical findings include RA en RV enlargement, increased pulmonary artery pressure and the LRS across the atrial septum, using color-Doppler flow.[43] TEE provides much better anatomic characterization of the septum, the size of the defect, and adjacent structures.[44] Recently, real-time three-dimensional TEE has been introduced to optimize ASD visualization and to guide closing procedures.[45, 46] In current practice, cardiac catheterization with saturation measurements and shunt fraction calculation, is reserved for when there is discrepancy between clinical and echocardiographic findings or when there is suspicion of the presence of pulmonary hypertension or anomalous drainage of a pulmonary vein.

Treatment options

ASD closure is indicated when patients are symptomatic or in case of pulmonary-to-systemic shunt with flow ratios greater than 1.5:1.0. Less than a decade ago, surgical repair was considered the standard of care for all types of ASDs.[47] Nowadays, surgery is performed in case of type I ASD or sinus venosus defect. For type II ASDs, there has been a dramatic shift towards percutaneous closure. This technique was first described in 1974, but no devices were available until the 1990s.[48] Currently, percutaneous ASD closure provides durable results paralleling those of surgery but with less morbidity and shorter hospital stay.[49, 50] To permit percutaneous closure, there should be adequate tissue margins at the superior and inferior rims of the defect to anchor the device. Furthermore, large defects need large devices, which might predispose to erosion of the aortic root, dislocation and embolization or interaction with the mitral valve (MV). When the anatomy is unsuitable for device closure, surgery is the only option.

The Mitral Valvular Complex

Anatomy

It was the Belgian anatomist Andreas Vesalius who suggested the term "mitral" to describe the left atrioventricular valve owing to its resemblance to a bishop's mitre.[51] In 1972, Perloff and Roberts put forward the concept of a "mitral valve complex" made up of integrated components with a harmonious structural relationship.[52] The "functional anatomy" of the MV includes the left ventricle (LV) myocardium, the subvalvular apparatus (including papillary muscles and chordae tendinae), the 2 leaflets, the mitral annulus (or atrioventricular junction) and the LA (Figure 3). The anterior MV leaflet is in fibrous continuity with the aortic valve, has a rounded free edge, and occupies one-third of the annular circumference. The opposing posterior leaflet is longer and narrow, guarding the remainder of the junctional circumference. The corresponding terms for anterior and posterior are aortic and mural.[53] Both leaflets are divided in 3 segments or scallops described as lateral, middle and medial or A1, A2, A3 and P1, P2, P3 for the anterior and posterior leaflet, respectively.[54] In systole, the leaflets coapt along their solitary zone of apposition which creates an arc shaped closure line, recognized as the "mitral smile" looking from the LA. Both ends of the closure line are designated the anterolateral and posteromedial commissures. The LV atrioventricular junction supports the MV leaflets and has a characteristic saddle-shape appearance due to its elevated septal and lateral segments. The coronary sinus (CS) and its tributary, the great cardiac vein, parallel the MV annulus along its posterior and lateral aspect. The papillary muscles normally arises from the apical and middle thirds of the LV wall and are located beneath the commissures, occupying anterolateral and posteromedial positions.[55] The tendinous cords or chordae tendinae are fibrocollageneous string-like structures originating from the papillary muscles or directly from the ventricular wall and attach to the free edges of the leaflets. Different types and orders of cords can be distinguished according to their appearance and the site of attachment to the leaflets.[56, 57]

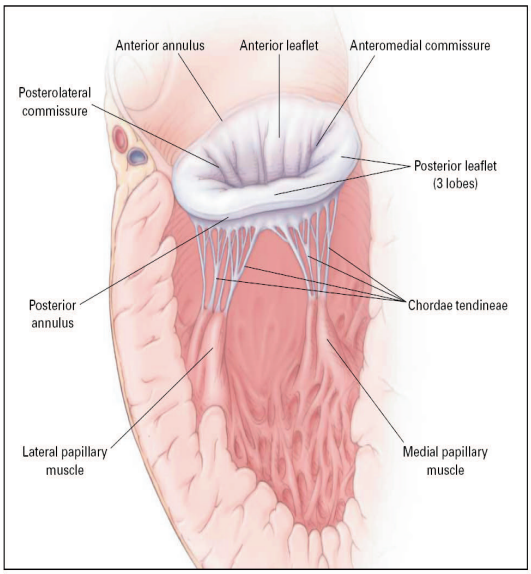

Figure 3. Normal anatomy of the mitral valve complex.[58] (With permission of the Massachusetts Medical Society)

Mitral valve regurgitation

Mitral regurgitation (MR) compromises 24% of adults with valvular heart disease and 7% of the population ≥ 75 years.[59] Competency of the MV is dependent on the proper function of each of the components of the MV complex. The pathophysiological triad of MR was originally described by Carpentier in 1983.[60] It included the etiology of the valve lesion, the valve lesion itself, and the resultant valve dysfunction. He subsequently described a classification which is still commonly used and relevant for patient selection and evaluation of percutaneous MV repair (Figure 4). Patients with type I dysfunction have normal leaflet motion and their valvular incompetence is due to annular dilatation or leaflet perforation. In type II dysfunction there is increased leaflet motion (prolapse) of one or both leaflets with failure of coaptation. These are typically patients with myxomatous or degenerative disease with or without chordal rupture and papillary muscle elongation. Type IIIa dysfunction includes patients with restrictive leaflet motion during both systole and diastole due to leaflet and subvalvular apparatus thickening and fusion, typically seen in rheumatic heart disease. Patients with type IIIb dysfunction have restricted leaflet motion during systole due to apical

displacement of the papillary muscles due to ventricular enlargement as seen with dilated cardiomyopathy and papillary muscle dysfunction as seen in ischaemic MR. Patients may have a combination of causes of dysfunction, especially in advanced disease. Patients with MR can broadly be categorized as having primary MR due to abnormalities of one or more components of the MV complex (type II) and secondary MR which is not a valve disease, but represents the valvular consequences of a LV disease (type I or type IIIb). In primary MR, the most common disorder of the leaflets is myxomatous degeneration (Barlow's syndrome / fibroelastic dysplasia) causing MV prolapse. Therefore, primary MR is often referred as degenerative MR. Secondary MR is defined as functional MR and is caused by geometric LV remodelling due to dilated cardiomyopathy or myocardial damage from infarction. In the latter clinical setting, secondary functional MR is called ischaemic MR.

MR imposes a pure volume overload on the LV. In primary chronic MR, eccentric LV hypertrophy develops by lengthening of the myocytes, leading to LV end-diastolic dilatation and increased total and forward stroke volumes.[61, 62] Both LV and LA compliance increase to accommodate the regurgitant volume.[63] The LA gradually dilates while maintaining a normal LA pressure. This haemodynamic state may remain compensated for many years. Progressive LV dilatation eventually occurs as the regurgitant volume increases and as concentric hypertrophy does not develop, the increased LV volume is not compensated by increased thickness, which maintains increased systolic and diastolic stress. Although it might seem that afterload is decreased in MR patients due to ejection into the low pressure LA, the increased radius-thickness ratio may actually increase afterload, especially in chronic decompensated MR.[64] Additionally, neurohumoral mechanisms are activated, leading to progressive contractile dysfunction.[65]

Pathophysiology of functional ischaemic MR is much more complex than that of primary MR.[66] Here, myocardial dysfunction has caused an anatomically normal valve to leak. In the vast majority of patients with chronic ischaemic MR, the volume overload contributes to a vicious circle: the more remodelled LV, the more severe MR which begets further LV dilatation and thus, further progression of MR. LV dilatation leads to worsened LV performance, rise in LA pressure and pulmonary arterial hypertension.[67]

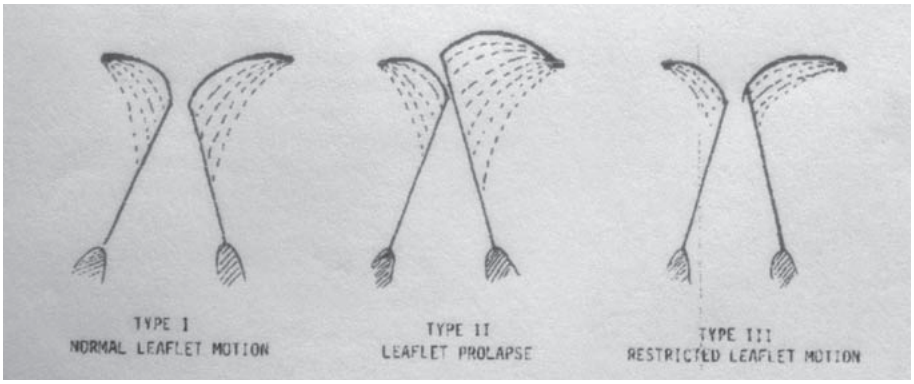

Figure 4. The Carpentier classification of mitral regurgitation based on leaflet motion [68].

The current treatment for chronic mitral regurgitation.

Medical therapy

The role of medication for chronic MR remains a subject of debate. As afterload is not excessive in most patients, systemic vasodilator therapy may not provide additional benefit. Studies of angiotensin-converting enzyme (ACE) inhibitors have been inconclusive and angiotensin receptor blockers also have produced uneven results.[69, 70] Therefore, these agents are not recommended by the current guidelines.[71] Experimental data suggest that beta-blockers may be more beneficial than ACE-inhibitors, but there are no clinical data to justify chronic beta-blocker therapy.[72] An exception are patients with heart failure and symptomatic patients with severe MR who are not candidates for surgery, who should receive standard, aggressive management for heart failure.

Surgical therapy

Surgical MV repair or replacement remains the standard of care for patients with haemodynamically significant primary MR. The decision to repair or to replace the valve is of critical importance, and MV repair is strongly recommended whenever possible because it is associated with lower operative mortality and better long-term survival.[73-75] The surgical treatment of functional MR remains controversial.[76, 77]

Despite the guidelines, the European Heart Survey demonstrated that up to one-half of patients with symptomatic severe MR are not referred for surgery, mainly because of advanced age and the presence of comorbidities.[78, 79] The challenge of managing these patients will only increase in the coming years and has opened the door for several innovative transcatheter techniques.

Percutaneous mitral valve repair

Percutaneous transcatheter MV therapy became a reality more than 25 years ago with the first description of balloon valvuloplasty for rheumatic MV stenosis.[80] Although MR remains largely the purview of surgery, the potential for less invasive approaches without the need for thoracotomy or cardiopulmonary bypass has generated considerable interest. Most of these device-oriented percutaneous techniques are modifications of existing surgical approaches and can be broadly divided into procedures that address the various components of the MV complex.[81-83] Those various technologies are at different stages of investigation. In the group that affects the MV leaflets, the MitraClip® device (Abbott Vascular, Santa Clara, California, USA) has proven its safety and feasibility in the EVEREST trial program and is undergoing increasingly wide use in Europe, especially in patients at high risk for surgery.[84-87] This metallic clip is delivered after transseptal puncture to grasp and approximate the free edges of both leaflets, mimicking the “double orifice” surgical repair introduced by Alfieri (Figure 5).[88] The second group contains the annuloplasty approaches, in which we distinguish the indirect and the direct annuloplasty techniques. Indirect approaches use the coronary sinus (CS) to deliver a device that partially encircles the MV annulus, thereby reducing its anterior-posterior dimension.[89-92] Major limitations to the use of the CS include the variability in the relation of the CS to the annulus, the risk to compress the circumflex coronary artery, the risk of CS perforation and the interaction with CS pacing leads.[93] Direct annuloplasty would overcome some of these limitations as it reshapes the annulus directly via the LA or LV, mimicking more closely the surgical technique.[94] Thirdly, techniques were developed to reduce the anterior-posterior dimension of the LV which indirectly decreases the MV annulus and shifts the papillary muscles closer to the leaflets.[95] Finally, the novel technology of percutaneous MV replacement is in pre-clinical evaluation and might become a treatment option in patient with a low probability of successful repair.[96]

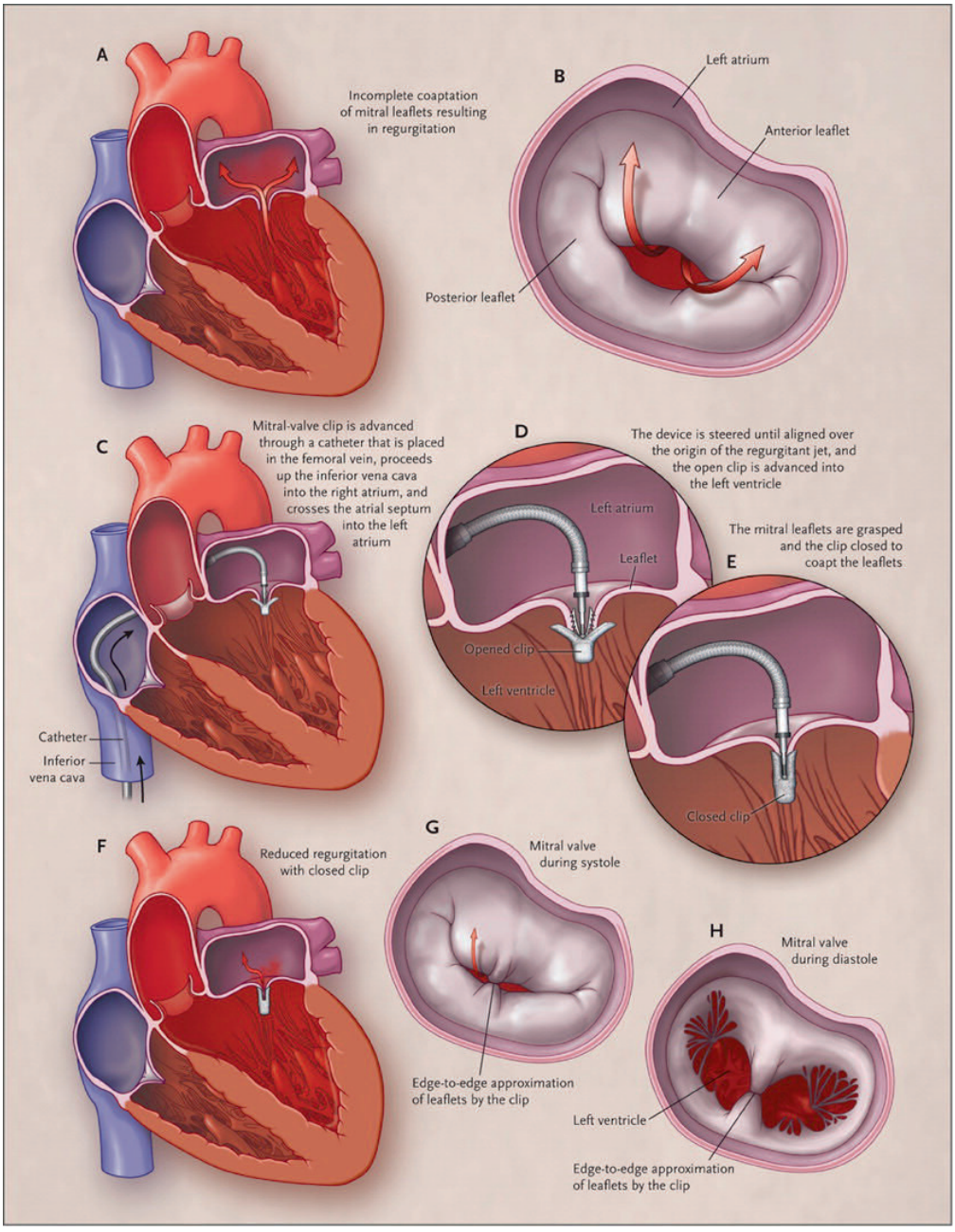

Figure 5. The edge-to-edge mitral valve repair using the MitraClip®.[97] (With permission of the Massachusetts Medical Society)

Aims and outline of the thesis

This thesis concerns the application of new closure devices in the treatment of PFO and ASD, and the innovative transcatheter treatment of MR using the edge-to-edge technique.

In *chapters 2 and 4* the feasibility, efficacy, and safety of percutaneous PFO closure is examined using a new bioabsorbable closure device (BioSTAR®). In *chapter 3*, this bioabsorbable device is compared with the non-bioabsorbable CardioSEAL® device.

In *chapter 5* we describe the results of PFO and ASD closure with the novel Occlutech Figulla® closure device. *Chapter 6* contains a comparative examination of the Occlutech Figulla® device and its competitor, the Amplatzer® device in ASD closure.

Chapter 7 and 8 describes the outcomes of high-surgical-risk patients treated percutaneously with the edge-to-edge MV repair technique. Finally, in *chapter 9* we describe a MitraClip® case which was complicated by partial clip detachment, and in another case we demonstrate the usefulness of three-dimensional TEE guidance during the procedure.

Reference List

(1) Hara H, Virmani R, Ladich E et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status. *J Am Coll Cardiol* 2005 November 1;46(9):1768-76.

(2) Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984 January;59(1):17-20.

(3) Lechat P, Mas JL, Lascault G et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988 May 5;318(18):1148-52.

(4) Germonpre P, Hastir F, Dendale P, Marroni A, Nguyen AF, Balestra C. Evidence for increasing patency of the foramen ovale in divers. *Am J Cardiol* 2005 April 1;95(7):912-5.

(5) Cohnheim J. Thrombose und Embolie. Verlosung uber allgemeine Patholgie. *Berlin, Hirschwald* 1877;134.

(6) Shanoudy H, Soliman A, Raggi P, Liu JW, Russell DC, Jarmukli NF. Prevalence of patent foramen ovale and its contribution to hypoxemia in patients with obstructive sleep apnea. *Chest* 1998 January;113(1):91-6.

(7) Cheng TO. Platypnea-orthodeoxia syndrome: etiology, differential diagnosis, and management. *Catheter Cardiovasc Interv* 1999 May;47(1):64-6.

(8) Di Tullio M, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. *Ann Intern Med* 1992 September 15;117(6):461-5.

(9) Torti SR, Billinger M, Schwerzmann M et al. Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. *Eur Heart J* 2004 June;25(12):1014-20.

(10) Post MC, Thijs V, Herroelen L, Budts WI. Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. *Neurology* 2004 April 27;62(8):1439-40.

(11) Sacco RL, Ellenberg JH, Mohr JP et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol* 1989 April;25(4):382-90.

(12) Agmon Y, Khandheria BK, Meissner I et al. Frequency of atrial septal aneurysms in patients with cerebral ischemic events. *Circulation* 1999 April 20;99(15):1942-4.

(13) Hausmann D, Mugge A, Daniel WG. Identification of patent foramen ovale permitting paradoxic embolism. *J Am Coll Cardiol* 1995 October;26(4):1030-8.

(14) Steiner MM, Di Tullio MR, Rundek T et al. Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. *Stroke* 1998 May;29(5):944-8.

(15) Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000 October 24;55(8):1172-9.

(16) Mas JL, Arquizan C, Lamy C et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001 December 13;345(24):1740-6.

(17) de Belder MA, Tourikis L, Griffith M, Leech G, Camm AJ. Transesophageal contrast echocardiography and color flow mapping: methods of choice for the detection of shunts at the atrial level? *Am Heart J* 1992 December;124(6):1545-50.

(18) Pearson AC, Labovitz AJ, Tatineni S, Gomez CR. Superiority of transesophageal echocardiography in detecting cardiac source of embolism in patients with cerebral ischemia of uncertain etiology. *J Am Coll Cardiol* 1991 January;17(1):66-72.

(19) Daniels C, Weytjens C, Cosyns B et al. Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale. *Eur J Echocardiogr* 2004 December;5(6):449-52.

(20) Souteyrand G, Motreff P, Lusson JR et al. Comparison of transthoracic echocardiography using second harmonic imaging, transcranial Doppler and transesophageal echocardiography for the detection of patent foramen ovale in stroke patients. *Eur J Echocardiogr* 2006 March;7(2):147-54.

(21) Maffe S, Dellavesa P, Zenone F et al. Transthoracic second harmonic two- and three-dimensional echocardiography for detection of patent foramen ovale. *Eur J Echocardiogr* 2010 January;11(1):57-63.

(22) Attaran RR, Ata I, Kudithipudi V, Foster L, Sorrell VL. Protocol for optimal detection and exclusion of a patent foramen ovale using transthoracic echocardiography with agitated saline microbubbles. *Echocardiography* 2006 August;23(7):616-22.

(23) Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002 June 4;105(22):2625-31.

(24) Mohr JP, Thompson JL, Lazar RM et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001 November 15;345(20):1444-51.

(25) Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van MG. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. Lausanne Stroke with Paradoxal Embolism Study Group. *Neurology* 1996 May;46(5):1301-5.

(26) Mas JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. *Am Heart J* 1995 November;130(5):1083-8.

(27) Braun M, Gliech V, Boscheri A et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. *Eur Heart J* 2004 March;25(5):424-30.

(28) Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. *Circulation* 1992 December;86(6):1902-8.

(29) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003 November 4;139(9):753-60.

(30) Martin F, Sanchez PL, Doherty E et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation* 2002 August 27;106(9):1121-6.

(31) Windecker S, Wahl A, Chatterjee T et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000 February 29;101(8):893-8.

(32) Wohrle J. Closure of patent foramen ovale after cryptogenic stroke. *Lancet* 2006 July 29;368(9533):350-2.

(33) Luermans JG, Post MC, Schrader R et al. Outcome after percutaneous closure of a patent foramen ovale using the Intrasept device: a multi-centre study. *Catheter Cardiovasc Interv* 2008 May 1;71(6):822-8.

(34) Kutty S, Brown K, Asnes JD, Rhodes JF, Latson LA. Causes of recurrent focal neurologic events after transcatheter closure of patent foramen ovale with the CardioSEAL septal occluder. *Am J Cardiol* 2008 May 15;101(10):1487-92.

(35) Schuchlenz HW, Weihs W, Berghold A, Lechner A, Schmidt R. Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale. *Int J Cardiol* 2005 May 11;101(1):77-82.

(36) Windecker S, Wahl A, Nedeltchev K et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J Am Coll Cardiol* 2004 August 18;44(4):750-8.

(37) Furlan A. CLOSURE I Trial: a prospective, multicenter, randomized, controlled trial to evaluate the safety and efficacy of the STARFlex septal closure system versus best medical therapy in patients with stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale. *Presented at: American Heart Association Scientific Sessions 2010, Nov 13-17, Chicago* 2010;(Abstract 21572).

(38) Sacco RL, Adams R, Albers G et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Circulation* 2006 March 14;113(10):e409-e449.

(39) Kizer JR, Devereux RB. Clinical practice. Patent foramen ovale in young adults with unexplained stroke. *N Engl J Med* 2005 December 1;353(22):2361-72.

(40) Campbell M. Natural history of atrial septal defect. *Br Heart J* 1970 November;32(6):820-6.

(41) Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. *N Engl J Med* 2000 January 27;342(4):256-63.

(42) Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. *Circulation* 1968 May;37(5):805-15.

(43) Shub C, Dimopoulos IN, Seward JB et al. Sensitivity of two-dimensional echocardiography in the direct visualization of atrial septal defect utilizing the subcostal approach: experience with 154 patients. *J Am Coll Cardiol* 1983 July;2(1):127-35.

(44) Ishii M, Kato H, Inoue O et al. Biplane transesophageal echo-Doppler studies of atrial septal defects: quantitative evaluation and monitoring for transcatheter closure. *Am Heart J* 1993 May;125(5 Pt 1):1363-8.

(45) Georgakis A, Radtke WA, Lopez C et al. Complex atrial septal defect: percutaneous repair guided by three-dimensional echocardiography. *Echocardiography* 2010 May;27(5):590-3.

(46) Saric M, Perk G, Purgess JR, Kronzon I. Imaging atrial septal defects by real-time three-dimensional transesophageal echocardiography: step-by-step approach. *J Am Soc Echocardiogr* 2010 November;23(11):1128-35.

(47) Murphy JG, Gersh BJ, McGoon MD et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med* 1990 December 13;323(24):1645-50.

(48) King TD, Mills NL. Nonoperative closure of atrial septal defects. *Surgery* 1974 March;75(3):383-8.

(49) Du ZD, Hijazi ZM, Kleinman CS, Silverman NH, Larntz K. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol* 2002 June 5;39(11):1836-44.

(50) Luermans JG, Post MC, ten Berg JM, Plokker HW, Suttorp MJ. Long-term outcome of percutaneous closure of secundum-type atrial septal defects in adults. *EuroIntervention* 2010 November;6(5):604-10.

(51) Ho SY. Anatomy of the mitral valve. *Heart* 2002 November;88 Suppl 4:iv5-10.

(52) Perloff JK, Roberts WC. The mitral apparatus. Functional anatomy of mitral regurgitation. *Circulation* 1972 August;46(2):227-39.

(53) Muresian H. The clinical anatomy of the mitral valve. *Clin Anat* 2009 January;22(1):85-98.

(54) Carpentier A, Deloche A, Dauptain J et al. A new reconstructive operation for correction of mitral and tricuspid insufficiency. *J Thorac Cardiovasc Surg* 1971 January;61(1):1-13.

(55) Brock RC. The surgical and pathological anatomy of the mitral valve. *Br Heart J* 1952 October;14(4):489-513.

(56) Lam JH, Ranganathan N, Wigle ED, Silver MD. Morphology of the human mitral valve. I. Chordae tendineae: a new classification. *Circulation* 1970 March;41(3):449-58.

(57) Van der Bel-Kahn, Becker AE. The surgical pathology of rheumatic and floppy mitral valves. Distinctive morphologic features upon gross examination. *Am J Surg Pathol* 1986 April;10(4):282-92.

(58) Otto CM. Clinical practice. Evaluation and management of chronic mitral regurgitation. *N Engl J Med* 2001 September 6;345(10):740-6.

(59) Iung B, Baron G, Butchart EG et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003 July;24(13):1231-43.

(60) Carpentier A. Cardiac valve surgery--the “French correction”. *J Thorac Cardiovasc Surg* 1983 September;86(3):323-37.

(61) Matsuo T, Carabello BA, Nagatomo Y et al. Mechanisms of cardiac hypertrophy in canine volume overload. *Am J Physiol* 1998 July;275(1 Pt 2):H65-H74.

(62) Carabello BA. The relationship of left ventricular geometry and hypertrophy to left ventricular function in valvular heart disease. *J Heart Valve Dis* 1995 October;4 Suppl 2:S132-S138.

(63) Corin WJ, Murakami T, Monrad ES, Hess OM, Krayenbuehl HP. Left ventricular passive diastolic properties in chronic mitral regurgitation. *Circulation* 1991 March;83(3):797-807.

(64) Corin WJ, Monrad ES, Murakami T, Nonogi H, Hess OM, Krayenbuehl HP. The relationship of afterload to ejection performance in chronic mitral regurgitation. *Circulation* 1987 July;76(1):59-67.

(65) Mehta RH, Supiano MA, Grossman PM et al. Changes in systemic sympathetic nervous system activity after mitral valve surgery and their relationship to changes in left ventricular size and systolic performance in patients with mitral regurgitation. *Am Heart J* 2004 April;147(4):729-35.

(66) Pierard LA, Carabello BA. Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment. *Eur Heart J* 2010 December;31(24):2996-3005.

(67) Carabello BA. Ischemic mitral regurgitation and ventricular remodeling. *J Am Coll Cardiol* 2004 February 4;43(3):384-5.

(68) Carpentier A. Cardiac valve surgery--the "French correction". *J Thorac Cardiovasc Surg* 1983 September;86(3):323-37.

(69) Nemoto S, Hamawaki M, De FG, Carabello BA. Differential effects of the angiotensin-converting enzyme inhibitor lisinopril versus the beta-adrenergic receptor blocker atenolol on hemodynamics and left ventricular contractile function in experimental mitral regurgitation. *J Am Coll Cardiol* 2002 July 3;40(1):149-54.

(70) Perry GJ, Wei CC, Hankes GH et al. Angiotensin II receptor blockade does not improve left ventricular function and remodeling in subacute mitral regurgitation in the dog. *J Am Coll Cardiol* 2002 April 17;39(8):1374-9.

(71) Vahanian A, Baumgartner H, Bax J et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007 January;28(2):230-68.

(72) Tsutsui H, Spinale FG, Nagatsu M et al. Effects of chronic beta-adrenergic blockade on the left ventricular and cardiocyte abnormalities of chronic canine mitral regurgitation. *J Clin Invest* 1994 June;93(6):2639-48.

(73) David TE. Outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. *Semin Thorac Cardiovasc Surg* 2007;19(2):116-20.

(74) Enriquez-Sarano M, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. *Circulation* 1995 February 15;91(4):1022-8.

(75) Jokinen JJ, Hippelainen MJ, Pitkanen OA, Hartikainen JE. Mitral valve replacement versus repair: propensity-adjusted survival and quality-of-life analysis. *Ann Thorac Surg* 2007 August;84(2):451-8.

(76) Pierard LA, Carabello BA. Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment. *Eur Heart J* 2010 December;31(24):2996-3005.

(77) Enriquez-Sarano M, Loulmet DF, Burkhoff D. The conundrum of functional mitral regurgitation in chronic heart failure. *J Am Coll Cardiol* 2008 January 29;51(4):487-9.

(78) Iung B, Baron G, Butchart EG et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003 July;24(13):1231-43.

(79) Mirabel M, Iung B, Baron G et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J* 2007 June;28(11):1358-65.

(80) Inoue K, Owaki T, Nakamura T, Kitamura F, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984 March;87(3):394-402.

(81) Chiam PT, Ruiz CE. Percutaneous transcatheter mitral valve repair: a classification of the technology. *JACC Cardiovasc Interv* 2011 January;4(1):1-13.

(82) van Mieghem NM, Piazza N, Anderson RH et al. Anatomy of the mitral valvular complex and its implications for transcatheter interventions for mitral regurgitation. *J Am Coll Cardiol* 2010 August 17;56(8):617-26.

(83) Feldman T, Cilingiroglu M. Percutaneous leaflet repair and annuloplasty for mitral regurgitation. *J Am Coll Cardiol* 2011 February 1;57(5):529-37.

(84) Feldman T, Foster E, Glower DG et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011 April 14;364(15):1395-406.

(85) Feldman T, Kar S, Rinaldi M et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol* 2009 August 18;54(8):686-94.

(86) Franzen O, Baldus S, Rudolph V et al. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. *Eur Heart J* 2010 June;31(11):1373-81.

(87) Tamburino C, Ussia GP, Maisano F et al. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. *Eur Heart J* 2010 June;31(11):1382-9.

(88) Alfieri O, Maisano F, De BM et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg* 2001 October;122(4):674-81.

(89) Harnek J, Webb JG, Kuck KH et al. Transcatheter implantation of the MONARC coronary sinus device for mitral regurgitation: 1-year results from the EVOLUTION phase I study (Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation). *JACC Cardiovasc Interv* 2011 January;4(1):115-22.

(90) Schofer J, Siminiak T, Haude M et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation* 2009 July 28;120(4):326-33.

(91) Palacios IF, Condado JA, Brandi S et al. Safety and feasibility of acute percutaneous septal sinus shortening: first-in-human experience. *Catheter Cardiovasc Interv* 2007 March 1;69(4):513-8.

(92) Sack S, Kahlert P, Bilodeau L et al. Percutaneous transvenous mitral annuloplasty: initial human experience with a novel coronary sinus implant device. *Circ Cardiovasc Interv* 2009 August;2(4):277-84.

(93) Lansac E, Di C, I, Al AN et al. Percutaneous mitral annuloplasty through the coronary sinus: an anatomic point of view. *J Thorac Cardiovasc Surg* 2008 February;135(2):376-81.

(94) Piazza N, Asgar A, Ibrahim R, Bonan R. Transcatheter mitral and pulmonary valve therapy. *J Am Coll Cardiol* 2009 May 19;53(20):1837-51.

(95) Pedersen WR, Block P, Leon M et al. iCoapsys mitral valve repair system: Percutaneous implantation in an animal model. *Catheter Cardiovasc Interv* 2008 July 1;72(1):125-31.

(96) Chiam PT, Ruiz CE. Percutaneous transcatheter mitral valve repair: a classification of the technology. *JACC Cardiovasc Interv* 2011 January;4(1):1-13.

(97) Feldman T, Foster E, Glower DG et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011 April 14;364(15):1395-406.

Part two

The bioabsorbable device in percutaneous patent foramen ovale closure

2

New bioabsorbable septal repair implant for percutaneous closure of a patent foramen ovale: short-term results of a single-centre experience

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Abstract

Background: Permanent implants for closure of a patent foramen ovale (PFO) has a number of possible disadvantages including erosions, thrombus formation, and allergic reactions. The incidence of adverse events may be lower using a bioabsorbable device.

Objective: To evaluate the short-term safety and efficacy of a new bioabsorbable closure device.

Methods: All 35 consecutive patients (21 female, mean age 47.9 ± 10.8 years), who underwent percutaneous PFO closure with the bioabsorbable closure device between November 2007 and July 2008, were included. All complications were reported. The efficacy was based on the residual shunting the day after implant and at one month follow-up and was graded as minimal, moderate, or severe, using contrast transthoracic echocardiography with the Valsalva manoeuvre.

Results: The only in-hospital complication was a surgical device retrieval from the femoral vein. Four patients developed a minimal inguinal haematoma. One day after closure, residual shunting was present in 56% of the patients (minimal 27%, moderate 23%, and severe 6%). At one month follow-up (n=33), one patient developed a transient neurological deficit and three patients suffered from paroxysmal atrial fibrillation. A residual shunt at one month was present in 45% of the patients (minimal 30%, moderate 12%, and severe 3%).

Conclusions: Percutaneous PFO closure using the bioabsorbable closure device seems to be safe. However, a high rate of residual shunting is present at one month follow-up. Long-term follow-up data are necessary to evaluate the efficacy and safety of this device.

Introduction

The presence of a patent foramen ovale (PFO) is associated with paradoxical embolic events, especially in patients younger than 55 years.[1-3] Transcatheter PFO closure has been used with increasing frequency during the last decade and has proven to be a safe and efficient therapy.[4-7] However, current types of closure devices are permanent synthetic implants which are mostly placed in the heart of relatively young patients. Short- and mid-term complications include thromboembolism, rhythm disturbances, friction lesions, erosion, persistent low-grade inflammation, and allergic reactions, whereas long-term adverse effects are largely unknown.[8-12] In addition, a permanent closure device obstructs the atrial wall, making transseptal access to the left atrium difficult in later life.

The new bioabsorbable closure device (BioSTAR®, NMT Medical, Boston, USA) consists of an acellular porcine intestinal collagen layer matrix, mounted on a framework which is similar to the Cardioseal® (NMT Medical, Boston, USA) device. The bioabsorbable device is shown in Figure 1. In a preclinical study, early neo-endothelialization and a low immune response were observed using this new device.[13, 14] In the first in human phase 1 trial, the use of the bioabsorbable closure device seemed to be safe with a high closure rate at one month and six months follow-up.[15]

We report the short-term results of a single-centre experience of percutaneous PFO closure with the bioabsorbable device, regarding safety and efficacy.

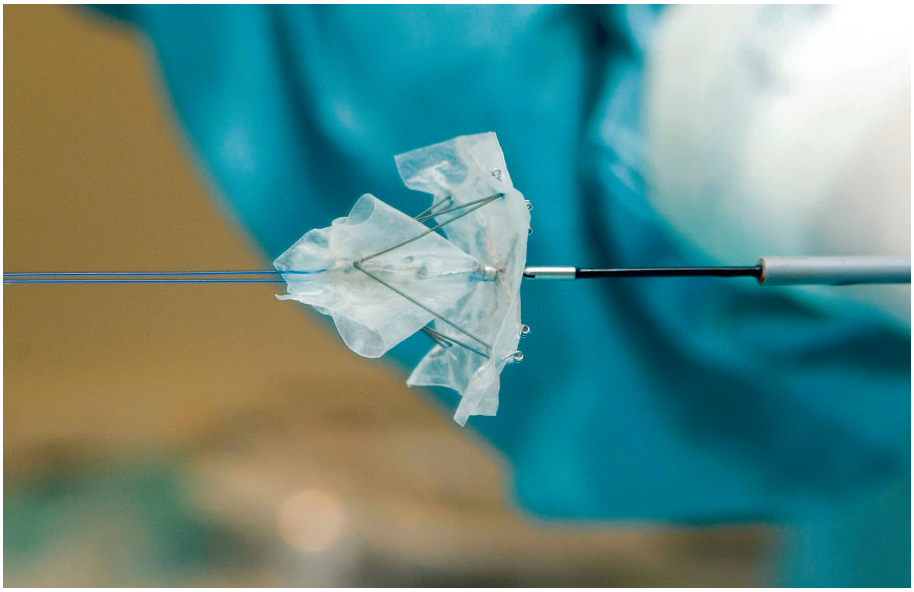

Figure 1. The bioabsorbable closure device (BioSTAR®, NMT Medical, Boston, USA).

Methods

Study population

All consecutive patients, who underwent a percutaneous closure of a symptomatic PFO in our centre between November 2007 and July 2008, were included. No other closure devices were implanted during this period. At the outpatient clinic, the PFO was diagnosed by standardized contrast transthoracic (cTTE) or transesophageal echocardiography (cTEE) with spontaneous or provokable right-to-left shunt, using 10 mL of blood- and air-mixed saline, injected in the right antecubital vein. An atrial septal aneurysm (ASA) was defined as a protrusion of the interatrial septum, or part of it, of at least 10 mm beyond the plane of the interatrial septum. A PFO was defined as symptomatic in patients who suffered a cryptogenic cerebral ischaemic event or decompression illness in the presence of a PFO. In case of presumed paradoxical embolism, other sources of systemic emboli were ruled out. All patients were treated with antiplatelet therapy prior to the closure procedure. The registry was approved by the local ethical commission.

Closing procedure

Closure was performed under general anaesthesia and TEE monitoring within the first six patients and under local anaesthesia using intracardiac echocardiographic (ICE) guidance thereafter, both with concomitant fluoroscopic guidance. Each patient received an intravenous prophylactic dose of antibiotics at the time of the procedure. Venous access, using a 12 French sheath, was gained via the right femoral vein. After rehydration in saline for 3 to 5 minutes, the bioabsorbable device was loaded in a delivery catheter and advanced into the left atrium. The left femoral vein was used in case of ICE-guidance, using a 8 French sheath. A bolus of 5000 U heparin was administered after accessing the right femoral vein. We used the "one size fits all approach" using a 28-mm device, only in case of a long-tunnel PFO a larger device was chosen. All patients had a 12-lead electrocardiogram before and after the procedure. A chest X-ray was performed within 24 hours after closure. A cTTE was performed within 24 hours and one month after the closure procedure. All patients were treated with antiplatelet therapy: aspirin 100 mg once a day for a period of six months after a loading dose of 300 mg and clopidogrel 75 mg once a day during one month, after a loading dose of 300 mg. Prophylaxis against bacterial endocarditis was advised for six months.

Outcome, complications, and efficacy

All procedural complications, related to the procedure within one month, were reported. Complications were divided into major and minor complications according to the classification scheme of Khairy et al.[16] According to this review article, major complications include haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure related surgical intervention, massive fatal pulmonary emboli, and death, related to the closing procedure. Minor complications were defined as device malpositioning with successful catheter repositioning, bleeding not requiring blood transfusion, occurrence of new onset atrial arrhythmias (atrial flutter or fibrillation), transient atrioventricular block, device arm fractures, device embolization with successful catheter retrieval, asymptomatic device thrombosis, need for recatheterization, transient air embolism, transient ST-segment elevation, femoral arteriovenous fistula formation, femoral haematoma, and other minor complications related to the closing procedure.

The efficacy of PFO closure was based on the presence of a residual shunt, using cTTE both with and without the Valsalva manoeuvre. Microbubbles were counted in the left atrium within three cardiac cycles after right heart opacification. Residual shunting was categorized as follows: small shunt (< 30 bubbles in the left atrium), moderate shunt (30-100 bubbles in the left atrium), and severe shunt (> 100 bubbles in the left atrium). Recently, we described an excellent inter-observer variability using cTTE for right-to-left shunt detection, using the grading scale as described earlier.[17] Two independent physicians performed the echocardiographic endpoint analysis.

Statistical analysis

Descriptive statistics were used to describe patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. Univariate statistical analysis was used to identify risk factors for residual shunting after PFO closure. All statistical analyses were performed by using SPSS software (version 14.0 for Windows).

Results

Patient and closure characteristics

In total, 35 patients (21 female, mean age 47.9 ± 10.8 years) underwent a percutaneous closure of a PFO with the bioabsorbable device. Thirty-four patients (97%) had a history of a cryptogenic stroke, one patient suffered from decompression illness. Patients' and PFO characteristics and the indications for closure are shown in Table I.

Table I. Baseline characteristics

Number	35
Mean age ± SD (y)	47.9 ± 10.8
Female, n (%)	21 (60)
BMI (kg/m^2)	25.5 ± 4.4
BP systolic	130 ± 14
BP diastolic	77 ± 8
Risk factors, n (%)	
Smoking	8 (23)
Diabetes	3 (9)
Arterial hypertension	8 (23)
Hypercholesterolemia	11 (31)
Family history	10 (29)
PFO characteristics, %	
RLS Valsalva	100
RLS Spontaneously	44
Aneurysm IAS	50
Indication for closure, n (%)*	
TIA, single	10 (29)
TIA, multiple	8 (23)
CVA, single	17 (49)
CVA, multiple	2 (6)
Decompression illness	1 (3)
SVT, n (%)	6 (17)

SD, standard deviation; y, years; n, number; BMI, body mass index; BP, bloodpressure; PFO, patent foramen ovale; RLS, right-to-left shunt; IAS, interatrial septum; TIA, transient ischemic attack; CVA, cerebrovascular accident; SVT, supraventricular tachycardia.
* Three patients had a history of both a TIA and a CVA.

In 91% of the patients, a 28-mm device was successfully delivered. In two patients, the 28-mm device was pulled through the defect and was successfully replaced by a 33-mm device. One patient with a long-tunnel PFO received a 33-mm device on the first attempt. A total of 29 patients underwent PFO closure under local anaesthesia and ICE-guidance, only the first six patients were treated under general anaesthesia and TEE-guidance. The closure characteristics are summarized in Table II.

Table II. Procedural characteristics

Diameter device, n (%)	
28-mm	32 (91)
33-mm	3 (9)
Anaesthesia, n (%)	6 (17)
Echocardiographic guidance, n (%)	
TEE	6 (17)
ICE	29 (83)
Radiation dose ± SD (Gy/cm2)	28 ± 14
Procedural complications, n (%)	
Minimal surgical intervention	1 (3)
Mean hospitalization stay (hours)	24

n, number; TEE, transesophageal echocardiography; ICE, intracardiac echocardiography; SD, standard deviation; Gy, Gray.

Outcome and short-term complications

In 34 patients (97%), the device was successfully delivered and deployed. In one patient, the device was pulled through the PFO before it was released, but could not be recovered into the sheath. Therefore, surgical exploration of the femoral vein was necessary to retrieve the device. This patient successfully received an Amplatzer® Septal Occluder (AGA Medical, Plymouth, Minnesota, USA) one month later. Four patients developed a minimal inguinal haematoma immediately after the procedure neither requiring a blood transfusion nor surgical intervention. At short-term follow-up, three patients experienced a supraventricular tachy-arrhythmia, treated successfully with antiarrhythmic drugs. One patient developed a transient recurrent neurologic event within one month after closure in the presence of a residual shunt at that time, and an ASA on baseline echocardiography. These data are summarized in Table III.

Table III. Complications and re-occurrence of stroke

	In-hospital	1 month
Number of patients, n	35	33
Major complications, n (%)		
Minimal surgical intervention	1 (3)	0
Minor complications, n (%)		
New SVT	0	3 (9)
Inguinal haematoma	4 (11)	0
Reoccurrence ischaemic event, n (%)		
TIA	0	1 (3)*
CVA	0	0

n, number; SVT, supraventricular tachycardia; TIA, transient ischemic attack; CVA, cerebrovascular accident.
* with the presence of a residual shunt.

Efficacy

One day after closure, residual shunting was present in 56% of the patients. A small shunt was present in 27%, a moderate shunt in 23%, and a severe shunt in 6% of the patients. Follow-up echocardiography at one month after closure could be obtained in 33 patients (97%). One patient, who received an Amplatzer® Septal Occluder because of dislodgement of the bioabsorbable device, did not undergo echocardiographic follow-up at one day and one month, and one patient was not able to visit our echolab because of personal circumstances, not related to PFO closure. At one month, residual shunting was seen in 45% of the patients, 30% was defined as a small shunt, 12% as a moderate shunt, and 3% as a severe shunt (p=0.02 compared to one day follow-up). No predictor for the presence of a moderate or severe residual shunt could be found using the univariate analysis model. The efficacy data are shown in Figure 2.

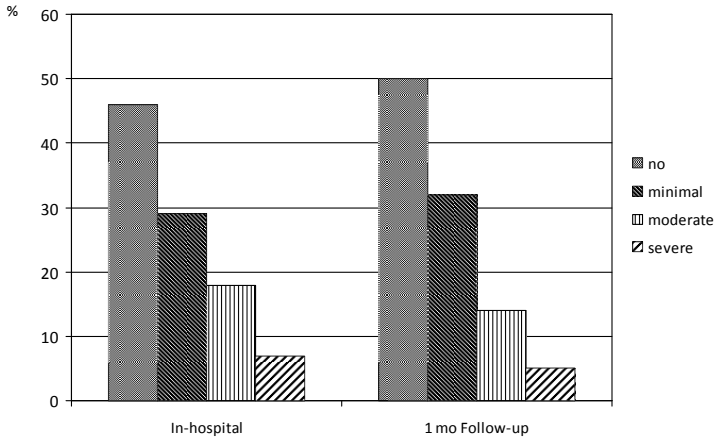

Figure 2. Percentage of residual shunting diagnosed by cTTE during follow-up.

Discussion

In the past, different types of devices have been used for percutaneous PFO closure.[18] Nowadays, this procedure is safe and effective. However, a permanent implant in the heart has a number of potential complications including thromboembolism, rhythm disturbances, erosion, persistent low-grade inflammation, and allergic reactions. Regarding these potential problems, a new bioabsorbable closure device has been developed. Other promising novel techniques are suture closure and closure using radiofrequency-based energy, leaving no device behind.[19, 20] Jux et al. compared the histology of the healing response of the Cardioseal® (n=10) and the bioabsorbable device (n=26) after transcatheter atrial septal defect (ASD) closure in 36 young sheep.[14] The bioabsorbable device showed an accelerated healing response with early neo-endothelialization and a transient and lower immune response compared with the non-bioabsorbable device. They observed a complete neo-endothelial coverage of the device after 30 days. Phagocytosis of the matrix by macrophages and giant cells started after one month. After two years in vivo, 90% of the matrix was fully resorbed and replaced by host tissue.[13, 14]

Percutaneous PFO closure, using different permanent devices, is safe with a major complication rate of less than 1% in large observational studies.[4, 21] The first in-human phase 1 trial, using the bioabsorbable closure device was published by Mullen et al. in 2006.[15] A total of 58 patients received the bioabsorbable device, 54 (93%) for closure of a PFO, four (7%) for closure of an ASD. Overall procedural success in case of PFO closure appeared to be 98% (53/54), one device had to be retrieved because of malposition and was successfully replaced by a larger device. They reported no major complications, five patients (9%) developed a supraventricular tachycardia, and one patient developed a mobile thrombus which resolved after treatment with oral anticoagulation. In our prospective observational study, a major complication occurred in one patient (3%), and three patients (9%) experienced supraventricular tachycardia, successfully treated medically.

At short-term follow-up, the prevalence of a residual shunt after percutaneous PFO closure varies between 10 and 50%.[22, 23] The large differences can be explained by the PFO characteristics prior to closure, the device used for closure, different definitions of residual shunting, and/or different diagnostic tools.[22] In the study by Mullen et al., using the bioabsorbable device, a moderate or large residual shunt, diagnosed by cTTE, was found in 8% at 30-days follow-up. The rate of minimal shunting was not reported. In their study, 30% of the interatrial defects were associated with an ASA.[15] In our study, a moderate or severe residual shunt at one month follow-up was found in 15% of the patients, who received a bioabsorbable closure device, and an ASA was present in about 50% of the patients prior to closure. The latter might explain the higher shunt rate in our patient group. In a recent study, an association between the presence of an ASA prior to closure and a residual shunt after percutaneous PFO closure had been described.[24] However, we could not find an association between the patients' and PFO characteristics and the presence of a residual shunt after closure, probably due to the small number of included patients.

Limitations of our study are the small number of patients and the short follow-up time. During mid- and long-term follow up we will perform cTTE to evaluate the closure rate.

Conclusions

This study demonstrates that percutaneous PFO closure, using the new bioabsorbable closure device is feasible and safe. We report a low periprocedural and one month complication rate. However, a high rate of residual shunts is present at one month follow-up. Long-term follow-up data are necessary to evaluate the residual shunting and safety of this new bioabsorbable closure device.

Reference List

(1) Mas JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. *Am Heart J* 1995 November;130(5):1083-8.

(2) Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000 October 24;55(8):1172-9.

(3) Webster MW, Chancellor AM, Smith HJ et al. Patent foramen ovale in young stroke patients. *Lancet* 1988 July 2;2(8601):11-2.

(4) Braun M, Gliech V, Boscheri A et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. *Eur Heart J* 2004 March;25(5):424-30.

(5) Meier B. Closure of patent foramen ovale: technique, pitfalls, complications, and follow up. *Heart* 2005 April;91(4):444-8.

(6) Wahl A, Krumsdorf U, Meier B et al. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol* 2005 February 1;45(3):377-80.

(7) Windecker S, Wahl A, Chatterjee T et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000 February 29;101(8):893-8.

(8) Alaeddini J, Feghali G, Jenkins S, Ramee S, White C, bi-Samra F. Frequency of atrial tachyarrhythmias following transcatheter closure of patent foramen ovale. *J Invasive Cardiol* 2006 August;18(8):365-8.

(9) Amin Z, Hijazi ZM, Bass JL, Cheatham JP, Hellenbrand WE, Kleinman CS. Erosion of Amplatzer septal occluder device after closure of secundum atrial septal defects: review of registry of complications and recommendations to minimize future risk. *Catheter Cardiovasc Interv* 2004 December;63(4):496-502.

(10) Divekar A, Gaamangwe T, Shaikh N, Raabe M, Ducas J. Cardiac perforation after device closure of atrial septal defects with the Amplatzer septal occluder. *J Am Coll Cardiol* 2005 April 19;45(8):1213-8.

(11) Sherman JM, Hagler DJ, Cetta F. Thrombosis after septal closure device placement: a review of the current literature. *Catheter Cardiovasc Interv* 2004 December;63(4):486-9.

(12) Wertman B, Azarbal B, Riedl M, Tobis J. Adverse events associated with nickel allergy in patients undergoing percutaneous atrial septal defect or patent foramen ovale closure. *J Am Coll Cardiol* 2006 March 21;47(6):1226-7.

(13) Jux C, Wohlsein P, Bruegmann M, Zutz M, Franzbach B, Bertram H. A new biological matrix for septal occlusion. *J Interv Cardiol* 2003 April;16(2):149-52.

(14) Jux C, Bertram H, Wohlsein P, Bruegmann M, Paul T. Interventional atrial septal defect closure using a totally bioresorbable occluder matrix: development and preclinical evaluation of the BioSTAR device. *J Am Coll Cardiol* 2006 July 4;48(1):161-9.

(15) Mullen MJ, Hildick-Smith D, De Giovanni JV et al. BioSTAR Evaluation STudy (BEST): a prospective, multicenter, phase I clinical trial to evaluate the feasibility, efficacy, and safety of the BioSTAR bioabsorbable septal repair implant for the closure of atrial-level shunts. *Circulation* 2006 October 31;114(18):1962-7.

(16) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003 November 4;139(9):753-60.

(17) Post MC, Gent van MWF, Swaans MJ et al. Transthoracic contrast echocardiography grading to predict the presence of treatable pulmonary arteriovenous malformations on chest CT. Eur J Echocardiogr 9[supplement 1], S173. 1-12-2008. Ref Type: Abstract

(18) Post MC, Van DK, Budts W. Percutaneous closure of a patent foramen ovale: single-centre experience using different types of devices and mid-term outcome. *Acta Cardiol* 2005 October;60(5):515-9.

(19) Ruiz CE, Kipshidze N, Chiam PT, Gogorishvili I. Feasibility of patent foramen ovale closure with no-device left behind: first-in-man percutaneous suture closure. *Catheter Cardiovasc Interv* 2008 June 1;71(7):921-6.

(20) Sievert H, Fischer E, Heinisch C, Majunke N, Roemer A, Wunderlich N. Transcatheter closure of patent foramen ovale without an implant: initial clinical experience. *Circulation* 2007 October 9;116(15):1701-6.

(21) Taaffe M, Fischer E, Baranowski A et al. Comparison of three patent foramen ovale closure devices in a randomized trial (Amplatzer versus CardioSEAL-STARflex versus Helex occluder). *Am J Cardiol* 2008 May 1;101(9):1353-8.

(22) Luermans JG, Post MC, Schrader R et al. Outcome after percutaneous closure of a patent foramen ovale using the Intrasept device: a multi-centre study. *Catheter Cardiovasc Interv* 2008 May 1;71(6):822-8.

(23) Martin F, Sanchez PL, Doherty E et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation* 2002 August 27;106(9):1121-6.

(24) Zajarias A, Thanigaraj S, Lasala J, Perez J. Predictors and clinical outcomes of residual shunt in patients undergoing percutaneous transcatheter closure of patent foramen ovale. *J Invasive Cardiol* 2006 November;18(11):533-7.

3

The BioSTAR® device versus the CardioSEAL® device in patent foramen ovale closure: comparison of mid-term efficacy and safety

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Abstract

Aims: To compare the mid-term efficacy and safety of the bioabsorbable BioSTAR® device with the non-bioabsorbable CardioSEAL® device for percutaneous patent foramen ovale (PFO) closure.

Methods and results: All 81 consecutive patients who underwent PFO closure with the CardioSEAL® or BioSTAR® device between June 2003 and July 2008 were included. The presence of a residual shunt (minimal, moderate or large) was measured in both groups at six months follow-up, using contrast transthoracic echocardiography. Forty-four patients (48.4 ± 11.4 years) received the CardioSEAL® device and 37 patients the BioSTAR® device (47.9 ± 10.7 years). There were no significant differences in short-term complications. Two patients who received the BioSTAR® device developed a recurrent transient cerebral ischaemic event. Overall, atrial arrhythmias occurred in 19%, with no difference between both groups. At six months, a residual shunt was present in 29% (27% minimal, 2% moderate) using the CardioSEAL® device compared to 28% (17% minimal, 11% moderate) using the BioSTAR® device (p=0.18). A predictor for residual shunt could not be found.

Conclusions: There is no difference in safety and efficacy at six months between the CardioSEAL® and BioSTAR® device used for PFO closure. However, using the BioSTAR ® device tends to be associated with a higher percentage of moderate shunting.

Introduction

A patent foramen ovale (PFO) has been associated with paradoxical embolic events such as cryptogenic stroke, peripheral embolism, and decompression illness in divers, especially in young adults.[1-3] These patients are at increased risk of recurrent thromboembolic events, despite the use of anticoagulation or antiplatelet therapy.[4-6] Moreover, patients with an atrial septal aneurysm (ASA) have a higher risk of stroke recurrence.[7-9] Since the initial report in 1992[10], percutaneous PFO closure has been used with increasing frequency and has shown promising results regarding safety and efficacy. Various occlusion systems have been used, with different complication and success rates.[11-14] A new bioabsorbable device (BioSTAR®, NMT Medical, Boston, USA) has been developed to avoid potential problems such as thromboembolism, erosion, and inflammation which have been attributed to permanent synthetic implants. The BioSTAR® device consists of a totally biodegradable matrix made of a porcine intestinal collagen layer, mounted on a nitinol framework. Initially, promising results were shown in the first in-human trial.[15] However, a high rate of residual shunting was noticed at short-term follow-up.[16] Another self-expanding, double umbrella device mounted on the same framework is the CardioSEAL® device (NMT Medical, Boston, USA). This non-bioabsorbable, permanent device is widely used and associated with a low incidence of complications and recurrent thromboembolic events.[17, 18] Both devices are shown in Figure 1. The aim of our study is to compare these two devices in patients with presumed paradoxical embolism undergoing percutaneous PFO closure with respect to periprocedural and mid-term complications, the recurrence of paradoxical embolism, and the efficacy of PFO closure.

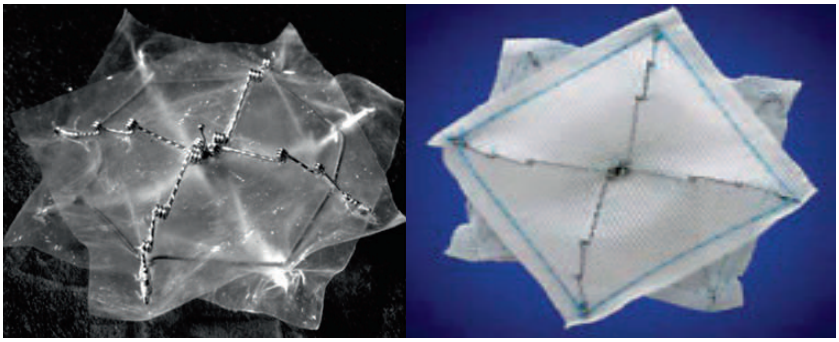

Figure 1. The BioSTAR® device (left) and the CardioSEAL® device (right).

Methods

Study population

All 81 patients who underwent a PFO closure in our centre using the CardioSEAL® or BioSTAR® device between between June 2003 and July 2008 were included. During that study period, 87 PFO closing procedures were performed. In six patients, an Amplatzer® PFO occluder (AGA Medical, Plymouth, Minnesota, USA) was used and these patients were excluded. Between June 2003 and October 2007 the CardioSEAL® device was used in 44 patients. From November 2007 until July 2008 the BioSTAR® device was used for PFO closure in 37 consecutive patients. A PFO was identified by standardized contrast transthoracic echocardiography (cTTE) using second harmonic imaging or contrast transesophageal echocardiography (cTEE) with spontaneous or provokable right-to-left shunt, after injection of 10 mL of agitated saline in an antecubital vein. An ASA was defined as an excursion of the interatrial septum of at least 10 mm. The study was approved by the local ethical committee.

Closing procedure

As described previously, closure of the PFO was performed under general anaesthesia and TEE monitoring in all patients who received the CardioSEAL® device and in the first six patients who received the BioSTAR® device.[16, 19] Thereafter, the BioSTAR® device was implanted under local anaesthesia using intracardiac echocardiographic

(ICE) guidance. Concomitant biplane fluoroscopic guidance was used in all patients. All patients were treated with antiplatelet therapy prior to the closing procedure. A bolus of 5000 U of heparin was administered after accessing the right femoral vein and each patient received an intravenous prophylactic dose of antibiotics at the time of the procedure. The left femoral vein was used in case of ICE-guidance. The PFO was passed using a standard multipurpose catheter and exchange wire. After thoroughly flushing to prevent air embolism, the loaded implantation system was advanced across the atrial septum and the device expanded and released under fluoroscopic and echocardiographic guidance. Within 24 hours after closure, an electrocardiogram, chest X-ray, and cTTE were performed. All patients were discharged on aspirin 100 mg once a day for a period of six months and clopidogrel 75 mg once a day during one month. Patients on oral anticoagulant therapy before the procedure were discharged on a combination of oral anticoagulant therapy and clopidogrel for one month. Endocarditis prophylaxis precautions were recommended for six months.

Successful device implantation was defined as completion of the procedure without the occurrence of major events (death, device embolisation, device malpositioning with replacement or need for surgical intervention).

Complications and outcome

All procedural complications, immediately related to the procedure within six months, were reported. Complications were divided into major and minor complications according to the classification scheme of Khairy et al.[20] According to this review article, major complications include haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure related surgical intervention, massive fatal pulmonary emboli and death, related to the closing procedure. Minor complications were defined as device malpositioning with successful catheter repositioning, bleeding not requiring blood transfusion, occurrence of new onset atrial arrhythmias (atrial flutter or fibrillation), transient atrioventricular block, device arm fractures, device embolization with successful catheter retrieval, asymptomatic device thrombosis, need for re-catheterization, transient air embolism, transient ST-segment elevation, femoral arteriovenous fistula formation, femoral haematoma, and other minor complications related to the closing procedure.

Clinical information was obtained by an outpatient visit to a cardiologist at six months. New-onset supraventricular tachyarrhythmias (SVT) were diagnosed by a 12-lead electrocardiogram or Holter monitoring in patients without a history of SVT at baseline. The history of recurrence of stroke or TIA was confirmed by a neurologist using the appropriate imaging techniques.

Efficacy

The routine follow-up program for the CardioSEAL® device group included TTE without contrast at 24 hours and cTTE at six months after device implantation. The group who received the BioSTAR® device had a cTTE at 24 hours and at six months, and an additional cTTE one month after implantation. All echocardiographic examinations, six months after device implantation, were reviewed by two independent physicians. The efficacy of PFO closure was based on the residual shunt. Microbubbles were counted in the left atrium within three cardiac cycles after right heart opacification. Residual shunting was categorized as follows: small shunt (< 30 bubbles in the left atrium), moderate shunt (30-100 bubbles in the left atrium), and severe shunt (> 100 bubbles in the left atrium). Recently, an excellent interobserver variability has been demonstrated using cTTE for right-to-left shunt detection.[21] All cTTE examinations were performed using second harmonic imaging.[22]

Statistical analysis

Descriptive statistics were used to describe patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. Univariate statistical analysis was used to identify risk factors for residual shunting after PFO closure. All statistical analyses were performed by using SPSS software (version 14.0 for Windows).

Results

Patient population

Baseline and PFO characteristics of the patient population are listed in Table I. In 44 patients PFO closure was performed with the CardioSEAL® device. Thirty-six percent were female with a mean age of 48.4 ± 11.4 years. In the BioSTAR® device group, 60% were women with a mean age of 47.9 ± 10.7 years. An ASA was detected in 46% and 49% in the CardioSEAL® device group and in the BioSTAR® device group, respectively. All patients in the CardioSEAL® device group underwent PFO closure because of cryptogenic stroke or TIA. In the other group, one patient was treated because of decompression illness. Twenty-one patients (26%) had a history of more than one thromboembolic event.

Table I. Baseline characteristics

	Cardioseal®	Biostar®	p-value
Total	44	37	
Mean age ± SD (y)	48.4 ± 11.4	47.9 ± 10.7	0.85
Female, n (%)	16 (36)	22 (60)	0.05
Weight (kg) ± SD	82 ± 14	78 ± 15	0.28
Risk factors, %			
Hypertension	29	22	0.61
Hypercholesterolaemia	34	32	1.00
Diabetes	5	8	0.66
Family history	26	30	0.80
Smoking	26	24	1.00
PFO characteristics, %			
RLS Spontaneously	69	42	0.03
ASA	46	49	0.83
Indication for closure, n*			
TIA, single	13	11	
TIA, multiple	8	9	
CVA, single	26	18	
CVA, multiple	2	2	
Decompression illness	0	1	

SD, standard deviation; y, years; n, number; PFO, patent foramen ovale; RLS, right-to-left shunt; ASA, Atrial septal aneurysm; TIA, transient ischemic attack; CVA, cerebrovascular accident.
*21 patients had a history of more than one event.

Periprocedural complications

The implantation of the CardioSEAL® device was successful in 98% of the patients. In one patient a 28-mm device was malpositioned and successfully replaced by a 33-mm device. A 28-mm device was delivered in 86% of the patients in this group. One patient developed a minimal groin haematoma immediately after the procedure not requiring a blood transfusion nor surgical intervention. There were no other in-hospital complications.

In the BioSTAR® device group, 36 patients (97 %) had a successful device delivery and deployment. In one patient the device was pulled through the PFO before it was released, but could not be recovered into the sheath. Therefore, surgical exploration of the femoral vein was necessary to retrieve the device. This patient successfully received an Amplatzer® PFO Occluder one month later. A 28-mm device was implanted in 92% of the patients in this group. Four patients (11%) developed a minimal inguinal haematoma. The closure characteristics are summarized in Table II. The in-hospital complications are shown in Table III.

Mid-term complications and outcome

Within six months after closure, no major complications occurred in either of the two groups. In the CardioSEAL® device group, nine patients (21%) developed a SVT. Seven patients were treated successfully with antiarrhytmic drugs, two patients needed electrical conversion. No other complications occurred in this group. No re-occurrence of stroke or TIA was reported.

In the BioSTAR® device group, six patients (17%) experienced a new paroxysmal SVT, one patient needed electrical cardioversion, three patients were treated medically, the other two patients had a transient atrial tachycardia which resolved spontaneously. No predictor for the development of SVT after PFO closure could be identified by using univariate analysis. A 51-year-old male patient developed a TIA within one month after closure with the BioSTAR® device. This patient had a residual shunt at that time and an ASA on baseline echocardiography. A 50-year-old female patient suffered from a recurrent TIA, six months after closure in the absence of a residual shunt on cTTE (Table III).

Table II. Procedural characteristics

	Cardioseal®	Biostar®
Total	44	37
Diameter device, n (%)		
23-mm	5 (11)	0
28-mm	38 (86)	34 (92)
33-mm	1 (2)	3 (8)
Echocardiography, n (%)		
TEE	44 (100)	6 (16)
ICE	0	31 (84)
Anaesthesia, n (%)	44 (100)	6 (16)
Procedural complications, n (%)		
Minimal surgical intervention	0	1 (3)
Device malposition	1 (2)	0
Hospital stay (days)	2	2

n, number; TEE, transesophageal echocardiography ; ICE, intracardiac echocardiography.

Table III. Complications and re-occurrence of cerebral ischaemia

	In-hospital		6 months	
	Cardioseal®	Biostar®	Cardioseal®	Biostar®
Total	44	37	44	36
Major complications, n (%)				
Surgical intervention	0	1 (3)	0	0
Minor complications, n (%)				
Inguinal haematoma	1 (2)	4 (11)	0	0
New SVT	0	0	9 (21)	6 (17)
Re-occurrence ischaemia				
TIA	0	0	0	2 (6)

n, number; SVT, supraventricular tachycardia; TIA, transient ischemic attack.
No significant differences between both groups.

Efficacy

At six months follow-up, complete closure was present in 71% of the patients who received the CardioSEAL® device and in 72% of the patients who received the BioSTAR® device (p=0.18). In the CardioSEAL® device group, 27% had a trivial shunt and 2% had a moderate shunt, compared with 17% and 11% respectively in the BioSTAR® device group. No large shunts were detected. The efficacy data are shown in Figure 2. Combining moderate and large shunts results in a non-significant higher percentage of residual shunt in the BioSTAR® device group (11% versus 2%, p=0.17). No predictor for the presence of a residual shunt at 6-month follow-up could be identified using univariate analysis.

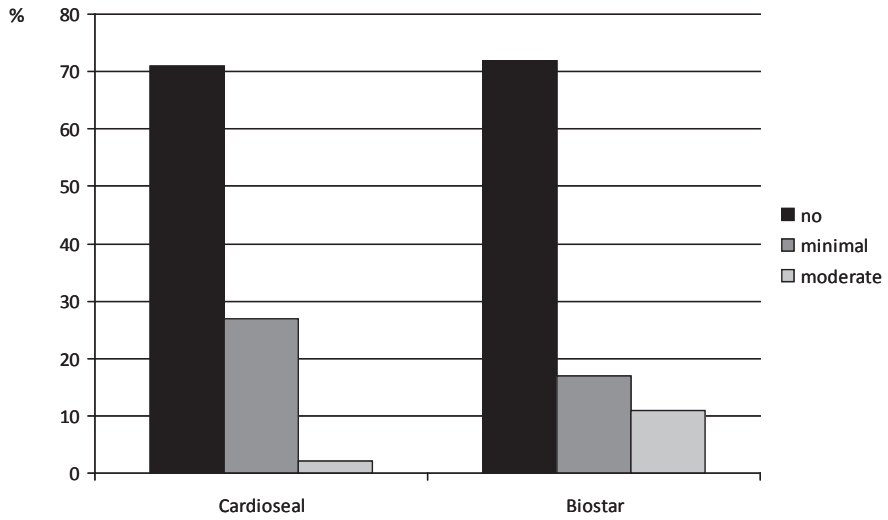

Figure 2. Percentage of residual shunting diagnosed by cTTE at six months follow-up.

Discussion

In the past, several occluder systems have been used for transcatheter PFO closure.[13, 14, 23] They all have different designs and consist of a synthetic matrix, which is encapsulated by fibrous tissue over time. Inherent risks include device embolization

and device fracture, infection, erosion, thrombus formation, and arrhythmias.[24-26] Therefore, a bioabsorbable closure device has been introduced recently. It is associated with the ability to induce a host connective tissue response and should lead to a more rapid and complete neo-endothelialization. The collagen matrix is gradually resorbed over a period of about two years, leaving only the frame behind.[27, 28] The non-bioabsorbable CardioSEAL® device, used in our study, is constructed from a knitted Dacron® fabric, mounted on the same low profile nitinol framework as the bioabsorbable device. We accomplished the first "head-to-head" comparison of these two devices in a single-centre setting.

Complications

The rate of complications of PFO closure with the CardioSEAL® device is described in several studies. The periprocedural major complication rate varies between 1.6 and 4.6%.[29, 30] We found a periprocedural complication rate of 2% in the CardioSEAL® device group. Recently, Taaffe et al. described a randomized comparison of the CardioSEAL® device with the Amplatzer® and Helex® device.[23] They examined 660 patients, with 220 patients per group and found more thrombus formation (3.6%) and atrial fibrillation (4.5%) one month after the procedure, in the group who received the CardioSEAL® device. Anzai et al. showed that the CardioSEAL® device is more likely (22%) to have thrombus formation than the Amplatzer® device, using cTEE.[31] We found a short-term complication rate of 21% in the CardioSEAL® group, all related to supraventricular arrhythmias. We did not detect any thrombus in the CardioSEAL® group, realizing that thrombus assessment with TTE only might be not revealing.

In the BEST trial, 58 patients (54 PFO, 4 ASD) were treated with the BioSTAR® device.[15] In two patients (3%), the device was malpositioned. In one of them a larger device was introduced and in the other patient the defect was closed with an alternative device. Furthermore, they described no major adverse events during follow-up. Five patients (8.6%) were treated for supraventricular arrhythmia, one patient developed urticaria and in one patient a mobile echogenic mass was seen on the right atrial side of the device, which resolved after anticoagulation therapy. As previously reported, we had a procedural complication in one patient (3%).[16] In our series, 17% developed a new transient SVT, no other complications occurred during

mid-term follow-up. Comparing the BioSTAR® device and the CardioSEAL® device, no significant differences could be observed regarding periprocedural, short- and mid-term complications. However, quite a high percentage of new SVT is seen in both groups. On the other hand, there seems to be a trend towards a higher percentage of inguinal haematoma (11% versus 2%) in the BioSTAR® device group, probably due to the extra access site using ICE. In two reports which compared PFO closure guidance with ICE and TEE, no differences could be found regarding safety.[32, 33]

Re-occurrence of thromboembolic events

A recent report showed an annual re-event rate of 0.9% for stroke and a combined annual event rate for stroke and TIA of 3.4% in 216 patients treated with the CardioSEAL® device.[34] Interestingly, they found that 30% of the patients with a recurrent event had clear evidence of pathology unrelated to a cardio-embolic source. In our CardioSEAL® group, no recurrence of stroke or TIA occurred within six months after PFO closure.

In the BEST trial, no tromboembolic events were noticed after six months follow-up.[15] We report two patients (5.6%) with symptoms of recurrent TIA in the BioSTAR® device group. Previous studies support the hypothesis of the increased risk of re-events in the presence of a residual shunt and/or ASA.[7, 8] One patient indeed had a residual shunt and an ASA. In the other patient PFO closure was achieved and confirmed by cTTE and no thrombus was seen on the device. It may be presumed that the cause of recurrent TIA might be other than paradoxical embolism.

Residual shunt

The presence of a residual right-to-left shunt after PFO closure is widely described in literature. Recently, Wahl and Meier addressed that complete PFO closure is achieved in 51-100% of patients, using a variety of devices.[35] According to this review paper, complete PFO closure at six months using the CardioSEAL® device varies between 51% and 89% .[8, 17, 18, 30, 36] Braun et al. reported a residual shunt, using cTEE, in 28% of the patients after one month and in 20% of the patients after six months, using the CardioSEAL® device.[29] At six months after the procedure, we found an overall residual shunt rate (including small shunts) of 29% for the CardioSEAL® device. Only 2% of the patients had a moderate shunt and no large shunts were detected.

The BEST trial showed a residual shunt rate of 8% at one month and of 4% at six months, using cTTE. Successful defect closure was defined as procedural success with no shunt or trivial (< 10 bubbles) shunt, so only moderate and large shunts were reported.[15] In our series, a residual shunt rate of 28% was noticed at 6-month follow-up. We earlier reported a residual shunt rate of 45% (minimal 30%, moderate 12%, severe 3%) in 33 patients, one month after the implantation of the BioSTAR® device.[16] Comparison of our results with the results of the BEST trial is difficult concerning the difference in shunt grading. When we only count moderate and large shunts, a residual shunt rate of 15% at one month and of 11% at six months was achieved.

Overall, a comparable closure rate is seen between the CardioSEAL® and the BioSTAR® device. However, more moderate shunts were detected (11% versus 2%) using the BioSTAR® device. A hypothesis for the difference in residual shunting is that in some patients, a mechanical occlusion of the defect with a synthetic device might result more rapidly in defect closure compared to the more natural healing process using the BioSTAR® device. This is in contrast to the findings of Jux et al., who showed a significantly more thorough coverage of the device by tissue in a sheep model.[27] Maybe there is an inter-individual difference regarding the formation of neo-endothelium and granulation tissue in response to the BioSTAR® device.

Limitations of the study are the non-randomized, retrospective design, the single-centre characteristics, and the small number of patients. Regarding complications, we must stress that we only performed TTE during follow-up, which is less sensitive for thrombus detection on the devices.

Conclusions

Our study shows that percutaneous PFO closure can be achieved safely with the CardioSEAL® device and with the BioSTAR® device. No significant differences could be revealed regarding implantation success, periprocedural, short-term, and mid-term complications. The efficacy of closure is comparable, however the use of the BioSTAR® device is associated with a higher percentage of moderate shunting. Larger, randomized trials are necessary to determine the optimal closure device in this patient population.

Reference List

(1) Cabanes L, Mas JL, Cohen A et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. *Stroke* 1993 December;24(12):1865-73.

(2) Lechat P, Mas JL, Lascault G et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988 May 5;318(18):1148-52.

(3) Webster MW, Chancellor AM, Smith HJ et al. Patent foramen ovale in young stroke patients. *Lancet* 1988 July 2;2(8601):11-2.

(4) Mas JL, Arquizan C, Lamy C et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001 December 13;345(24):1740-6.

(5) Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van MG. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. Lausanne Stroke with Paradoxal Embolism Study Group. *Neurology* 1996 May;46(5):1301-5.

(6) Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002 June 4;105(22):2625-31.

(7) Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000 October 24;55(8):1172-9.

(8) Wahl A, Krumsdorf U, Meier B et al. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol* 2005 February 1;45(3):377-80.

(9) Mas JL, Zuber M. Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. *Am Heart J* 1995 November;130(5):1083-8.

(10) Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. *Circulation* 1992 December;86(6):1902-8.

(11) Windecker S, Wahl A, Chatterjee T et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000 February 29;101(8):893-8.

(12) Meier B. Closure of patent foramen ovale: technique, pitfalls, complications, and follow up. *Heart* 2005 April;91(4):444-8.

(13) Post MC, Van DK, Budts W. Percutaneous closure of a patent foramen ovale: single-centre experience using different types of devices and mid-term outcome. *Acta Cardiol* 2005 October;60(5):515-9.

(14) Luermans JG, Post MC, Schrader R et al. Outcome after percutaneous closure of a patent foramen ovale using the Intrasept device: a multi-centre study. *Catheter Cardiovasc Interv* 2008 May 1;71(6):822-8.

(15) Mullen MJ, Hildick-Smith D, De Giovanni JV et al. BioSTAR Evaluation STudy (BEST): a prospective, multicenter, phase I clinical trial to evaluate the feasibility, efficacy, and safety of the BioSTAR bioabsorbable septal repair implant for the closure of atrial-level shunts. *Circulation* 2006 October 31;114(18):1962-7.

(16) Van den Branden BJ, Post MC, Jaarsma W, ten Berg JM, Suttorp MJ. New bioabsorbable septal repair implant for percutaneous closure of a patent foramen ovale: short-term results of a single-centre experience. *Catheter Cardiovasc Interv* 2009 August 1;74(2):286-90.

(17) Harms V, Reisman M, Fuller CJ et al. Outcomes after transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Am J Cardiol* 2007 May 1;99(9):1312-5.

(18) Slavin L, Tobis JM, Rangarajan K, Dao C, Krivokapich J, Liebeskind DS. Five-year experience with percutaneous closure of patent foramen ovale. *Am J Cardiol* 2007 May 1;99(9):1316-20.

(19) Luermans JG, Post MC, Plokker HW, Ten Berg JM, Suttorp MJ. Complications and mid-term outcome after percutaneous patent foramen ovale closure in patients with cryptogenic stroke. *Neth Heart J* 2008 October;16(10):332-6.

(20) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003 November 4;139(9):753-60.

(21) van Gent MW, Post MC, Snijder RJ et al. Grading of Pulmonary Right-To-Left Shunt With Transthoracic Contrast Echocardiography: Does It Predict the Indication for Embolotherapy? *Chest* 2008 December 31.

(22) Daniels C, Weytjens C, Cosyns B et al. Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale. *Eur J Echocardiogr* 2004 December;5(6):449-52.

(23) Taaffe M, Fischer E, Baranowski A et al. Comparison of three patent foramen ovale closure devices in a randomized trial (Amplatzer versus CardioSEAL-STARflex versus Helex occluder). *Am J Cardiol* 2008 May 1;101(9):1353-8.

(24) Alaeddini J, Feghali G, Jenkins S, Ramee S, White C, bi-Samra F. Frequency of atrial tachyarrhythmias following transcatheter closure of patent foramen ovale. *J Invasive Cardiol* 2006 August;18(8):365-8.

(25) Amin Z, Hijazi ZM, Bass JL, Cheatham JP, Hellenbrand WE, Kleinman CS. Erosion of Amplatzer septal occluder device after closure of secundum atrial septal defects: review of registry of complications and recommendations to minimize future risk. *Catheter Cardiovasc Interv* 2004 December;63(4):496-502.

(26) Divekar A, Gaamangwe T, Shaikh N, Raabe M, Ducas J. Cardiac perforation after device closure of atrial septal defects with the Amplatzer septal occluder. *J Am Coll Cardiol* 2005 April 19;45(8):1213-8.

(27) Jux C, Bertram H, Wohlsein P, Bruegmann M, Paul T. Interventional atrial septal defect closure using a totally bioresorbable occluder matrix: development and preclinical evaluation of the BioSTAR device. *J Am Coll Cardiol* 2006 July 4;48(1):161-9.

(28) Jux C, Wohlsein P, Bruegmann M, Zutz M, Franzbach B, Bertram H. A new biological matrix for septal occlusion. *J Interv Cardiol* 2003 April;16(2):149-52.

(29) Braun M, Gliech V, Boscheri A et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. *Eur Heart J* 2004 March;25(5):424-30.

(30) Alameddine F, Block PC. Transcatheter patent foramen ovale closure for secondary prevention of paradoxical embolic events: acute results from the FORECAST registry. *Catheter Cardiovasc Interv* 2004 August;62(4):512-6.

(31) Anzai H, Child J, Natterson B et al. Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. *Am J Cardiol* 2004 February 15;93(4):426-31.

(32) Bartel T, Konorza T, Arjumand J et al. Intracardiac echocardiography is superior to conventional monitoring for guiding device closure of interatrial communications. *Circulation* 2003 February 18;107(6):795-7.

(33) Hijazi Z, Wang Z, Cao Q, Koenig P, Waight D, Lang R. Transcatheter closure of atrial septal defects and patent foramen ovale under intracardiac echocardiographic guidance: feasibility and comparison with transesophageal echocardiography. *Catheter Cardiovasc Interv* 2001 February;52(2):194-9.

(34) Kutty S, Brown K, Asnes JD, Rhodes JF, Latson LA. Causes of recurrent focal neurologic events after transcatheter closure of patent foramen ovale with the CardioSEAL septal occluder. *Am J Cardiol* 2008 May 15;101(10):1487-92.

(35) Wahl A, Meier B. Patent foramen ovale and ventricular septal defect closure. *Heart* 2009 January;95(1):70-82.

(36) Wahl A, Kunz M, Moschovitis A et al. Long-term results after fluoroscopy-guided closure of patent foramen ovale for secondary prevention of paradoxical embolism. *Heart* 2008 March;94(3):336-41.

4

Patent foramen ovale closure using a bioabsorbable closure device: safety and efficacy at 6-month follow-up

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Abstract

Objectives: The aim of this study was to assess the mid-term safety and efficacy of percutaneous patent foramen ovale (PFO) closure using a bioabsorbable device (BioSTAR®, NMT Medical, Boston, USA).

Background: Closure of PFO in patients with cryptogenic stroke has proven to be safe and effective using different types of permanent devices.

Methods: All consecutive patients who underwent percutaneous PFO closure with the bioabsorbable closure device between November 2007 and January 2009 were included. Residual shunt was assessed using contrast transthoracic echocardiography.

Results: Sixty-two patients (55% women, mean age 47.7 ± 11.8 years) underwent PFO closure. The in-hospital complications were a surgical device retrieval in two patients (3.2%), device reposition in one (1.6%), and a minimal groin haematoma in six patients (9.7%). The short-term complications at 1-month follow-up (n=60) were a transient ischemic attack (TIA) in the presence of a residual shunt in one patient and new supraventricular tachycardia in seven patients (11.3%). At 6-month follow-up (n=60), one patient without residual shunt developed a TIA and one developed atrial fibrillation. A mild or moderate residual shunt was noted in 51.7%, 33.9%, and 23.7% after 1-day, 1-month, and 6-month follow-up, respectively. A large shunt was present in 8.3%, 3.4%, and 0% after 1-day, 1-month, and 6-month follow-up.

Conclusions: Closure of PFO using the bioabsorbable device is associated with a low complication rate and a low recurrence rate of embolic events. However, a relatively high percentage of mild or moderate residual shunting is still present at 6-month follow-up.

Introduction

Percutaneous patent foramen ovale (PFO) closure has been advocated as an alternative strategy to anticoagulation or antiplatelet therapy to prevent recurrence of cryptogenic stroke in young patients. Although a number of series have suggested that percutaneous closure may be superior, no data from randomized trials are available and long-term data on the effectiveness of transcatheter closure are limited.[1-3] Currently, the available closure devices consists of a metal framework and a permanent, synthetic fabric in which defect closure is achieved trough a combination of mechanical closure and fibrous encapsulation. Despite the efficacy of these devices, potential complications such as friction lesions, perforations, inflammation, arrhythmias, and thrombus formation have been described, even at long-term follow-up.[4-6] Furthermore, these implants will obstruct a potential transseptal access to the left atrium for future treatment of acquired heart disease.

Therefore, new strategies of PFO closure without a permanently implanted device have been explored.[7-9] One of these new developments is the BioSTAR® device (NMT Medical, Boston, USA), which consists of a metal framework and a totally bioabsorbable matrix. We report the mid-term safety and efficacy of percutaneous PFO closure with this novel device.

Methods

Patient group

From November 2007 to January 2009, 62 consecutive patients (55% female, mean age 47.7 ± 11.8 years) underwent PFO closure with the BioSTAR® device. Most patients were referred by neurologists, mainly because of cryptogenic stroke or transient ischemic attack (TIA) (93.5%). One patient (1.6%) had suffered a renal infarction, and three patients (4.8%) had decompression illness. The study protocol was approved by the local ethical commission. Patients' characteristics and indications for closure are listed in Table I.

Table I. Baseline characteristics (n=62)

Age (y)	47.7 ± 11.8
Women	34 (54.8)
Weight (kg)	78.3 ± 13.4
BP systolic (mm Hg)	130.7 ± 14.8
BP diastolic (mm Hg)	78.9 ± 8.4
Risk factors	
Smoking	13 (21.0)
Diabetes	3 (4.8)
Arterial hypertension	18 (29.0)
Hypercholesterolaemia	21 (33.9)
Family history	20 (32.3)
Coronary artery disease	5 (8.1)
PFO characteristics	
RLS Valsalva	62 (100)
RLS Spontaneously	24 (38.7)
Aneurysm IAS	25 (40.3)
Indication for closure[#]	
TIA, single	20 (32.3)
TIA, multiple	14 (22.6)
CVA, single	26 (41.9)
CVA, multiple	4 (6.5)
Decompression illness	3 (4.8)
Renal infarction	1 (1.6)
SVT	7 (11.3)

Values are mean ± SD or n (%).
SD, standard deviation; y, years; BP, blood pressure; PFO, patent foramen ovale; RLS, right-to-left shunt; IAS, interatrial septum; TIA, transient ischemic attack; CVA, cerebrovascular accident; SVT, supraventricular tachycardia.
[#] Six patients had a history of both a TIA and a CVA.

Pre-procedure evaluation

All patients underwent comprehensive neurologic evaluation. An embolic event was considered to be due to paradoxical embolism when a PFO was present and any other obvious cardiac, aortic, or cerebrovascular cause was excluded. All patients were assessed by a standardized protocol before closure, including contrast transthoracic echocardiography (cTTE) with second harmonic imaging and/or contrast transesophageal echocardiography (cTEE). Agitated saline contrast was injected into an antecubital vein to demonstrate right-to-left shunt, both at rest and

following the Valsalva manoeuvre. Microbubbles were counted in the left atrium within three cardiac cycles after right heart opacification. As described by Attaran et al., an acceptable Valsalva manoeuvre is one in which the interatrial septum is seen to shift to the left, most dramatically upon the release phase.[10] The study protocol was based on a training phase including up to three Valsalva manoeuvre attempts. The patient was asked to press against the closed glottis for at least ten seconds, until septal shifting was observed. Then, contrast was injected as a rapid bolus that should have resulted in complete opacification of the right atrium. At that time point, the patient was asked to release pressure. If the contrast injection or the visualization was suboptimal, the test was repeated. An atrial septal aneurysm (ASA) was defined as a maximal protrusion of the interatrial septum, or a part of it, ≥ 10 mm beyond the plane of the septum. The PFO characteristics are shown in Table I.

Device description

The BioSTAR® device (Figure 1) is the first septal occluder with a totally biodegradable matrix, which is mounted on the MP35N STAR-Flex "double-umbrella" framework (NMT Medical, Boston, USA). The left and right atrial umbrellas are connected by microsprings, serving a self-centering mechanism. The matrix consists of an acellular porcine intestinal collagen layer, coated with a heparin-benzalkonium-chloride complex, which showed reduced thrombus formation in animal models.[7] Furthermore, accelerated neo-endothelialization and a lower immune response was seen compared to the STAR-Flex® device in a sheep model.[11] The matrix was rapidly incorporated into the interatrial septum, leading to a low profile and early sealing of the defect. Remodeling of the matrix already started after 30 days and over a period of two years, it is completely replaced by host tissue.

The BioSTAR® device is available in sizes 23, 28, and 33 mm.

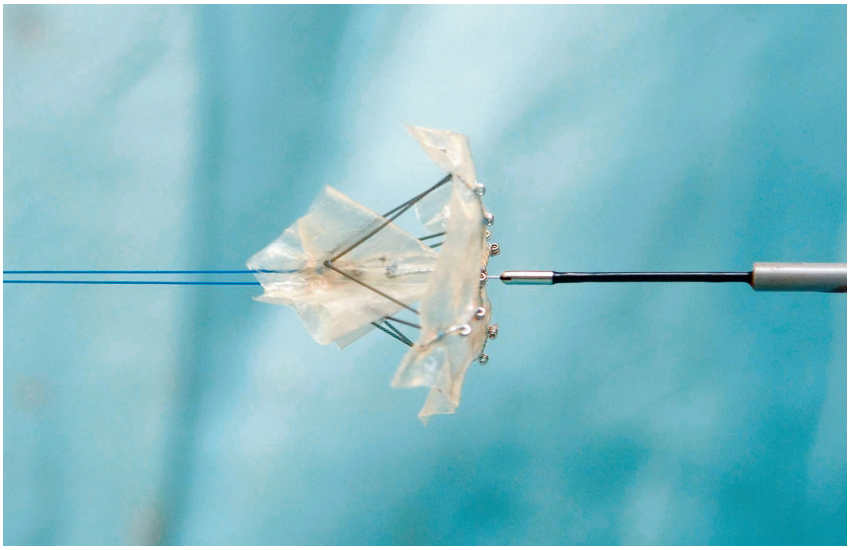

Figure 1. The BioSTAR® device.

The biodegradable matrix is mounted on the MP35N STAR-Flex "double-umbrella" framework. The left and right atrial umbrellas are connected by microsprings, serving as a self-centering mechanism.

Percutaneous PFO closure

As described previously, all procedures were performed in the cardiac catheterization laboratory, under general anaesthesia and TEE guidance in the first six patients, and under local anaesthesia with intracardiac echocardiographic (ICE) guidance thereafter.[12] Concomitant fluoroscopic guidance was used in all patients. The right femoral vein was used to advance a multipurpose catheter, to cross the PFO. The left femoral vein was used in case of ICE guidance. Intravenous heparin (5000 IE) and prophylactic antibiotics were administered. Delivery and deployment of the BioSTAR® device are similar to that previously described for the STAR-Flex® device.[13, 14] All patients were pre-treated with aspirin and clopidogrel.

Successful device implantation was defined as completion of the procedure without the occurrence of major events (death, device embolization, device malpositioning with replacement or need for surgical intervention). Complications were divided into major and minor complications according to the classification scheme of Khairy et al.[15]

Follow-up evaluation

Within 24 hours after closure, an electrocardiogram, chest X-ray, and cTTE were performed. All patients were discharged on aspirin 100 mg once a day for a period of six months and clopidogrel 75 mg once a day for one month. Antiplatelet therapy was continued in case of persistence of residual shunting on follow-up cTTE or if there was another indication. In patients on oral anticoagulant therapy before the procedure, clopidogrel was added for one month. Infective endocarditis prophylaxis was recommended for six months.

All patients were scheduled for cTTE (with Valsalva manoeuvre) at one month, six months, one year, and two years to determine residual shunting which was categorized as follows: small shunt (< 30 bubbles in the left atrium), moderate shunt (30-100 bubbles in the left atrium) and severe shunt (> 100 bubbles in the left atrium). All echocardiographic examinations were reviewed by two independent physicians. The 6-month TTE was combined with a visit to the outpatient clinic were a limited history and physical examination were obtained. New-onset supraventricular tachyarrhythmias (SVT) were diagnosed by a 12-lead electrocardiogram or 24-hours Holter monitoring. Patients with suspected recurrent stroke or TIA were re-examined by a neurologist, and a new imaging study of the brain (computed tomography or magnetic resonance imaging) was performed. Only definite recurrent cerebrovascular events were included in the analysis.

Statistical analysis

Descriptive statistics were used to describe patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. Univariate statistical analysis was used to identify risk factors for residual shunting and the development of new SVT after PFO closure. Predictors of untoward events were analysed by means of the Student's *t* test and Fisher exact test for continuous and categorical variables, respectively. For within-group comparison of proportions, the McNemar test was used. No formal adjustment for multiple comparisons was used. $p<0.05$ was considered to be statistically significant. All statistical analyses were performed by using SPSS software version 14.0 for Windows (SPSS, Chicago, IL, USA).

Results

Procedural and in-hospital outcome

Device implantation was successful in 59 patients (95.2%). In one patient, a 28-mm device was pushed trough the PFO in the left atrium, recovered into the delivery system, and successfully replaced by a 33-mm device during the same session. In another patient, the deployed device could not be retracted into the delivery system and therefore a femoral vein incision was needed to retrieve it. In a 75-year-old man with hypertension and recurrent TIA's, in which other thromboembolic sources were firmly excluded, the closure device embolized to the aorta, was retracted percutaneously by means of a snare into the femoral artery, and removed by the surgeon. There was no ASA or any other structural heart disease on his baseline TTE. Both patients received an Amplatzer® PFO Occluder (AGA Medical, Golden Valley, MN, USA) one month later. Furthermore, six patients (9.7%) had a minimal groin haematoma before discharge. There were no procedural deaths and none of the procedural complications resulted in mid-term sequelae. Procedural characteristics are listed in Table II and in-hospital complications in Table III.

Table II. Procedural characteristics

Diameter device	
23-mm	1 (1.6)
28-mm	53 (85.5)
33-mm	8 (12.9)
Anaesthesia	6 (9.6)
Echocardiographic guidance	
TEE	6 (9.6)
ICE	56 (90.4)
Radiation dose ± SD (Gy/cm^2)	31.1 ± 26.9
Procedural complications	
Device reposition	1 (1.6)
Minimal surgical intervention	2 (3.2)
Hospitalization stay (days)	2

Values are mean ± SD or n (%).
TEE, transesophageal echocardiography ; ICE, intracardiac echocardiography; Gy, Gray.

Mid-term outcome

Complications

During 6-month follow-up (n=60), no major complications occurred (Table III). Eight patients (12.9%) developed a new SVT, seven of whom during the first month. In two patients, Holter monitoring showed non-sustained atrial tachycardia for which no further treatment seemed indicated. Five patients were successfully treated for a short period with anti-arrhythmic drugs and one patient with therapy-resistant atrial fibrillation required electrical conversion. No predictor for the development of SVT after PFO closure could be identified using univariate analysis.

Table III. Complications and re-occurrence of stroke

	In-hospital	1 month	6 months
n	62	60	60
Major complications			
Minimal surgical intervention	2 (3.2)	0	0
Minor complications			
New SVT	0	7 (11.3)	1 (1.6)
Inguinal haematoma	6 (9.7)	0	0
Reposition device	1 (1.6)	0	0
Re-occurrence ischemic event			
TIA	0	1 (1.6)*	1 (1.6)#
CVA	0	0	0

Values are n (%).
n, number; SVT, supraventricular tachycardia; TIA, transient ischemic attack; CVA, cerebrovascular accident; with (*) and without (#) residual shunt.

Recurrent thromboembolic events

There were two recurrent TIAs. One TIA occurred within three weeks after PFO closure in a patient who was still on dual antiplatelet therapy. There was an ASA present on baseline echo and cTTE at discharge revealed a moderate residual shunt. An additional TTE a few days after the event did not reveal any thrombus on the device; however, there was still a small residual shunt present. Dual antiplatelet therapy was continued and at 6-month follow-up, cTTE did not reveal any residual shunt. A second TIA was noticed in another patient in the absence of a residual shunt or thrombus formation. Therefore, the TIA should not be related to a cardioembolic source. Both patients clinically recovered fully within 12 hours after onset of symptoms.

Residual shunt

The percentage of patients with complete occlusion after PFO closure with the BioSTAR® device progressively increased during follow-up. Complete PFO closure was achieved in 40%, 62.7%, and 76.3% after one day, one month, and six months of follow-up, respectively. Mild or moderate residual shunt was present in 51.7%, 33.9%, and 23.7% after one day, one month, and six months follow-up and a large shunt was present in 8.3%, 3.4%, and 0% after one day, one month, and six months follow-up, respectively (Figure 2). Unfortunately, no predictor for the presence of a residual shunt at 6-month follow-up could be identified using univariate analysis.

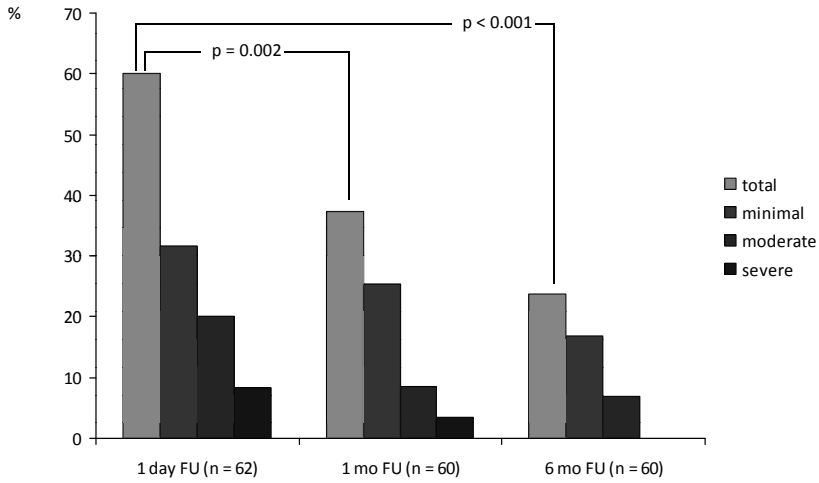

Figure 2. Residual shunt rate by contrast TTE.

This figure shows the residual shunt rate during follow-up assessed by contrast tranthoracic echocardiography (cTTE). The shunt declines gradually during follow-up but there is still 23.7% residual shunting (mild or moderate) six months after defect closure.

Discussion

As far as we know, this is the largest series of consecutive patients treated with the BioSTAR® device. Our data demonstrate that percutaneous closure with the bioabsorbabale device can be performed with a high success rate, a low complication rate, and that it is associated with a low risk for stroke recurrence during mid-term follow-up. Residual shunts decline gradually and no large shunts could be detected six months after closure.

The major advantage of using a biodegradable device should be that only a minimal amount of foreign material (i.e. the framework) remains on the interatrial septum, thus minimizing the potential risk for future complications. Furthermore, the "natural healing" of the defect and replacement of the device by host tissue should result in an earlier defect closure and a lower immune response. Those advantages were outlined in animal studies and the first in-human trial showed excellent results regarding safety and efficacy.[7, 11, 16]

Complications

In the BioSTAR evaluation study (BEST), 58 patients (54 PFO, 4 atrial septum defect (ASD)) with a mean age of 46 ± 8 years were treated with the BioSTAR® device.[16] Successful device implantation was achieved in 98% of the patients, one device prolapsed into the right atrium in an attempt to close an ASD and was replaced by an alternative device. In a patient with a PFO and a thick septum secundum, a 28-mm device was malpositioned and successfully replaced by a 33-mm device. No other procedural complications were noticed. Our procedural success rate was 95.2%; one device was malpositioned and replaced by a larger one. In this patient, a long tunnel PFO was present that was underestimated on echocardiography. Furthermore, we had one arterial device embolization and one device that had to be removed from the femoral vein after dislodgement from the septum and partial retrieval into the sheath. A possible explanation for these complications is that the BioSTAR® device is very soft and flexible. Furthermore, both cases occurred in our learning phase using ICE and therefore could be related to less adequate visualization. Six of our patients (9.7%) developed a minimal groin haematoma, but none required blood transfusion.

Atrial rhythm disturbances are a common short-term complication, using transseptal devices. Despite the low profile and the presumed rapid endothelialization of the BioSTAR® device, the incidence of new SVT in our study was 12.9%, comparable to the frequency of 7-15% reported in series with other devices.[17, 18] We did not observe any relationship between the occurrence of SVT and device size or the presence of an ASA.

Re-occurrence of thromboembolic events

The recurrence rate of stroke or TIA in our observation is low (3.2%) and concordant with findings previously reported. Two systematic reviews suggest that percutaneous PFO closure is more effective than medical treatment regarding secondary prevention of embolic events (recurrence rate: 0-4.9% versus 3.8-12% at one year).[1, 15] We did not detect any thrombus on the device in those two patients, but we realize that thrombus assessment with TTE only might be suboptimal.

Residual shunt

The residual shunt rate six months after PFO closure ranges from 8% to 20%.[19, 20] At six months, a mild or moderate residual shunt was observed in 23.7% of our study population. Direct comparison of the results of these studies is difficult because different types of devices and different methodological descriptions were used. Our method of shunt grading showed an excellent interobserver variability using cTTE.[21] In contrast to other investigators, who described predictors of residual shunt, such as the presence of ASA, larger PFO size, and larger device size, we could not identify predictive factors regarding residual shunt.[22-24] Therefore, we must hypothesize that the BioSTAR® device itself does not “close the door” appropriately. However, rapid endothelialization and defect closure was seen in a sheep model, the natural heeling of the defect induced by the matrix of the device may be postponed in some patients. Maybe, the role of platelets and platelet-inhibition is underestimated. When platelets are activated as a result of endothelial damage during PFO closure, they stimulate smooth muscle cell proliferation and migration, and contribute to the synthesis of connective tissue. Hence, when we treat our patients with aspirin and clopidogrel after PFO closure, the formation of neo-endothelium and the natural healing,

induced by the BioSTAR® device could be diminished. It is also known that there is a substantial interpatient variability regarding inhibition of platelet aggregation/activation with aspirin and clopidogrel. To underline our hypothesis, we must state that the sheep in the animal model, which did show early endothelialization, were not treated with antiplatelet agents.

The two other studies regarding PFO closure using the BioSTAR® device, report a much lower residual shunt rate.[16, 25] However, in BEST, only moderate and large shunts were reported.[16] As a result, 4% residual shunting was seen at six months, using cTTE. In another report, no residual shunt was observed in 19 patients, six months after PFO closure; however, the TTE studies were performed without contrast.[25] On the other hand, four of these patients (21%) had a trivial shunt on contrast-transcranial doppler. Maybe, our meticulous Valsalva manoeuvre protocol resulted in a higher amount of residual shunt, compared to the two previous studies.

Despite the high prevalence of residual shunting in our group, only one patient suffered a re-occurrence of TIA. It is known that the persistence of a significant shunt has been identified as a risk factor for embolic recurrence. On the other hand, it has been outlined that especially small shunts may close late; therefore, we will repeat cTTE at one year and two years after defect closure.

Limitations

First, our patient population was a selected cohort referred for percutaneous PFO closure, and there may be substantial differences with other series regarding patient selection and implantation technique.

Second, it is a single-centre study with a relatively small number of patients and a short follow-up time. Third, during follow-up we performed cTTE instead of cTEE, which is still defined as the “gold standard” for the detection of interatrial shunts. However, TEE is semi-invasive, time-consuming, and the performance of an adequate Valsalva manoeuvre is invariably impaired. Furthermore, cTTE with second harmonic imaging, as used in our study, seems to be a very good alternative for TEE as a first-line exam.[26]

Conclusions

Percutaneous closure of a symptomatic PFO using the BioSTAR® device seems to be safe and efficient, according to the low complication rates and the low recurrence rate of TIA/stroke. However, a relatively high percentage of residual shunting is present six months after closure. The BioSTAR® device was developed to extinguish potential complications which are inherent to permanent closure devices. We did not observe a decrease in atrial rhythm disturbances during the first month after closure. Nevertheless, we will perform long-term follow-up and hopefully ascertain the true advantages of this new device when it is gradually absorbed over time.

Reference List

(1) Homma S, Sacco RL. Patent foramen ovale and stroke. *Circulation* 2005 August 16;112(7):1063-72.

(2) Schuchlenz HW, Weihs W, Berghold A, Lechner A, Schmidt R. Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale. *Int J Cardiol* 2005 May 11;101(1):77-82.

(3) Windecker S, Wahl A, Chatterjee T et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000 February 29;101(8):893-8.

(4) Divekar A, Gaamangwe T, Shaikh N, Raabe M, Ducas J. Cardiac perforation after device closure of atrial septal defects with the Amplatzer septal occluder. *J Am Coll Cardiol* 2005 April 19;45(8):1213-8.

(5) Staubach S, Steinberg DH, Zimmermann W et al. New onset atrial fibrillation after patent foramen ovale closure. *Catheter Cardiovasc Interv* 2009 November 15;74(6):889-95.

(6) Luermans JG, Post MC, Yilmaz A. Late device thrombosis after atrial septal defect closure. *Eur Heart J* 2010 January;31(2):142.

(7) Jux C, Wohlsein P, Bruegmann M, Zutz M, Franzbach B, Bertram H. A new biological matrix for septal occlusion. *J Interv Cardiol* 2003 April;16(2):149-52.

(8) Ruiz CE, Kipshidze N, Chiam PT, Gogorishvili I. Feasibility of patent foramen ovale closure with no-device left behind: first-in-man percutaneous suture closure. *Catheter Cardiovasc Interv* 2008 June 1;71(7):921-6.

(9) Sievert H, Ruygrok P, Salkeld M et al. Transcatheter closure of patent foramen ovale with radiofrequency: acute and intermediate term results in 144 patients. *Catheter Cardiovasc Interv* 2009 February 15;73(3):368-73.

(10) Attaran RR, Ata I, Kudithipudi V, Foster L, Sorrell VL. Protocol for optimal detection and exclusion of a patent foramen ovale using transthoracic echocardiography with agitated saline microbubbles. *Echocardiography* 2006 August;23(7):616-22.

(11) Jux C, Bertram H, Wohlsein P, Bruegmann M, Paul T. Interventional atrial septal defect closure using a totally bioresorbable occluder matrix: development and preclinical evaluation of the BioSTAR device. *J Am Coll Cardiol* 2006 July 4;48(1):161-9.

(12) Van den Branden BJ, Post MC, Jaarsma W, ten Berg JM, Suttorp MJ. New bioabsorbable septal repair implant for percutaneous closure of a patent foramen ovale: short-term results of a single-centre experience. *Catheter Cardiovasc Interv* 2009 August 1;74(2):286-90.

(13) Hausdorf G, Kaulitz R, Paul T, Carminati M, Lock J. Transcatheter closure of atrial septal defect with a new flexible, self-centering device (the STARFlex Occluder). *Am J Cardiol* 1999 November 1;84(9):1113-6, A10.

(14) Hausdorf G. StarFlex ASD closure: deployment, techniques, equipment. *J Interv Cardiol* 2001 February;14(1):69-76.

(15) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003 November 4;139(9):753-60.

(16) Mullen MJ, Hildick-Smith D, De Giovanni JV et al. BioSTAR Evaluation STudy (BEST): a prospective, multicenter, phase I clinical trial to evaluate the feasibility, efficacy, and safety of the BioSTAR bioabsorbable septal repair implant for the closure of atrial-level shunts. *Circulation* 2006 October 31;114(18):1962-7.

(17) Alaeddini J, Feghali G, Jenkins S, Ramee S, White C, bi-Samra F. Frequency of atrial tachyarrhythmias following transcatheter closure of patent foramen ovale. *J Invasive Cardiol* 2006 August;18(8):365-8.

(18) Post MC, Van DK, Budts W. Percutaneous closure of a patent foramen ovale: single-centre experience using different types of devices and mid-term outcome. *Acta Cardiol* 2005 October;60(5):515-9.

(19) Braun M, Gliech V, Boscheri A et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. *Eur Heart J* 2004 March;25(5):424-30.

(20) Wahl A, Krumsdorf U, Meier B et al. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol* 2005 February 1;45(3):377-80.

(21) van Gent MW, Post MC, Snijder RJ et al. Grading of pulmonary right-to-left shunt with transthoracic contrast echocardiography: does it predict the indication for embolotherapy? *Chest* 2009 May;135(5):1288-92.

(22) Greutmann M, Greutmann-Yantiri M, Kretschmar O et al. Percutaneous PFO closure with Amplatzer PFO occluder: predictors of residual shunts at 6 months follow-up. *Congenit Heart Dis* 2009 July;4(4):252-7.

(23) Shafi NA, McKay RG, Kiernan FJ, Silverman IE, Ahlquist M, Silverman DI. Determinants and clinical significance of persistent residual shunting in patients with percutaneous patent foramen ovale closure devices. *Int J Cardiol* 2009 November 12;137(3):314-6.

(24) Zajarias A, Thanigaraj S, Lasala J, Perez J. Predictors and clinical outcomes of residual shunt in patients undergoing percutaneous transcatheter closure of patent foramen ovale. *J Invasive Cardiol* 2006 November;18(11):533-7.

(25) Ussia GP, Cammalleri V, Mule M et al. Percutaneous closure of patent foramen ovale with a bioabsorbable occluder device: single-centre experience. *Catheter Cardiovasc Interv* 2009 October 1;74(4):607-14.

(26) Maffe S, Dellavesa P, Zenone F et al. Transthoracic second harmonic two- and three-dimensional echocardiography for detection of patent foramen ovale. *Eur J Echocardiogr* 2010 January;11(1):57-63.

Part three

Atrial shunt closure using the Occlutech Figulla device

5

Percutaneous atrial shunt closure using the novel Occlutech Figulla® device: 6-month efficacy and safety

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Abstract

Background: The Occlutech Figulla® Occluder is a new innovative device for percutaneous closure of a patent foramen ovale (PFO) and an atrial septal defect (ASD). We describe the safety and efficacy of this new device at 6-month follow-up.

Methods: All 82 consecutive patients (51% female, mean age 49.0 ± 13.6 years) who underwent percutaneous PFO (n=48) or ASD (n=34) closure between October 2008 and October 2009 were included.

Results: Implantation success was 100%. The in-hospital complications were two new-onset supraventricular tachycardias (SVT) (2.4%, both ASD patients), nine minimal groin haematomas (11.0%, 4 PFO and 5 ASD patients), and one transient ST-segment elevation during the procedure (1.2%, ASD patient). During six months follow-up (n=79), no major complications or re-occurrences of cerebral thromboembolic events occurred. Seven patients (8.9%, 6 PFO and 1 ASD patient) experienced a new SVT. One patient developed a recurrent cerebral haemorrhage five months after ASD closure, which appeared not to be related to the procedure. Using contrast transthoracic echocardiography six months after PFO closure (n=45), a residual shunt was present in 30.2% of the patients (small 25.6%, moderate 4.6%, severe 0%). In the ASD group (n=34), a residual shunt was observed in 32.5% (small 17.7%, moderate 14.7%, severe 2.9%).

Conclusion: The Occlutech Figulla® Occluder appears to be easy to use, effective, and safe for percutaneous closure of PFO and ASD. We report a low complication rate but a relatively high percentage of small residual shunts six months after closure.

Introduction

Atrial-level shunts, such as an atrial septal defect (ASD) and a patent foramen ovale (PFO), are common cardiac defects. An ASD accounts for about one-third of all adults with congenital heart disease and a PFO is detected in up to 27% of the general population.[1, 2] Associated complications are well recognized and include cardiac failure, pulmonary hypertension, and arrhythmias due to right heart volume overload, but also cryptogenic stroke, decompression illness and migraine due to paradoxical embolization.[3, 4] Percutaneous closure of both defects has become a routine procedure in adults with a low risk of periprocedural complications and good long-term results.[5-10] In the past years, several different device systems have been designed and refined to improve feasibility, efficacy, and safety.[11-13] Currently, the Amplatzer® Septal Occluder (ASO) (AGA Medical, Golden Valley, MN, USA) is the most widely used device, with favourable follow-up results.[8, 11, 14]

A new device, the Occlutech Figulla® Occluder (Occlutech GmbH., Jena, Germany), has been introduced recently for percutaneous ASD and PFO closure. The novelty is the absence of the left atrial stainless steel hub, minimizing the amount of material on the left atrial side. Furthermore, the device is characterized by its high flexibility, its self-centering mechanism and the ability to reposition or recapture the device after deployment of the discs, before releasing it. The device appeared to be safe and effective in a swine model and in the first in-human application.[15, 16]

We report the 6-month safety and efficacy of percutaneous ASD and PFO closure with this novel device in our centre.

Materials and Methods

Patient selection

We included all consecutive patients between October 2008 and October 2009 who underwent percutaneous ASD or PFO closure in our centre. All patients received a Figulla® Occluder device. No other devices were implanted during this period.

Indications for percutaneous closure were a significant left-to-right shunt (pulmonary and systemic blood flow, Qp/Qs ratio > 1.5, measured invasively), volume overload of the right ventricle on transthoracic echocardiography (TTE), and/or clinical symptoms of dyspnea, reduced exercise capacity or paradoxical embolism in case of an ASD. Platypnoe syndrome or paradoxical embolism were indications for closure in case of the presence of a PFO.

Device description

The Figulla® Occluder device is constructed from 0.082 to 0.186 mm nitinol wires, tightly woven into two flat disks, with a 4-mm connecting waist in the center. A unique braiding technique allows forming a single hub (microscrew) at the right atrial disc for cable connection. As a consequence, there is no left atrial clamp, minimizing the amount of material implanted. The size of the Figulla® ASD occluder (Figure 1) is determined by the diameter of the waist, ranging from 6 to 40 mm in 1.5-mm increments up to 12 mm and in 3- mm increments thereafter, except from size 36 to 40 mm in 4-mm increment. The size of the Figulla® PFO occluder (Figure 2) is dictated by the diameter of the two discs (left atrium/right atrium) and is available in sizes 16/18, 23/25, 27/30, and 31/35 mm. The prosthesis is filled with a polyester patch to enhance thrombogenicity. The delivery sheath required ranges from 9 to 14 French.

Closing procedure

Our percutaneous closing technique has been extensively described in the literature.[13, 17] Briefly, most of the PFO's were closed under local anaesthesia with intracardiac echocardiographic (ICE) guidance. The majority of ASD closures was performed under general anaesthesia and continuous transesophageal echocardiographic (TEE) monitoring. In all ASD patients, balloon sizing using the "stop-flow" method was used. Concomitant fluoroscopy was used in all patients. The size of the device was chosen by the interventional cardiologist depending on the diameter of the ASD or the morphology of the PFO.

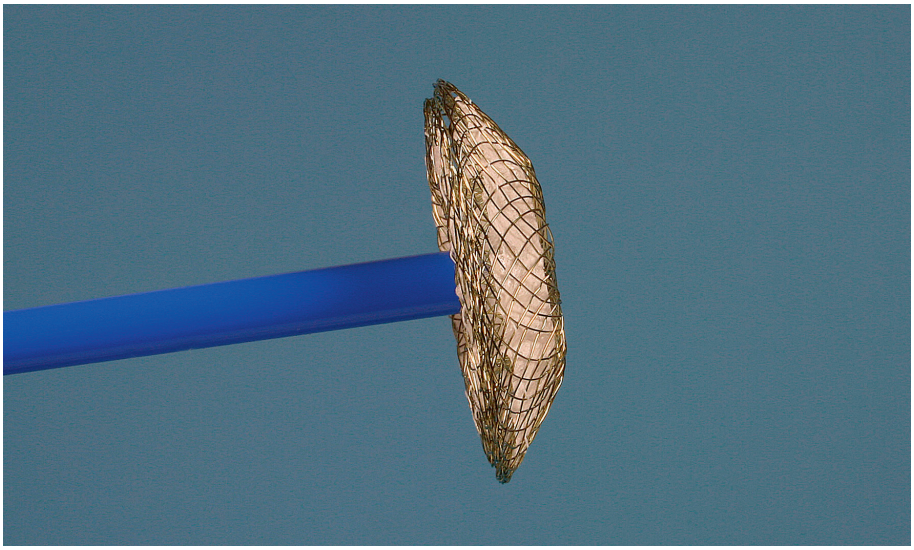

Figure1. The Occlutech Figulla® ASD occluder

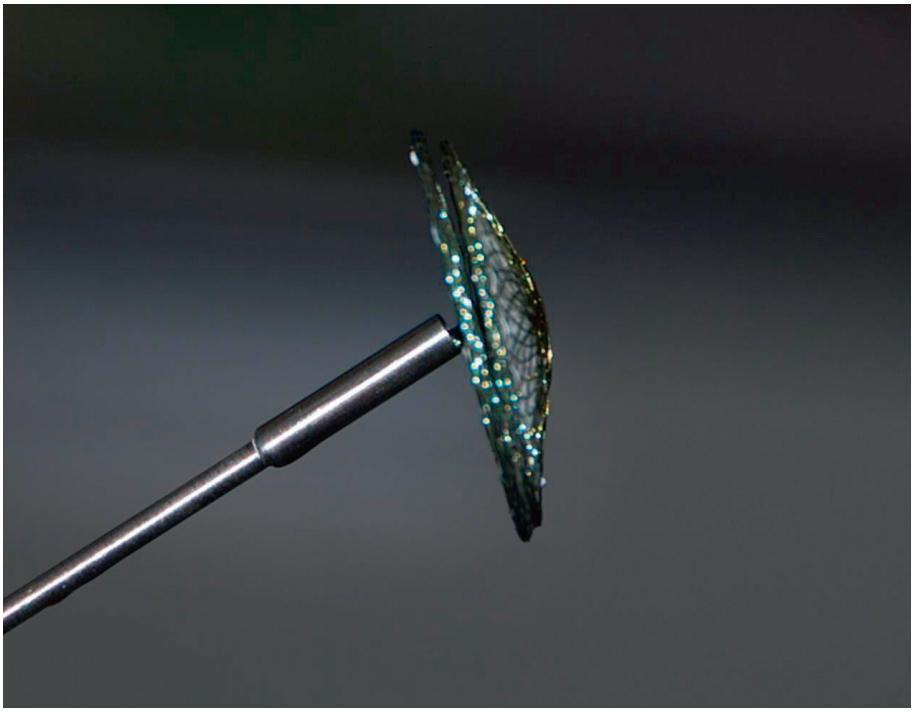

Figure 2. The Occlutech Figulla® PFO occluder

Follow-up evaluation

Within 24 hours after closure, an electrocardiogram, a chest X-ray, and a TTE were performed. All patients were scheduled for contrast transthoracic echocardiography (cTTE) at six months to establish the position of the device and to determine residual right-to-left shunting which was categorized as follows: small shunt (< 30 bubbles in the left atrium), moderate shunt (30-100 bubbles in the left atrium), and severe shunt (> 100 bubbles in the left atrium).[18, 19] In the ASD group we also looked for residual left-to-right shunting using color Doppler. All echocardiographic examinations were reviewed by two independent physicians. The 6-month TTE was combined with a visit to the outpatient clinic where a history and physical examination were obtained. All procedural complications, immediately related to the procedure within six months, were reported. Complications were divided into major and minor complications according to the classification scheme of Khairy et al.[7] New-onset supraventricular tachyarrhythmias (SVT) were diagnosed by a 12-lead electrocardiogram or 24-hour Holter monitoring.

All patients were discharged on dual antiplatelet therapy: aspirin for six months and clopidogrel for one month. Infective endocarditis prophylaxis was recommended for six months, counting from the closing procedure.

Statistical analysis

Descriptive statistics were used to describe patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation; if normal distribution is absent median with range is given. All statistical analyses were performed by using SPSS software version 17.0 for Windows (SPSS, Chicago, IL, USA).

Results

Patients' characteristics

Between October 2008 and October 2009 PFO closure was performed in 48 patients (mean age 46.7 ± 11.2 years, 58% male) and ASD closure in 34 patients (mean age 52.1 ± 16.1 years, 32% male) using the Occlutech Figulla® Occluder. In 90% of the

patients with a PFO, cryptogenic TIA or stroke was the indication for closure. One patient was treated because of extensive migraine headaches, two patients suffered from decompression illness, and two patients from the platypnea-orthodeoxia syndrome. In the ASD group, the majority of the patients underwent closure because of pulmonary hypertension with signs of volume overload of the right ventricle on TTE (71%). The mean pulmonary artery pressure was 30.7 ± 13.5 mmHg, and the ASD diameter was 14.1 ± 6.4 mm. Patients' characteristics and indications for closure are listed in Table I.

Table I. Patient demographics

	PFO	ASD
Number	48 (59)	34 (41)
Age (years)	46.7 ± 11.2	52.1 ± 16.1
Male	28 (58.3)	11 (32.4)
Female	20 (41.7)	23 (67.6)
BMI (kg/m^2)	25.8 ± 4.1	24.3 ± 2.8
BP systolic (mmHg)	130.0 ± 15.2	131.8 ± 9.0
BP diastolic (mmHg)	82.0 ± 8.6	78.1 ± 9.0
Diabetes	2 (4)	4 (12)
Hypertension	11 (23)	14 (41)
Coronary artery disease	3 (6)	5 (15)
SVT	2 (4)	9 (27)
Defect size (mm)	-	14.1 ± 6.4
ASA	22 (46)	12 (35)
PAP (mmHg)	-	30.7 ± 13.5
Reason for PFO/ASD closure		
Stroke/TIA	43 (90)	10 (29)
single	37 (77)	8 (24)
multiple	6 (13)	2 (5)
Migraine	1 (2)	0
Decompression illness	2 (4)	0
Pulmonary hypertension	0	24 (71)
Platypnoe syndrome	2 (4)	0

Data presented as n (%) or mean ± SD.
n, number; SD, standard deviation; BMI, body mass index; BP, blood pressure; SVT, supraventricular tachycardia; ASA, atrial septal aneurysm; PAP, pulmonary artery pressure; PFO, patent foramen ovale; ASD, atrial septal defect ; TIA, transient ischemic attack.

Periprocedural characteristics

In the PFO group, most of the procedures (92%) were performed under ICE guidance and local anaesthesia. All devices were implanted successfully on the first attempt and no procedural complications were reported.

Most ASD's (71%) were closed under TEE guidance and general anaesthesia, ten "PFO-like ASD's" (29%) were closed using ICE. Again, no procedural failure was observed. One patient developed atrial fibrillation during the procedure, probably due to catheter manipulation, and was converted medically. In another patient, transient ST-segment elevation was registered at the beginning of the procedure, which resolved spontaneously. It was thought that air bubbles embolization had occurred due to insufficient flushing of the catheter system. Procedural characteristics are summarized in Table II.

Table II. Procedural characteristics

	PFO (n=48)	ASD (n=34)
Device diameter (mm)	25 (18-35)	25 (12-33)
Fluoroscopy time (min)	3.2 (1.2-39.4)	2.5 (1.3-19)
Radiation dose (Gy/cm^2)	13.7 (4-198)	20 (5-154)
TEE guidance	4 (8)	24 (71)
ICE guidance	44 (92)	10 (29)
Procedural complications		
Atrial fibrillation	0	1 (3)
Transient ST-elevation	0	1 (3)

Data presented as median (range) or n (%)
mm, millimeters; min, minutes; Gy, Gray; TEE, transesophageal echocardiography; ICE, intracardiac echocardiography.

In-hospital outcome

Four patients (8.3%) in the PFO group and five patients (14.7%) in the ASD group developed a minimal inguinal haematoma at the puncture site, none requiring blood transfusion or surgical intervention. There was no direct relationship with the use of ICE, which was used in only two patients who developed a haematoma. In the ASD group, one patient had a transient SVT that was treated with a beta-blocker.

Conversion to sinus rhythm was documented within six hours. Mean hospitalization stay was 1.5 days.

Outcome at 6-month follow-up

Complications

During the first six months after device implantation, no major complications were observed.

A 75-year-old woman, known with arterial hypertension, diabetes, and Child-Pugh liver cirrhosis, suffered from a recurrent cerebral haemorrhage, five months after ASD closure. At the time of the event, she was only treated with aspirin. Consequently, it was thought that there was no relation with the closing procedure. A total of seven patients (8.9%) complained of palpitations due to new-onset SVT. In three patients, the tachycardia was self-limiting, three patients had to be treated with anti-arrhythmic drugs for a short period and one patient needed electrical conversion. There were no re-occurrences of TIA or stroke during mid-term follow-up. The follow-up results are listed in Table III.

Efficacy

The TTE characteristics, six months after closure, could be obtained in 77 patients (94%). A small right-to-left shunt was present in 22.1%, a moderate shunt in 9.1%, and a severe shunt in 1.3%. The prevalence of a residual shunt did not significantly differ between the PFO and the ASD group. However, more moderate (14.7% vs. 4.6%) and more severe (2.9% vs. 0%) residual shunting was present in the ASD group. Using color Doppler imaging, we only found 6% residual left-to-right shunts in the ASD group. The efficacy date are shown in Table III and Figure 3.

Table III. Follow-up results

	PFO	ASD	Total	p-value
In-hospital				
Patients	48	34	82	
Complications				
New SVT	0	1 (2.9)	1 (1.2)	
Inguinal haematoma	4 (8.3)	5 (14.7)	9 (11.0)	
Mid-term				
Patients	45	34	79	
Complications				
New SVT	6 (13.3)	1 (2.9)	7 (8.9)	
Cerebral haemorrhage	0	1 (2.9)	1 (1.3)	
Recurrent TIA/stroke	0	0	0	
Residual shunt*				
No	30 (69.8)	22 (64.7)	52 (67.5)	0.26
Trivial	11 (25.6)	6 (17.7)	17 (22.1)	
Moderate	2 (4.6)	5 (14.7)	7 (9.1)	
Severe	0	1 (2.9)	1 (1.3)	

Data presented as n or n (%).
n, number; SVT, supraventricular tachycardia; TIA, transient ischemic attack.
*data available in 43 PFO patients and 34 ASD patients.

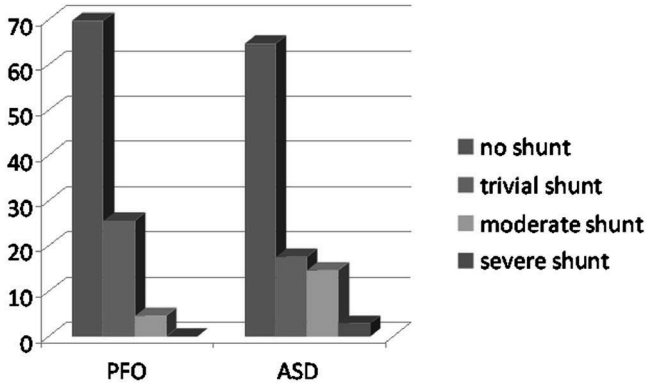

Figure 3. Percentage of residual shunting diagnosed by cTTE during 6 months follow-up.

Discussion

As far as we know, this is the largest series of consecutive patients treated with the Occlutech Figulla® Occluder. Our data demonstrate that percutaneous PFO and ASD closure with this device can be performed with a high success rate, a low complication rate and that it is associated with a low risk for stroke recurrence during 6-month follow-up. On the other hand, a relatively high percentage of small residual shunting was noticed six months after defect closure.

Since the initial reports of transcatheter ASD and PFO closure, the techniques and devices have been continuously improved[20, 21]. The Amplatzer® Septal Occluder is nowadays the most widely used device worldwide to close interatrial septal defects. The Occlutech Figulla® Occluder is an alternative device designed to close the full range of defects. Construction and implantation procedures are similar to the Amplatzer® device, but there are some structural innovations that could contribute to a lower complication rate. Most importantly is the reduction in amount of material on the left atrial disc to increase flexibility and to reduce thrombus formation and the risk of trauma with concomitant atrial arrhythmias.

Safety

Krizanic et al. showed good biocompatibility with rapid and complete neo-endothelialization in a swine model.[16] The first clinical trial by the same group showed feasibility and safety of the device.[15] Thirty-six patients (mean age 57 years) with cryptogenic stroke due to PFO were treated with the Occlutech Figulla® device. Implantation success was 100% and there were no periprocedural complications. One patient developed a groin bleeding post-procedure which required blood transfusion and in one patient atrial fibrillation was registered two hours after implantation. In a more recent report, the device was implanted in 29 patients with PFO and in 12 patients with secundum ASD and again showed maximal implantation success and the absence of short-term complications.[22] One patient with a successful ASD closure died of recurrent myocardial infarction. In a third trial, which compared the Occlutech® device (n=33) with the Amplatzer® device (n=42) in ASD closure, three Occlutech® devices had an unsatisfactory position across the septum.[23] Two

of them had to be replaced by a larger device; the third device was repositioned and embolized to the pulmonary artery two days after the procedure. No sustained SVT's were observed in the Occlutech® group. Our complication rates are in line with those previously described. We had no major periprocedural complications. Only two patients developed a SVT in-hospital. Furthermore, in 11% of our patients, a minimal groin haematoma was noticed, one day after the procedure. During six months follow-up, six patients (13.3%) suffered from a new SVT in the PFO group. We must state that this percentage is acceptable and comparable to the reported 7-15% in other series of PFO closure.[24] Spies et al. reported new-onset atrial fibrillation in 7% of patients after PFO closure (n=822) and in 12% of patients with underlying ASD (n=240).[25] In contrast, we found a lower SVT rate (2.9%) in the ASD group.

Efficacy and re-occurrence of stroke

The reported residual shunt rate at six months ranges from 8 to 20% after PFO closure and from 0 to 25% after ASD closure.[5, 8, 17, 26] The differences can be explained mainly by the differences in device selection, definition of residual shunting, and the use of different imaging modalities to diagnose residual shunting. Regarding the Occlutech® device, the residual shunt rate six months after closure, ranged from 0 to 23%. Pac et al. found no residual shunting after six months with the important limitation that they only used color flow mapping.[23] In a recent report by Saguner et al., a residual shunt rate of 23% was found (using cTEE, n = 31) six months after closure, compared to a 3% residual shunt rate in the Amplatzer® group (n = 31).[27] We found a total residual shunt rate of 32.5% (22.1% small, 9.1% moderate, and 1.3% severe) using cTTE with second harmonic imaging, which has proven to be an accurate method for the detection of right-to-left shunts.[28] In our opinion, cTTE is of much greater value than color Doppler imaging in assessing residual shunting after ASD closure. Because of the high echogenicity of the closure device, the ultrasound wave reflections make the conventional echocardiographic techniques unreliable.[19] Furthermore, we are aware that small shunts are not clinically important and tend to close late. Therefore, we continue antiplatelet therapy in these patients and perform additional cTTE six months later. Maybe, our meticulous Valsalva manoeuvre protocol resulted in a higher amount of small residual shunts. The higher prevalence of moderate and

severe residual shunts in the ASD group (14.7% and 2.9%, respectively) is difficult to explain but could be related to the larger amount of material of the ASD device that needs to be covered with endothelium. Another explanation could be that the "tunnel-like" defect as in case of a PFO is covered more completely immediately after device implantation, in contrast to the larger "hole-like" defect as in case of an ASD. In the report by Krizanic et al., one patient suffered from a recurrent stroke four months after implantation, without thrombus formation on the device or residual shunt on TEE and was therefore probably due to an extracardiac source.[15] We did not observe any re-occurrences of TIA or stroke during six months follow-up. Moreover, we did not detect any thrombus on the device during follow-up, but we realize that thrombus assessment with TTE only might be suboptimal.

Limitations

The first limitation of our study is the single-centre character and the related selection bias. Second, we used cTTE (with second harmonic imaging) to detect residual shunting. Both over- and underestimation of a right-to-left shunt compared with cTEE are possible with this technique. On the other hand, we are convinced that cTTE is a valid method that is less invasive to the patient compared to TEE and a good Valsalva manoeuvre is often more difficult to obtain during TEE, especially if the patient is sedated. Furthermore, we must acknowledge that the detection of thrombus formation on the device is less adequate using TTE.

Conclusion

Our study confirms that the new Occlutech Figulla® device appears to be easy to use, effective, and safe for percutaneous PFO and ASD closure. Despite the structural innovations, in order to reduce potential complications, we did not observe a reduction in supraventricular arrhythmias. In addition, a relatively high percentage of mainly small residual shunts was present at 6-month follow-up. Therefore, larger series, longer follow-up data, and head-to-head comparison with analogue devices such as the Amplatzer® occluder are warranted.

Reference List

(1) Campbell M. Natural history of atrial septal defect. *Br Heart J* 1970 November;32(6):820-6.

(2) Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984 January;59(1):17-20.

(3) Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. *Circulation* 1968 May;37(5):805-15.

(4) Lechat P, Mas JL, Lascault G et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988 May 5;318(18):1148-52.

(5) Braun M, Gliech V, Boscheri A et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. *Eur Heart J* 2004 March;25(5):424-30.

(6) Du ZD, Hijazi ZM, Kleinman CS, Silverman NH, Larntz K. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol* 2002 June 5;39(11):1836-44.

(7) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003 November 4;139(9):753-60.

(8) Masura J, Gavora P, Podnar T. Long-term outcome of transcatheter secundum-type atrial septal defect closure using Amplatzer septal occluders. *J Am Coll Cardiol* 2005 February 15;45(4):505-7.

(9) Wahl A, Kunz M, Moschovitis A et al. Long-term results after fluoroscopy-guided closure of patent foramen ovale for secondary prevention of paradoxical embolism. *Heart* 2008 March;94(3):336-41.

(10) Windecker S, Wahl A, Chatterjee T et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000 February 29;101(8):893-8.

(11) Post MC, Van DK, Budts W. Percutaneous closure of a patent foramen ovale: single-centre experience using different types of devices and mid-term outcome. *Acta Cardiol* 2005 October;60(5):515-9.

(12) Taaffe M, Fischer E, Baranowski A et al. Comparison of three patent foramen ovale closure devices in a randomized trial (Amplatzer versus CardioSEAL-STARflex versus Helex occluder). *Am J Cardiol* 2008 May 1;101(9):1353-8.

(13) Van den Branden BJ, Post MC, Jaarsma W, ten Berg JM, Suttorp MJ. New bioabsorbable septal repair implant for percutaneous closure of a patent foramen ovale: short-term results of a single-centre experience. *Catheter Cardiovasc Interv* 2009 August 1;74(2):286-90.

(14) Fischer G, Stieh J, Uebing A, Hoffmann U, Morf G, Kramer HH. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients. *Heart* 2003 February;89(2):199-204.

(15) Krizanic F, Sievert H, Pfeiffer D, Konorza T, Ferrari M, Figulla HR. Clinical evaluation of a novel occluder device (Occlutech) for percutaneous transcatheter closure of patent foramen ovale (PFO). *Clin Res Cardiol* 2008 December;97(12):872-7.

(16) Krizanic F, Sigler M, Figulla HR. Transvenous closure of patent foramen ovale: preliminary results with a new self-expanding nitinol wire mesh in a Swine model. *Cardiol Res Pract* 2009;2009:943453.

(17) Post MC, Suttorp MJ, Jaarsma W, Plokker HW. Comparison of outcome and complications using different types of devices for percutaneous closure of a secundum atrial septal defect in adults: a single-center experience. *Catheter Cardiovasc Interv* 2006 March;67(3):438-43.

(18) van Gent MW, Post MC, Snijder RJ et al. Grading of pulmonary right-to-left shunt with transthoracic contrast echocardiography: does it predict the indication for embolotherapy? *Chest* 2009 May;135(5):1288-92.

(19) Soliman OI, Geleijnse ML, Meijboom FJ et al. The use of contrast echocardiography for the detection of cardiac shunts. *Eur J Echocardiogr* 2007 June;8(3):S2-12.

(20) Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. *Circulation* 1992 December;86(6):1902-8.

(21) King TD, Mills NL. Nonoperative closure of atrial septal defects. *Surgery* 1974 March;75(3):383-8.

(22) Krizanic F, Sievert H, Pfeiffer D et al. The Occlutech Figulla PFO and ASD occluder: a new nitinol wire mesh device for closure of atrial septal defects. *J Invasive Cardiol* 2010 April;22(4):182-7.

(23) Pac A, Polat TB, Cetin I, Oflaz MB, Balli S. Figulla ASD occluder versus amplatzer septal occluder: a comparative study on validation of a novel device for percutaneous closure of atrial septal defects. *J Interv Cardiol* 2009 December;22(6):489-95.

(24) Alaeddini J, Feghali G, Jenkins S, Ramee S, White C, bi-Samra F. Frequency of atrial tachyarrhythmias following transcatheter closure of patent foramen ovale. *J Invasive Cardiol* 2006 August;18(8):365-8.

(25) Spies C, Khandelwal A, Timmermanns I, Schrader R. Incidence of atrial fibrillation following transcatheter closure of atrial septal defects in adults. *Am J Cardiol* 2008 October 1;102(7):902-6.

(26) Wahl A, Krumsdorf U, Meier B et al. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol* 2005 February 1;45(3):377-80.

(27) Saguner A.M., Wahl A, Windecker S et al. Figulla patent foramen ovale occluder vs. Amplatzer patent foramen ovale occluder: a single-centre experience comparing both devices for percutaneous closure of patent foramen ovale. *EuroIntervention* 2010 May 1;6(Supplement H, abstracts of EuroPCR):H155.

(28) Maffe S, Dellavesa P, Zenone F et al. Transthoracic second harmonic two- and three-dimensional echocardiography for detection of patent foramen ovale. *Eur J Echocardiogr* 2010 January;11(1):57-63.

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The Occlutech Figulla® device versus the Amplatzer® device in percutaneous atrial septal defect closure

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Submitted

Abstract

Objectives: The purpose of this study was to compare the 6-month outcome of the novel Occlutech Figulla® septal occluder (FSO) with its competitor, the Amplatzer® septal occluder (ASO) for transcatheter atrial septal defect (ASD) closure in adults.

Background: The ASO is currently the most widely used closure device. The new FSO is constructed to diminish the amount of material and to lower the complication risk.

Methods: Between October 2000 and December 2010, a total of 185 patients underwent ASD closure with the FSO or the ASO and completed 6-month clinical and echocardiographic follow-up. All complications related to the procedure were reported.

Results: The FSO was used in 53 patients (mean age 50.0 ± 17.2 years; 71.7% female) and the ASO in 132 patients (mean age 47.4 ± 16.8 years; 68.9% female). In-hospital, 2 devices embolized in each group (3.8% vs. 1.5% for the FSO and ASO group, respectively). Similar rates of new-onset supraventricular tachycardias (SVT) were observed in-hospital (1.9% vs. 1.5%). During follow-up, three patients (5.9%) in the FSO group and four patients (3.1%) in the ASO group reported a SVT. At six months, the residual shunt rate (assessed with contrast transthoracic echocardiography) was significantly higher in the FSO group (total 39.5%, 25.6% minimal, 11.6% moderate, 2.3% large) compared to the ASO group (total 10.6%, 7.9% minimal, 1.8% moderate, 0.9% large) ($p<0.001$).

Conclusions: The use of the FSO in percutaneous ASD closure is associated with a comparable safety profile as the ASO. Despite the structural innovations of the FSO we observed more residual shunts during follow-up.

Introduction

Atrial septal defect (ASD) is one of the most common congenital heart defects in adults and accounts for approximately 10% of all congenital heart diseases.[1] The secundum type ASD is located in the central region of the fossa ovalis and makes up 75% of all ASD's.[2] The chronic left-to-right shunt (LRS) through the ASD results in volume overload of the right heart and may lead to a variety of complications including right ventricular failure, pulmonary arterial hypertension (PAH), arrhythmias, and paradoxical embolism.[3-5] Percutaneous ASD closure is an increasingly widespread alternative to surgical closure and has become routine practice.[6] Since the first percutaneous ASD closure was performed by King and Miles in 1974, a large number of closure devices have been developed and used in clinical practice.[7-9] The Amplatzer® septal occluder (ASO) (AGA Medical, Plymouth, Minnesota, USA) was initiated in 1997 and is the most frequently used device worldwide with excellent follow-up results.[10-12] Recently, the Occlutech Figulla® septal occluder (FSO) (Occlutech GmbH., Jena, Germany) has been introduced for ASD and patent foramen ovale (PFO) closure.[13] This device is designed with an unique braiding technology which allows a reduction of material on the left atrial side (about 50% reduction compared with the ASO) and should provide a greater flexibility and a lower risk of clot formation, trauma, and arrhythmias. In the present study we compared the overall safety and efficiency of both devices in percutaneous ASD closure.

Materials and Methods

Patients

We included all patients who underwent percutaneous ASD closure with the FSO and the ASO and completed clinical and echocardiographic follow-up at six months. Indications for percutaneous closure were signs of volume overload of the right ventricle (RV) on transthoracic echocardiography (TTE), PAH, a haemodynamically significant LRS ratio (Qp:Qs > 1.5) measured invasively using oxygen saturations, clinical symptoms of dyspnea and reduced exercise capacity, palpitations or

paradoxical embolism in association with an ASD. All secundum ASD's were identified with TTE and tranesophageal echocardiography (TEE) using color Doppler techniques with or without contrast administration. Patients were excluded for percutaneous closure if the ASD diameter was ≥ 35 mm or if there was insufficient rim to anchor the device.

Devices and closing procedure

The FSO and the ASO devices have been described previously.[14, 15] The FSO is currently available in sizes from 6 to 40 mm, the ASO from 4 to 40 mm. The unique braiding technique of nitinol wires used in the FSO, allows forming a single microscrew at the right atrial disc for cable connection. There is no left atrial clamp, minimizing the amount of material implanted. On contrary, the ASO is made up of a nitinol wire tube that is clamped in two stainless steel hubs, one on each side of the disc. Both devices are shown in Figure 1.

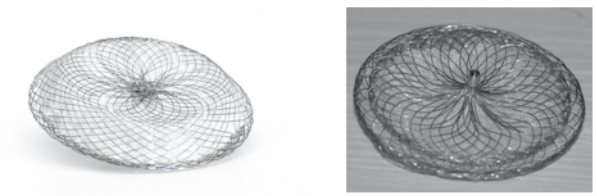

Figure 1. The Occlutech Figulla® ASD occluder (left) and the Amplatzer® ASD occluder (right). Note the absence of the clamp on the left atrial disk of the Occlutech Figulla® device.

Our percutaneous closing technique has been extensively described in the literature and is comparable for both devices.[8] The majority of the procedures were performed under general anaesthesia and continuous TEE monitoring. During the past few years, local anaesthesia with intracardiac echocardiographic (ICE) guidance was preferred in case of relatively small ASD's. In all patients, accurate balloon sizing using the "stop-flow" method was used. Concomitant fluoroscopy was used in all patients. A fluoroscopic image of both devices is shown in Figure 2. The size of the device was chosen by the interventional cardiologist depending on the diameter of the ASD.

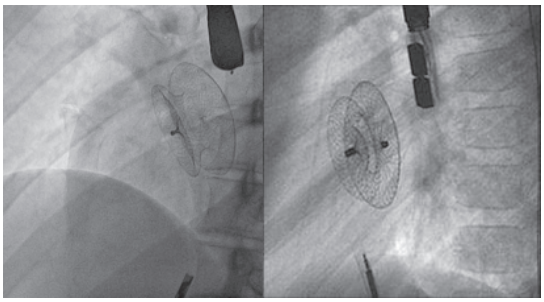

Figure 2. Fluoroscopic image of the Occlutech Figulla® device (left) and the Amplatzer® device (right) after release, fixed at the interatrial septum.

Follow-up evaluation

All patients were scheduled for contrast TTE (cTTE) at six months follow-up to establish the position of the device and to determine negative contrast effect or residual right-to-left shunting which was categorized as follows: small shunt (< 30 bubbles in the left atrium), moderate shunt (30-100 bubbles in the left atrium), and severe shunt (> 100 bubbles in the left atrium).[16, 17] Color Doppler interrogation was performed to detect residual LRS. Furthermore, we evaluated the position and the shape of the device and looked for thrombus on the device. The relationship between the device and the atrioventricular valves was evaluated. All echocardiographic examinations were reviewed by two experienced physicians. The 6-month TTE was combined with a visit to the outpatient clinic were a history and physical examination were obtained. All procedural complications and all complications related to the procedure within six months were reported. Complications were divided into major and minor complications according to the classification scheme of Khairy et al.[18] New-onset supraventricular tachyarrhythmias (SVT) were diagnosed by a 12-lead electrocardiogram or 24-hours Holter. Some patients underwent ASD closure because of a cryptogenic embolic event. Therefore, the recurrence of thromboembolic events was evaluated during follow-up. All neurological events needed to be established by a neurological evaluation and, in case of stroke, confirmed by the appropriate cerebral imaging studies.

Statistical Analysis

Descriptive statistics were used to describe patients' characteristics. Continuous variables with normal distribution are presented as mean ± standard deviation. If normal distribution is absent, median with range is given. Differences between both devices were analyzed by unpaired Student's t test for continuous variables and Chi-square test for nominal variables. All statistical analyses were performed by using SPSS software version 17.0 for Windows (SPSS, Chicago, IL, USA).

Results

Patient characteristics

Between October 2000 and December 2010, a total of 203 patients underwent transcatheter closure of an isolated secundum type ASD in our centre. Sixteen patients received a Cardioseal® device and two a BioSTAR® device (both NMT Medical, Boston, USA), all were excluded from this study. The ASO was used in 122 patients between October 2000 and October 2008. Thereafter, the FSO was introduced in our hospital and implanted in the majority of cases. Ten ASO devices were used in the past two years, mainly because the FSO was not in stock or according to the preference of the interventional cardiologist. Mean age was comparable between both groups but the patients in the FSO group had a higher prevalence of coronary artery disease and cardiovascular risk factors. The majority of the patients (74.6%) underwent ASD closure because of RV volume overload with PAH and/or dyspnea. Cryptogenic TIA or stroke was the closure indication in 26.4% of the patients in the FSO group and in 21.2% of the patients in the ASO group. Mean maximal defect diameter measured by TEE was 15.0 ± 6.3 in the FSO group and 19.0 ± 6.4 in the ASO group. All baseline demographics and indications for closure are listed in Table I.

Table I. Baseline characteristics

	FSO (n = 53)	ASO (n = 132)
Mean age ± SD (y)	50.0 ± 17.2	47.4 ± 16.8
Female, n (%)	38 (71.7)	91 (68.9)
Weight (kg)	72.0 ± 12.9	72.9 ± 14.5
Risk factors and co-morbidities (%)		
Hypertension	35.8	25.0
Hypercholesterolemia	22.6	7.6
Diabetes	7.5	5.3
Family history of CVD	22.6	18.9
Smoking	13.2	18.2
CAD	13.2	6.1
History of SVT	22.6	31.1
Indication for closure, n (%)		
Dyspnea/fatigue	16 (30.2)	21 (15.9)
Rhythm disorders/palpitations	2 (3.8)	3 (2.3)
RV volume overload/PAH	21 (39.6)	80 (60.6)
Cryptogenic TIA/stroke	14 (26.4)	28 (21.2)
RVSP (mmHg) *	36.0 ± 12.2	35.4 ± 9.5
ASD diameter (mm)#	15.0 ± 6.3	19.0 ± 6.4

SD, standard deviation; y, years; n, number; FSO, Figulla septal occluder; ASO, Amplatzer septal occluder; CVD, cardiovascular disease; CAD, coronary artery disease; RV, right ventricle; PAH, pulmonary artery hypertension; TIA, transient ischaemic attack; RVSP, right ventricular systolic pressure; ASD, atrial septal defect.
Data are presented as mean ± SD.
*on transthoracic echocardiography.
#on transesophageal echocardiography.

Procedural and in-hospital outcome

In 64.2% of the FSO treated patients and in 97.0% of the ASO treated patients, the procedure was performed under general anaesthesia and continuous TEE monitoring. We started to use ICE by June 2008, especially in case of small-to-moderate ASD's (up to 30 mm) with sufficient rim and low risk of compromising the mitral valve. About one-third of the patients who received a FSO were successfully guided with ICE. In two patients, the FSO embolized to the left ventricle within 12 hours after initial successful implantation (3.8%). The first patient was a 25-year-old female with an extremely floppy interatrial septum. She required urgent surgery to remove the

device and close the ASD. The other patient regards a 35-year-old female who also needed immediate surgery. The ASD had an asymmetric oval shape with insufficient inferior rim and the device appeared to be undersized. In the ASO group one device embolized to the left ventricle in a 56-year-old male, a few hours after the procedure. Surgery was uneventful. Another patient suffered ASO embolization to the abdominal aorta, the device could be retrieved into the femoral artery by means of a snare but had to be removed surgically from the groin. The patient underwent surgical ASD closure one month later. Minor complications occurred in 13.2% of the patients in the FSO group and in 6.8% of the patients in the ASO group. In the FSO group we observed a minimal groin haematoma in 5 patients, in the ASO group in 3 patients (9.4% vs. 2.3%, p=0.01). Two patients in the ASO group experienced an allergic reaction during the procedure, one was related to the antibiotic administration, the second was probably due to aspirin allergy. A new SVT was observed in 1 patient in the FSO group (1.9%) and in 2 patients in the ASO group (1.5%). Procedural and in-hospital data are summarized in Table II.

Table II. Procedural characteristics

	FSO (n = 53)	ASO (n = 132)	p-value
Diameter device (mm)*	25 (10-39)	24 (12-38)	
Echocardiographic guiding, n (%)			
TEE	34 (64.2)	128 (97.0)	<0.0001
ICE	19 (35.8)	4 (3.0)	
General anaesthesia, n (%)	34 (64.2)	128 (97.0)	<0.0001
In-hospital complications, n (%)			
Device embolization	2 (3.8)	2 (1.5)	
New-onset SVT	1 (1.9)	2 (1.5)	
Allergic reaction	0	2 (1.5)	
Fever	0	1 (0.8)	
Groin hematoma	5 (9.4)	3 (2.3)	0.01
Transient ST-segment elevation	1 (1.9)	1 (0.8)	
Tamponade	0	0	
Hospital stay (days)*	2 (2-9)	2 (2-4)	

n, number; TEE, transesophageal echocardiography; ICE, intracardiac echocardiography; SVT, supraventricular tachycardia.
Non-significant p-values were not reported
*Data presented as median (range).

Follow-up results

Six-month clinical follow-up data were available in all patients. The patients who underwent surgical closure after device embolization were excluded from follow-up (Table III). A 75-year-old female, known with arterial hypertension, diabetes and Child-Pugh liver cirrhosis, suffered from a recurrent cerebral haemorrhage, five months after ASD closure. At the time of the event, she was treated with aspirin. Because she already used aspirin before the closing procedure, we could not relate this event to the procedure. In the patients who were treated because of a cryptogenic thromboembolic event (n=42), we did not observe any recurrences of TIA or stroke. In the FSO group, three patients suffered a new SVT during follow-up versus four patients in the ASO group (5.9% vs. 3.1% respectively). The majority of SVT's occurred in the first two months after device placement. All SVT's (including in-hospital SVT's) except from one (which needed electrical conversion) were self-limiting in the FSO group (n=4). The arrhythmias in the ASO group (n=6) were more persistent and all needed therapy (67% medication, 33% electrical conversion). Echocardiographic follow-up could be obtained in 84.3% in the FSO group and in 87.7% in the ASO group (Table III). We observed significantly more residual shunts in the patients who received the FSO (39.5% vs. 10.6%, $p<0.001$). The greatest part of the residual shunts in the FSO group were minimal. Still, when combining moderate and large shunts, the difference between the two groups was obvious (13.9% vs. 2.6%, $p=0.006$). No thrombus formation was detected in neither of the two groups.

Table III. Six-month follow-up results

	FSO	ASO	p-value
Clinical follow-up available, n (%)	51 (96.2)	130 (98.4)	
Major complications, n (%)	0	0	
Minor complications, n (%)			
Groin haematoma	0	0	
New-onset SVT	3 (5.9)	4 (3.1)	
Reoccurrence TIA/stroke	0	0	
TTE follow-up available, n (%)	43 (84.3)	114 (87.7)	
Shunt, n (%)			<0.001
No shunt	26 (60.5)	102 (89.4)	
Grade 1	11 (25.6)	9 (7.9)	
Grade 2	5 (11.6)	2 (1.8)	
Grade 3	1 (2.3)	1 (0.9)	
No or minimal	36 (86.1)	111 (97.4)	0.006
Moderate or large	6 (13.9)	3 (2.6)	
Thrombus formation	0	0	

n, number; SVT, supraventricular tachycardia; TIA, transient ischaemic attack; TTE, transthoracic echocardiography.
Non-significant p-values were not reported.

Discussion

The present study demonstrates that percutaneous closure of an ASD with the novel FSO is associated with a similar safety profile compared to its competitor, the ASO. On the other hand, at six months we reported more residual shunts in the FSO treated patients.

Safety of ASD closure

The ASO is currently the most frequently used device worldwide with excellent outcomes reported up to 9 years.[12] Major complications associated with ASO implantation are rare and tend to occur early in the vast majority of the patients.[12, 19] For example, the incidence of early device embolization is approximately 0.5-0.7%.[20, 21] The most common minor complication after ASD closure is atrial arrhythmia,

occurring in about 12%.[22] In a recent comparative study by Luermans et al., the ASO performed better than the Cardioseal® device with major complication rates of 2.9% vs. 17.2% (p=0.005) and minor complication rates of 8.7% vs. 17.2% (p=0.23).[10] The FSO was launched as an improved modification of the ASO because it is individually braided, avoiding a distal clamp at the left atrial disk.[23] This may lower the chance of potential complications related to the presence of a foreign body at the interatrial septum. According to the novelty of the device, data on ASD closure using FSO are scares and mainly limited to short-term follow-up. In a recent report by Cansel et al., the FSO (range in device size 12-36 mm) was implanted in 68 patients with a secundum type ASD. They observed no major complications and only two patients (2.9%) experienced a new-onset SVT during 6-month follow-up.[24] Another study included 28 patients, one patient (3.6%) developed atrial fibrillation.[25] Pac et al. compared the FSO (n=33) and the ASO (n=42) in ASD closure and found no significant differences in complication rate between the two groups.[26] One FSO (3%) embolized to the pulmonary trunk and was retrieved percutaneously. Four patients in the FSO group (12.1%) suffered SVT compared to seven patients in the ASO group (16.7%). In the present study, two devices embolized in each group (FSO 3.8%, ASO 1.5%). Both patients of the FSO received a 25-mm device, which was probably undersized. A disadvantage of the FSO device is that only 15 different sizes are available compared to 27 different sizes for the ASO, making the selection of the appropriate device size more difficult. Overall, we found no significant differences in the occurrence of SVT's between both groups. Although there was a slightly higher percentage SVT's in the FSO group (7.5% vs. 4.5%), they were mostly transient compared with the SVT's in the ASO group, which all needed therapy. A possible explanation for the latter is the increased flexibility and the smaller amount of material of the FSO device. We observed more femoral haematomas in the FSO group which could be explained by the need of a larger delivery sheath (14 Fr compared to 12 Fr for the ASO). Secondly, we used ICE guidance in 35.8% of the FSO procedures, requiring bilateral femoral vein puncture. Furthermore, we must emphasize that non of the haematomas required blood transfusion and that a femoral haematoma is not a device-related complication. We did not found any thrombus on the devices but we are aware that thrombus detection is less adequate using TTE.

Effectiveness of ASD closure

Residual shunting during follow-up after percutaneous ASD closure with the ASO varies between 0 and 20%.[8, 10, 12, 27] Most likely, these differences can be explained by the use of different imaging modalities and different quantification of shunt severity. We found residual shunting, diagnosed by cTTE, in 10.6% of the patients, six months after ASO implantation. In the FSO group, 39.5% of the patients showed residual shunt after six months, 25.6% minimal, 13.9% moderate or large. This is much higher than the reported 0%-1.5% residual shunting (at six months) in the other three FSO-reports, who all used color Doppler techniques.[24-26] We do agree that color Doppler imaging is the technique of choice to diagnose LRS through an ASD. However, cTTE is very useful for the assessment of residual shunt after device closure. Because of the high echogenicity of the closure device, the ultrasound wave reflections make the conventional echocardiographic techniques (including color Doppler) unreliable. A residual LRS can be seen as a negative contrast effect in the contrast-filled right atrium. Residual right-to-left shunt (in rest and/or after the Valsalva manoeuvre) indicates incomplete closure of the defect and justifies longer echocardiographic follow-up.[17] On the other hand, the most important goal in ASD closure is to eliminate the LRS, except in case of cryptogenic stroke. Only in the patient with grade 3 residual shunt on cTTE, a LRS was observed according to negative contrast effect and color Doppler flow. Noteworthy, of the 14 patients who underwent ASD closure with the FSO because of cryptogenic TIA or stroke, 8 patients (57.1%) had a residual right-to-left shunt, which requires further follow-up. The difference in residual shunt rate between the two devices in this study could be related to the smaller right atrial disc of the FSO device, as already proposed by Pac et al., who found significant higher residual shunt rates (using color Doppler) immediate after the procedure in the FSO-group compared to the ASO-group (24.3% vs. 7.1%, p=0.04).[26] At six months, they found no shunts in both groups. In addition, Saguner et al. recently reported significantly more residual shunts after PFO closure with the Occlutech Figulla® PFO occluder compared to the Amplatzer® PFO-occluder (39% vs. 0% at six months using cTEE).[28] We acknowledge that it is difficult to compare ASD and PFO closure devices, but the new braiding technique accompanied with less amounts of material is the same for the Occlutech® ASD and PFO occluder. We can only speculate that the more

robust ASO device leads to a better fixation at the left side of the septum and that "less material is associated with less defect closure". Otherwise we assume that the clinical relevance of residual right-to-left shunt is negligible in patient who have their ASD closed because of right heart volume overload due to LRS. As we know that residual shunt diminishes over time, we must await our long-term echocardiographic follow-up results to draw more definite conclusions about the efficacy of ASD closure with the FSO.

The major limitation of our study is the non-randomized design. Second, we acknowledge the single centre character and the fact that the echocardiograms were not reviewed by an independent core-lab. Furthermore, the number of patients in the FSO is relatively small. However, our series is one of the largest presented so far. A prospective randomized trial with larger groups and longer follow-up is needed to asses the true differences in safety and efficacy between the two devices.

Conclusions

Percutaneous ASD closure using the novel FSO device appears to be safe. Compared to the ASO device, the closure rate is lower at mid-term follow-up.

Reference List

(1) Seldon WA, Rubinstein C, Fraser AA. The incidence of atrial septal defect in adults. *Br Heart J* 1962 September;24:557-60.

(2) Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. *N Engl J Med* 2000 January 27;342(4):256-63.

(3) Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. *Circulation* 1968 May;37(5):805-15.

(4) Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med* 1999 March 18;340(11):839-46.

(5) Konstam MA, Idoine J, Wynne J et al. Right ventricular function in adults with pulmonary hypertension with and without atrial septal defect. *Am J Cardiol* 1983 April;51(7):1144-8.

(6) Du ZD, Hijazi ZM, Kleinman CS, Silverman NH, Larntz K. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol* 2002 June 5;39(11):1836-44.

(7) King TD, Mills NL. Nonoperative closure of atrial septal defects. *Surgery* 1974 March;75(3):383-8.

(8) Post MC, Suttorp MJ, Jaarsma W, Plokker HW. Comparison of outcome and complications using different types of devices for percutaneous closure of a secundum atrial septal defect in adults: a single-center experience. *Catheter Cardiovasc Interv* 2006 March;67(3):438-43.

(9) Rao PS, Berger F, Rey C et al. Results of transvenous occlusion of secundum atrial septal defects with the fourth generation buttoned device: comparison with first, second and third generation devices. International Buttoned Device Trial Group. *J Am Coll Cardiol* 2000 August;36(2):583-92.

(10) Luermans JG, Post MC, ten Berg JM, Plokker HW, Suttorp MJ. Long-term outcome of percutaneous closure of secundum-type atrial septal defects in adults. *EuroIntervention* 2010 November;6(5):604-10.

(11) Fischer G, Stieh J, Uebing A, Hoffmann U, Morf G, Kramer HH. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients. *Heart* 2003 February;89(2):199-204.

(12) Masura J, Gavora P, Podnar T. Long-term outcome of transcatheter secundum-type atrial septal defect closure using Amplatzer septal occluders. *J Am Coll Cardiol* 2005 February 15;45(4):505-7.

(13) Krizanic F, Sievert H, Pfeiffer D, Konorza T, Ferrari M, Figulla HR. Clinical evaluation of a novel occluder device (Occlutech) for percutaneous transcatheter closure of patent foramen ovale (PFO). *Clin Res Cardiol* 2008 December;97(12):872-7.

(14) Masura J, Gavora P, Formanek A, Hijazi ZM. Transcatheter closure of secundum atrial septal defects using the new self-centering amplatzer septal occluder: initial human experience. *Cathet Cardiovasc Diagn* 1997 December;42(4):388-93.

(15) Van den Branden BJ, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Percutaneous atrial shunt closure using the novel occlutech figulla device: 6-month efficacy and safety. *J Interv Cardiol* 2011 June;24(3):264-70.

(16) van Gent MW, Post MC, Snijder RJ et al. Grading of pulmonary right-to-left shunt with transthoracic contrast echocardiography: does it predict the indication for embolotherapy? *Chest* 2009 May;135(5):1288-92.

(17) Soliman OI, Geleijnse ML, Meijboom FJ et al. The use of contrast echocardiography for the detection of cardiac shunts. *Eur J Echocardiogr* 2007 June;8(3):S2-12.

(18) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003 November 4;139(9):753-60.

(19) Majunke N, Bialkowski J, Wilson N et al. Closure of atrial septal defect with the Amplatzer septal occluder in adults. *Am J Cardiol* 2009 February 15;103(4):550-4.

(20) Amin Z, Hijazi ZM, Bass JL, Cheatham JP, Hellenbrand WE, Kleinman CS. Erosion of Amplatzer septal occluder device after closure of secundum atrial septal defects: review of registry of complications and recommendations to minimize future risk. *Catheter Cardiovasc Interv* 2004 December;63(4):496-502.

(21) Butera G, Carminati M, Chessa M et al. CardioSEAL/STARflex versus Amplatzer devices for percutaneous closure of small to moderate (up to 18 mm) atrial septal defects. *Am Heart J* 2004 September;148(3):507-10.

(22) Spies C, Khandelwal A, Timmermanns I, Schrader R. Incidence of atrial fibrillation following transcatheter closure of atrial septal defects in adults. *Am J Cardiol* 2008 October 1;102(7):902-6.

(23) Halabi A, Hijazi ZM. A new device to close secundum atrial septal defects: first clinical use to close multiple defects in a child. *Catheter Cardiovasc Interv* 2008 May 1;71(6):853-6.

(24) Cansel M, Pekdemir H, Yagmur J et al. Early single clinical experience with the new Figulla ASD Occluder for transcatheter closure of atrial septal defect in adults. *Arch Cardiovasc Dis* 2011 March;104(3):155-60.

(25) Ilkay E, Kacmaz F, Ozeke O et al. The efficiency and safety of percutaneous closure of secundum atrial septal defects with the Occlutech Figulla device: initial clinical experience. *Turk Kardiyol Dern Ars* 2010 April;38(3):189-93.

(26) Pac A, Polat TB, Cetin I, Oflaz MB, Balli S. Figulla ASD occluder versus amplatzer septal occluder: a comparative study on validation of a novel device for percutaneous closure of atrial septal defects. *J Interv Cardiol* 2009 December;22(6):489-95.

(27) Knepp MD, Rocchini AP, Lloyd TR, Aiyagari RM. Long-term follow up of secundum atrial septal defect closure with the amplatzer septal occluder. *Congenit Heart Dis* 2010 January;5(1):32-7.

(28) Saguner AM, Wahl A, Praz F et al. Figulla PFO occluder versus Amplatzer PFO occluder for percutaneous closure of patent foramen ovale. *Catheter Cardiovasc Interv* 2011 April 1;77(5):709-14.

Part four

Transcatheter mitral valve repair using the edge-to-edge clip technique

7

Percutaneous mitral valve repair using the edge-to-edge technique in a high-risk population

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Abstract

Background: Percutaneous mitral valve (MV) repair, using the edge-to-edge clip technique, might be an alternative for patients with significant mitral regurgitation (MR) and an unacceptable high risk for operative repair or replacement. We report the short-term safety and efficacy of this new technique in a high-risk population.

Methods: All consecutive high-risk patients who underwent percutaneous MV repair with the Mitraclip® between January 2009 and August 2009 were included. All complications related to the procedure were reported. Transthoracic echocardiography for MR grading and right ventricular systolic pressure (RVSP) measurement were performed before, and at three and 30 days after the procedure. Differences in NYHA functional class and quality of life (QoL) index were reported.

Results: Nine patients were enrolled (78% male, mean age 75.9 ± 9.0 years, logistic EuroSCORE 33.8 ± 9.0%). One patient developed inguinal bleeding. In one patient partial clip detachment occurred, a second clip was placed successfully. The MR grade before repair was ≥ 3 in 100%, one month after repair a reduction in MR grade to ≤ 2 was present in 78% (p=0.001). RVSP decreased from 43.9 ± 12.1 to 31.6 ± 11.7 mmHg (p=0.009), NYHA functional class improved from median 3 (range 3 to 4) to 2 (range 1 to 4) (p=0.04), and QoL index improved from 62.9 ± 16.3 to 49.9 ± 30.7 (p=0.12).

Conclusions: In high-risk patients, transcatheter MV repair seems to be safe and a reduction in MR can be achieved in most patients, resulting in a short-term improvement of functional capacity and QoL.

Introduction

Mitral valve repair, rather than replacement, has become the preferred surgical treatment for severe mitral regurgitation (MR).[1] The mainstay of surgical repair is annuloplasty, which is associated with excellent outcome.[2] In 1991, a simple technique for mitral valve repair was introduced by Otavio Alfieri, involving the placement of a surgical suture in the mid-portion of the anterior en posterior leaflets, creating a double-orifice mitral valve.[3] This technique ensures a fixed area of coaptation during systole, without disturbing the subvalvular and annular function, preserving left ventricular function[4] and seems to be associated with improved functional status and freedom from re-operation.[5] However, most patients treated with the "Alfieri-stitch" also needed an annuloplasty. The surgical literature suggests that the absence of a ring is associated with suboptimal results and the frequent need for reoperation in patients with more severe MR.[6] Therefore the technique was used in patients who are not candidates for conventional surgical repair.

Recently, a catheter-based, percutaneous method was introduced to accomplish the double-orifice repair. Using the transseptal approach, a clip device is delivered into the left atrium. The clip can grasp the free edges of the mitral valve simultaneously. The first phase I clinical trial has shown safety and feasibility of this technique in non-high-risk patients.[7] It might be an alternative strategy in patients with a high or prohibitive risk for standard surgery. We report the short-term results of percutaneous mitral valve repair in a high-risk population.

Methods

Patient selection

All patients with moderate-to-severe or severe, highly symptomatic MR were discussed in our team of cardiac surgeons and cardiologists. Patients were considered to be eligible for the percutaneous approach when they were not candidates for mitral valve surgery because of a too high peri-operative risk, according to the logistic EuroSCORE (> 20%), and had a suitable valve anatomy as judged by the interdisciplinary team.

Pre-procedural work-up

All patients had a standard diagnostic work-up containing physical examination, quality of life (QoL)/functional capacity assessment (New York Heart Association (NYHA) class, six-minutes walking test, and Minnesota questionnary), ECG, laboratory measurements (including NT-pro-BNP), transthoracic and transesophageal echocardiography (TTE and TEE), coronary angiography, and right heart catheterization.

Procedure

All procedures were performed in the catheterization laboratory under general anaesthesia and both fluoroscopic and transesophageal echocardiographic (two-dimensional (2D) and three-dimensional (3D)) guidance. Venous access, using a 24 French sheath, was gained via the right femoral vein. A catheter was placed in the radial artery for continuous haemodynamic monitoring. Before the initial procedure, right heart catheterization was performed with a 7 French multipurpose catheter via the left femoral vein. Prophylactic antibiotics were given before the procedure. All patients were pretreated with aspirin or coumadin.

Post-procedure

Post-procedure, repeat right heart catheterization was performed. A figure eight suture was used to obtain haemostasis at the 24 French access site and removed 24 hours later. All patients were treated with aspirin 100 mg once a day for a period of six months if they had not received coumadin prior the procedure. Endocarditis prophylaxis for six months was advised.

Before discharge, all patients underwent TTE to assess the position of the clip and residual MR as described previously. An ECG and laboratory testing were performed within 24 hours.

All periprocedural and short-term complications were reported. Major complications include haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure related surgical intervention, endocarditis, clip detachment, clip dislodgement/embolization, stroke, and death. Minor complications were defined as mitral valve injury, device thrombosis, bleeding not requiring blood transfusion, femoral arteriovenous fistula formation and femoral haematoma.

One month after the procedure, patients were seen at the outpatient clinics. An assessment of functional capacity and QoL was made using the NYHA class and the Minnesota questionnaire. Within the same day, ECG, laboratory testing, and echocardiography were repeated.

Transthoracic echocardiography

Echocardiographic parameters included left ventricular ejection fraction (LVEF) using the Simpson's method, left ventricular end-systolic and end-diastolic diameters (LVESD, LVEDD), left atrial (LA) dimension and volume, right ventricular systolic pressure (RVSP) using tricuspid regurgitation flow velocity and right atrial pressure using vena cava inferior dimensions. The severity of MR was assessed using a variety of parameters, according to recommendations published earlier.[8-10] Severity scale of 1 to 4 using color flow Doppler (color flow mapping) and color flow jet area (jet area/LA area) appeared to be the best reproducible parameters. Vena contracta and regurgitant orifice were recorded if possible but not included as parameters for MR assessment because they have not been validated for a double orifice valve. Two independent physicians performed the TTE endpoint analysis.

The echocardiographic evaluation was performed before and three days after the ten procedures in nine patients. One-month follow-up data were available in nine patients, because one patient received two clips within one month.

Statistical analysis

Descriptive statistics were used to report patients' characteristics. Continuous variables with normal distribution are reported by mean ± standard deviation. Median and range were used when normal distribution was absent. Percentages were used to report categorical variables. Patients' data before and after the procedure were compared with Chi-square or Fisher exact test for nominal variables and independent Student's *t* test for continuous variables. Paired samples *t* test was used for within-patient comparison of continuous variables. All tests were two sided and $p<0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS software (SPSS Inc., version 14.0 for Windows).

Results

Patient characteristics

A total of 22 patients were screened for percutaneous mitral valve repair in our centre. In 11 patients the mitral valve itself was not amenable, due to severe calcification or rheumatic deformations. One patient was excluded because of a thrombus in the LV. As a result, ten consecutive patients underwent percutaneous mitral valve repair between January and August 2009. One 66-year-old male with a dilated LV and severe MR (grade 4) was in NYHA class II, and had a low logistic EuroSCORE (8.4%) and a Minnesota QoL index of 7. He refused cardiac surgery and preferred mitral valve clipping. One month after the uncomplicated procedure the MR grade was reduced to 3 and the NYHA functional class improved to I. Because of the low risk he was excluded from the main analysis. All other patients (78% male, mean age of 75.9 ± 9.0 years) were in NYHA functional class III (89%) or IV (11%) before the procedure and four patients (44%) had atrial fibrillation. The aetiology of MR was functional (56% ischaemic, 44% non-ischaemic), with an MR grade of ≥ 3 in all patients. Mean LVEF was 28.0 ± 13.5%, LVEDD 62.4 ± 8.0 mm, and the RVSP 43.9 ± 12.1 mmHg. Mean logistic EuroSCORE was estimated at 33.8 ± 9.0%. Baseline characteristics are shown in Table I. Echocardiographic characteristics at baseline are listed in Table II.

Procedural and in-hospital results

Overall procedure time, defined as the time from femoral vein access to sheath removal, was 207 ± 63 minutes, with the last three procedures being performed within three hours. The clip was implanted successfully in all nine patients. Partial clip detachment from the anterior mitral leaflet occurred in one patient. This was recognized at the 24-hour post-procedure TTE and a second clip was placed five days later, with a good final result. The patient was discharged two days later without clinical events related to the clip detachment. One patient (the first enrolled) developed femoral bleeding which required blood transfusion (two units packed cells). No other complications occurred. Mean hospitalization time was seven days, with a maximum of 15 days for the patient who received a second clip. Procedural and in-hospital characteristics are shown in Table III.

Table I. Baseline characteristics (n=9)

Sex	
Female	2 (22.2)
Male	7 (77.8)
Age (years)	75.9 ± 9.0
BMI (kg/m^2)	24.5 ± 3.4
Blood pressure (mmHg)	
Systolic	128.2 ± 21.6
Diastolic	74.7 ± 11.1
NYHA class (I/II/III/IV)	0/0/8/1
QoL index	62.9 ± 16.3
6 MWT (m)	237.6 ± 74.4
Medication	
Loop diuretic	9 (100)
Spironolactone	6 (67)
ACEI/ARB	6 (67)
Beta-blocker	3 (33)
Coumadin	6 (67)
Aspirin	4 (44)
Laboratory	
Hb (mmol/l)	7.8 ± 1.3
Creatinine (μmol/l)	155.8 ± 50.5
eGFR (ml/min)	41.1 ± 12.6
Log NT-pro-BNP (pg/ml)	8.3 ± 1.0
ECG	
Rhythm (SR/AF/PM)	4 (44)/4 (44)/1 (11)
QRS width (ms)	164.4 ± 26.3
LBBB	5 (56)
Haemodynamics (mmHg)	
PAP systolic	43.6 ± 14.0
PAP diastolic	19.0 ± 4.4
PAP mean	25.0 ± 8.1
EuroSCORE (%)	
Standard	11.9 ± 1.3
Logistic	33.8 ± 9.0
MR aetiology	
Functional	9 (100)
Ischaemic	5 (56)
Non-ischaemic	4 (44)
Degenerative	0

Data presented as n (%) or mean ± SD.
n, number; BMI, Body Mass Index; NYHA, New York Heart Association; QoL, Quality of life; 6 MWT, Six-minutes walking test; ACEI, angiotensine converting enzyme Inhibitor; ARB, angiotensine receptor blocker; Hb, haemoglobin; eGFR, estimated glomerular filtration rate; Log NT-Pro-BNP, Logarithmic NTerminal-pro-brain natriuretic peptide; ECG, electrocardiogram; SR, sinus rhythm; AF, atrial fibrillation; PM, pacemaker rhythm; LBBB, left bundle branch block; PAP, pulmonary artery pressure; MR, mitral regurgitation.

Table II. Echocardiographic and clinical follow-up characteristics.

	Baseline	Day 3	p (vs baseline)	Day 30	p (vs baseline)
Echocardiography					
LVEDD (mm)	62.4 ± 8.0	62.8 ± 6.5	0.75	61.6 ± 8.7	0.82
LVESD (mm)	53.7 ± 9.9	55.1 ± 8.9	0.53	52.8 ± 9.9	0.93
LVEDV (ml)	193.0 ± 63.1	214.8 ± 85.0	0.21	194.9 ± 93.2	0.03
LVESV (ml)	146.8 ± 66.3	165.4 ± 85.6	0.29	139.8 ± 76.4	0.11
LVEF (%)	28.0 ± 13.5	27.2 ± 14.2	0.82	30.6 ± 12.9	0.86
LA volume index (ml/BSA)	40.7 ± 13.6	35.5 ± 11.4	0.42	51.1 ± 7.9	0.12
LA dimension (mm)	47.3 ± 4.2	48.0 ± 6.2	0.61	45.9 ± 4.5	0.19
MR grade (1/2/3/4)	0/0/3/7	3/5/1/1	0.002	3/4/2/0	0.001
MR/LA area (%)	48.2 ± 16.7	30.9 ± 16.0	0.004	23.4 ± 8.5	0.007
RVSP (mmHg)	43.9 ± 12.1	35.5 ± 13.4	0.01	31.6 ± 11.7	0.009
RA pressure (mmHg)	6.3 ± 2.3	5.6 ± 1.8	0.35	6.3 ± 2.3	0.60
NYHA class (I/II/III/IV)	0/0/8/1	-	-	3/3/1/2	0.04
QoL index	62.9 ± 16.3	-	-	49.9 ± 30.7	0.12
Lab					
Log NT-Pro-BNP (pg/ml)	8.3 ± 1.0	-	-	8.7 ± 1.2	0.26

Data presented as n or mean ± SD.
LVEDD, Left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume, LVESV, left ventricular end-systolic volume; LVEF, Left ventricular ejection fraction; LA, left atrium; MR, mitral regurgitation; RVSP, right ventricular systolic pressure; RA, right atrium; NYHA, New York Heart Association; QoL, quality of life; Log NT-Pro-BNP, Logarithmic N Terminal-pro-brain natriuretic peptide.

Follow-up results

Eight patients (89%) were discharged with a reduction in MR severity to ≤ 2 (p=0.002). MR versus LA area decreased significantly from 48.2 ± 16.7% to 30.9 ± 16.0% on day three (p=0.004) and to 23.4 ± 8.5%, 30 days after the procedure (p=0.007). At one month follow-up, seven patients (78%) had MR ≤ 2 (p=0.001 vs. baseline) and one patient experienced a recurrence of MR grade 3. RVSP decreased significantly from 43.9 ± 12.1 to 31.6 ± 11.7 mmHg (p=0.009), without change in LV geometry and function. There was no difference in log NT-pro-BNP before and one month after the procedure (8.3 ± 1.0 vs. 8.7 ± 1.2 pg/mL, p=0.26).

Six patients (67%) improved to NYHA functional class I or II, two patients (22%) had no change in NYHA class, and one patient with refractory heart failure worsened to NYHA class IV (Figure 4). Overall non-significant improvement of QoL was seen after one month (p=0.12). As a result, the diuretic dose could be reduced in four patients, one month after the procedure. During short-term follow-up, no procedure-related complications occurred. Echocardiographic and clinical follow-up results are listed in Table II.

Table III. Procedural en in-hospital characteristics

Clips, n (%)	
Total	10
1 per patient	9 (90)
2 per patient	1 (10)
Procedure time (min)	207 ± 63
Radiation time (min)	50.2 ± 12.7
Radiation dose (Gy/cm^2)	309 ± 97
Hospitalization (days)	
Total	7 (4-15)
ICU	1.5 (1-6)
Complications, n (%)	
Major bleeding	1 (10)
Partial clip detachment	1 (10)

Data presented as n (%) or mean ± SD or median (range).
n, number; min, minutes; Gy, Gray; ICU, intensive care unit.

Figure 1. The Mitraclip® device.

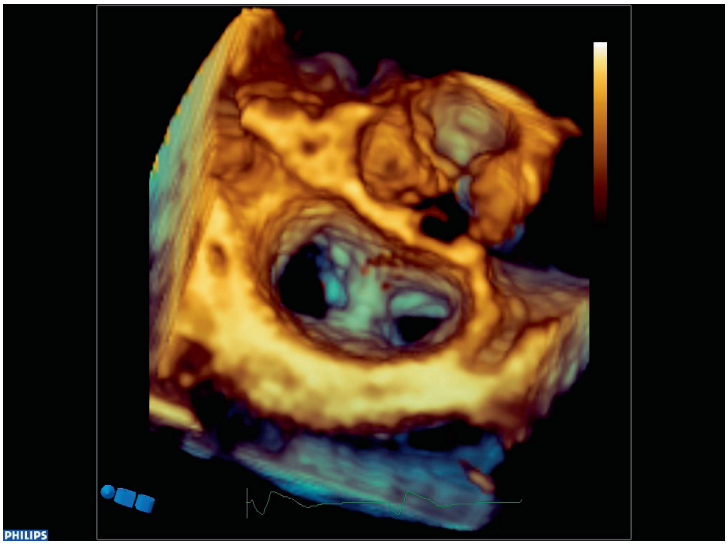

Figure 2. Three-dimensional TEE image showing a double-orifice after successful clip placement.

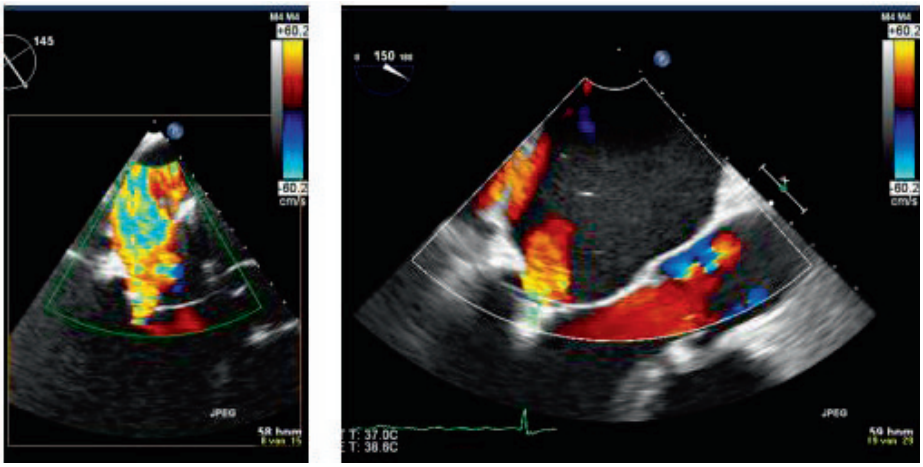

Figure 3. Two-dimensional TEE image before (left side) and after (right side) mitral valve clipping showing a reduction in MR.

The MitraClip® repair device (Evalve Inc., Menlo Park, CA, USA) was used in all patients. The device consists of a metal clip, covered with polyester to stimulate leaflet-to-leaflet healing. The clip is "V-shaped", has a diameter of 4 mm in closed position and a grasping span of about 2 cm when the two arms are opened. On the inner portion of the arms there are two grippers which "capture" the leaflets and ensure stabilization from the atrial aspect (Figure 1). The clip is mounted on a tri-axial guiding and delivery catheter system which is steerable in medial-lateral and anterior-posterior direction. The clip delivery system was advanced into the left atrium after a standard transseptal puncture and intravenous heparine was administered to maintain an activated clotting time above 300 sec. The clip was centred over the mitral orifice, the arms were opened and rotated perpendicular to the line of leaflet coaptation, above the origin of the MR-jet. Then the clip was advanced into the left ventricle and retracted during systole, grasping the mitral valve leaflets creating a double orifice (Figure 2). The clip was partially closed and the quality of the grasp, the position of the clip, and the reduction of MR was thoroughly assessed by TEE (Figure 3). When the result was suboptimal, the clip arms were re-opened and a second attempt was undertaken. After adequate reduction of MR and adequate clip positioning, the clip was closed and detached from the delivery catheter.

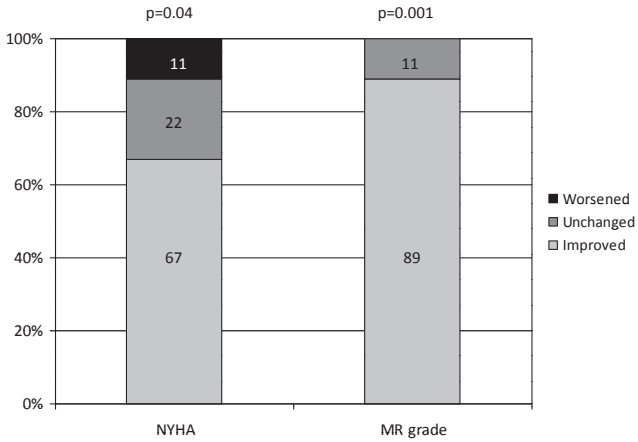

Figure 4. Change in NYHA class and MR grade at one month of follow-up.

Discussion

We report the safety and efficacy of percutaneous mitral valve repair using the edge-to-edge technique in a high-risk population who were not candidates for conventional surgery. Our results indicate that even in this specific population, a high procedural success rate, a low complication rate, and improvement in functional capacity can be obtained. Today, the different guidelines (ESC/ACC/AHA) do not recommend mitral valve surgery for patients with an ejection fraction of 30% or less and associated comorbidity (Class IIb, Level of evidence C).[11, 12] The treatment of MR in such patients is a common clinical dilemma. Operative mortality has been reported between 5 and 18% with two-year survival rates of 70% and five-year survival rates of 61%.[13-16] However, recent studies have shown that valve surgery does not improve survival in patients with LV dysfunction.[17, 18] Therefore, different percutaneous techniques were developed, offering an alternative treatment for MR in patients who are poor candidates for surgery.[7, 19, 20]

One of the recent developments is the edge-to-edge technique using a clip. St Goar and colleagues demonstrated for the first time that this technique can be performed successfully on the beating heart in a porcine model.[21, 22] Adequate tissue response

and healing with complete encapsulation of the clip was demonstrated[23] and it has been hypothesized that the clip-initiated tissue bridge may help prevent future annular dilatation.[24] The six-month follow-up of the first phase I clinical trial, EVEREST I (Endovascular Valve Edge-to-Edge Repair Study) has been reported.[7] In this study, the clip was successfully placed in 24 of 27 non-high-risk patients and 22 patients were discharged with a clip in place. There were no procedural complications and four major (18%) adverse events occurred within 30 days: post-procedural stroke due to hypotension in one patient and partial clip detachment in three patients (11%). Finally, 82% (18/22) of the patients were discharged with MR ≤ 2+. At one-month follow-up, 63% (14/22) of the patients continued with MR ≤ 2+. In our study group, partial clip detachment occurred in one patient one day after the procedure and one patient needed blood transfusion after femoral bleeding. Eight of our patients (89%) left the hospital with an improvement of MR to ≤ 2+, which was maintained at one month in seven patients (78%). We also reported an improvement in functional capacity and QoL, which was not studied in the EVEREST trial. In contrast to our study population, the patients included in the EVEREST study were all candidates for conventional surgery. Furthermore, LVEF < 30% and LVESD > 55 mm were exclusion criteria and only 59% of the patients had a history of congestive heart failure.

Recently, mid-term durability of the edge-to-edge technique in the EVEREST cohort was published.[25] A total of 107 patients were treated, 9% had a major adverse event, in another 9% partial clip detachment occurred. One year after clip placement, 66% of the patients was free from death, mitral valve surgery or MR > 2+. However, the high-risk population was not included in this cohort (median LVEF 62%, 46% in NYHA class III or IV). Our results are in line with two recent reports which showed feasibility of MitraClip® therapy in the high-risk population.[26, 27]

Limitations of our study are the small number of patients and the short follow-up time, but we continue to select patients for this type of mitral valve repair and will perform mid- and long-term follow-up regarding survival, functional capacity (including six-minutes walking test) and MR reduction. Secondly, it is an observational study, not comparing the percutaneous technique to the conventional mitral valve repair. This is currently investigated in a multicenter pivotal trial (EVEREST II). However, in this study high-risk patients were also excluded. Thirdly, the observational non-blinded design of the study might induce a placebo effect regarding the QoL questionnaire.

Conclusion

Percutaneous mitral valve repair using the edge-to-edge technique seems to be a safe and efficient alternative therapy for inoperable/high-risk patients with symptomatic MR. After one month, the majority of these patients experience an amelioration in functional class and a non-significant improvement in QoL thanks to a sustained reduction in MR.

Reference List

(1) Enriquez-Sarano M, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. *Circulation* 1995 February 15;91(4):1022-8.

(2) David TE, Ivanov J, Armstrong S, Christie D, Rakowski H. A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse. *J Thorac Cardiovasc Surg* 2005 November;130(5):1242-9.

(3) Alfieri O, Maisano F, De BM et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg* 2001 October;122(4):674-81.

(4) Umana JP, Salehizadeh B, DeRose JJ, Jr. et al. "Bow-tie" mitral valve repair: an adjuvant technique for ischemic mitral regurgitation. *Ann Thorac Surg* 1998 November;66(5):1640-6.

(5) Maisano F, Torracca L, Oppizzi M et al. The edge-to-edge technique: a simplified method to correct mitral insufficiency. *Eur J Cardiothorac Surg* 1998 March;13(3):240-5.

(6) Bhudia SK, McCarthy PM, Smedira NG, Lam BK, Rajeswaran J, Blackstone EH. Edge-to-edge (Alfieri) mitral repair: results in diverse clinical settings. *Ann Thorac Surg* 2004 May;77(5):1598-606.

(7) Feldman T, Wasserman HS, Herrmann HC et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol* 2005 December 6;46(11):2134-40.

(8) Foster E, Wasserman HS, Gray W et al. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. *Am J Cardiol* 2007 November 15;100(10):1577-83.

(9) Grayburn PA. How to measure severity of mitral regurgitation: valvular heart disease. *Heart* 2008 March;94(3):376-83.

(10) Zoghbi WA, Enriquez-Sarano M, Foster E et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003 July;16(7):777-802.

(11) Bonow RO, Carabello BA, Kanu C et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with

the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006 August 1;114(5):e84-231.

(12) Vahanian A, Baumgartner H, Bax J et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007 January;28(2):230-68.

(13) Bax JJ, Braun J, Somer ST et al. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. *Circulation* 2004 September 14;110(11 Suppl 1):II103-II108.

(14) Bolling SF, Pagani FD, Deeb GM, Bach DS. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. *J Thorac Cardiovasc Surg* 1998 February;115(2):381-6.

(15) Gillinov AM, Wierup PN, Blackstone EH et al. Is repair preferable to replacement for ischemic mitral regurgitation? *J Thorac Cardiovasc Surg* 2001 December;122(6):1125-41.

(16) Romano MA, Bolling SF. Update on mitral repair in dilated cardiomyopathy. *J Card Surg* 2004 September;19(5):396-400.

(17) Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2005 February 1;45(3):381-7.

(18) Mehra MR, Griffith BP. Is mitral regurgitation a viable treatment target in heart failure? The plot just thickened. *J Am Coll Cardiol* 2005 February 1;45(3):388-90.

(19) Mack MJ. New techniques for percutaneous repair of the mitral valve. *Heart Fail Rev* 2006 September;11(3):259-68.

(20) Schofer J, Siminiak T, Haude M et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation* 2009 July 28;120(4):326-33.

(21) Fann JI, St Goar FG, Komtebedde J et al. Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: efficacy and healing response. *Circulation* 2004 August 24;110(8):988-93.

(22) St Goar FG, Fann JI, Komtebedde J et al. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. *Circulation* 2003 October 21;108(16):1990-3.

(23) Luk A, Butany J, Ahn E et al. Mitral repair with the Evalve MitraClip device: histopathologic findings in the porcine model. *Cardiovasc Pathol* 2008 August 12.

(24) De Bonis M., Lapenna E, La CG et al. Mitral valve repair for functional mitral regurgitation in end-stage dilated cardiomyopathy: role of the «edge-to-edge» technique. *Circulation* 2005 August 30;112(9 Suppl):I402-I408.

(25) Feldman T, Kar S, Rinaldi M et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol* 2009 August 18;54(8):686-94.

(26) Franzen O, Baldus S, Rudolph V et al. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. *Eur Heart J* 2010 June;31(11):1373-81.

(27) Tamburino C, Ussia GP, Maisano F et al. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. *Eur Heart J* 2010 June;31(11):1382-9.

8

Percutaneous edge-to-edge mitral valve repair in high-surgical-risk patients: do we hit the target?

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Submitted

Abstract

Objectives: To asses the feasibility and safety of percutaneous edge-to-edge mitral valve (MV) repair in patients with an unacceptable high operative risk.

Background: MV repair for mitral regurgitation (MR) can be accomplished by use of a clip that approximates the free edges of the mitral leaflets.

Methods: All patients were declined for surgery because of a high logistic EuroSCORE (> 20%) or the presence of other specific surgical risk factors. Transthoracic echocardiography was performed before and six months after the procedure. Differences in NYHA functional class, quality of life (QoL) using the Minnesota questionnaire, and 6-minutes walking test (6-MWT) distances were reported.

Results: Fifty-five procedures were performed in 52 patients (69.2% male, age 73.2 ± 10.1 years, logistic EuroSCORE 27.1 ± 17.0%). In three patients partial clip detachment occurred, a second clip was placed successfully. One patient experienced cardiac tamponade. Two patients developed an inguinal bleeding, of whom one needed surgery. Six patients (11.5%) died during six months follow-up (five patients due to progressive heart failure and one non-cardiac death). The MR grade before repair was ≥ 3 in 100%, after six months a reduction in MR grade to ≤ 2 was present in 79% of the patients. Left ventricular (LV) end-diastolic diameter, LV ejection fraction and systolic pulmonary artery pressure improved significantly. Accompanied improvements in NYHA functional class, QoL-index, 6-MWT distances and log NT-pro-BNP were observed.

Conclusions: In a high-risk population, MR reduction can be achieved by percutaneous edge-to-edge valve repair, resulting in LV remodelling with improvement of functional capacity after six months.

Introduction

Mitral valve regurgitation (MR) is an important clinical issue as MR represents >30% of native valve diseases.[1] Patients with symptomatic MR have a poor prognosis with a 5% annual mortality rate in the absence of surgery.[2] Optimal medical management can improve symptoms of heart failure but does not affect survival.[3] Therefore, surgery is recommended by the current guidelines for patients with symptomatic severe MR or asymptomatic severe MR with evidence of left ventricular (LV) dysfunction or dilatation.[4, 5] Despite those guidelines, a recent European survey established that one-half of these patients are not referred for surgery, mainly because of advanced age and the presence of co-morbidity.[5, 6] Mitral valve (MV) repair is the preferred surgical strategy whenever feasible and is associated with lower morbidity and mortality and better preservation of LV function, compared to MV replacement.[7] Reported in-hospital mortality rates range from 1 to 2% in low-risk patients, increasing up to 25% in high-risk or elderly patients.[8, 9] Therefore, new percutaneous techniques are developed to avoid surgery in high-risk patients. The transcatheter edge-to-edge MV repair using the MitraClip® system (Abbott Vascular, Santa Clara, California, USA) creates a double MV orifice by means of a clip in the mid-portion of the two leaflets and mimics the surgical procedure introduced by Alfieri.[10] The first clinical trials with the MitraClip® showed very promising results regarding feasibility and safety of the device and functional improvement of the patient.[11-13] We report the 6-month outcomes of our patient cohort treated with this device.

Methods

Patients

Between January 2009 and November 2010, the interdisciplinary team of cardiac surgeons and cardiologists of our hospital evaluated 52 patients suitable for MitraClip® therapy. All patients had moderate-to-severe or severe (grade 3+ or 4) MR and were symptomatic or asymptomatic with LV dysfunction (ejection fraction < 60%) or LV dilatation (LV end systolic diameter > 45mm), and consequently had

an indication for intervention according to the European Society of Cardiology Task Force recommendation.[5] In addition, all patients were at high-risk for conventional surgery (logistic EuroSCORE > 20% or the presence of specific risk factors associated with excessive morbidity and mortality). Furthermore, echocardiographic parameters played a crucial role in the assessment of the suitability for clip implantation: the coaptation length had to be at least 2 mm, excessive calcification or cleft at the grasping area had to be absent, and in case of a flail leaflet, the flail gap had to be ≤ 10 mm and the flail width ≤ 15mm.[11]

All patients underwent a standard pre-procedural screening, containing physical examination, functional capacity assessment (New York Heart Association (NYHA) class and 6-minutes walk test (6-MWT)), quality of life (QoL) assessment using the Minnesota questionnaire, ECG, chest X-ray, laboratory measurements (including NT-pro-BNP), transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), coronary angiography, and right heart catheterisation.

Procedural technique

All procedures were performed as previously described.[14] In brief, the clip device system is delivered to the left atrium (LA) via a transseptal puncture, advanced into the LV and retracted during systole, grasping the MV leaflets. This results in permanent leaflet approximation and creation of a double-orifice. The clip is a 4-mm wide cobalt-chromium implant with 2 arms. On the inner portion of the clip arms are small "grippers" to secure the leaflets when the arms are closed. Correct positioning of the clip device over the mitral orifice, perpendicular to the line of leaflet coaptation, above the origin of the MR-jet is mandatory to prevent clip disengagement and to obtain an acceptable MR reduction. A second (or third) clip was placed if further reduction of MR was needed. The procedure was performed under general anaesthesia and both fluoroscopic and TEE (two- and three-dimensional) guidance.[15]

Follow-up

All peri-procedural and mid-term complications were reported. Major complications included haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure related surgical intervention, endocarditis, clip detachment, clip

dislodgement or embolization, stroke and death. Minor complications were defined as MV injury, device thrombosis, bleeding not requiring blood transfusion, femoral arteriovenous fistula formation and femoral haematoma.

Post-procedural anticoagulation management was based on an individualized protocol. All patients were discharged on aspirin 100 mg once a day for a period of six months and clopidogrel 75 mg once a day during one month. In patients on oral anticoagulant therapy before the procedure, clopidogrel was added for one month. Infective endocarditis prophylaxis was recommended for six months.

Six months after the procedure, all patients underwent clinical examination, laboratory testing, TTE, and assessment of functional capacity and QoL using the NYHA functional class, the Minnesota questionnaire and a 6-MWT.

Echocardiographic measurements

The severity of MR at baseline was assessed using a variety of parameters, according to recommendations published earlier.[16] At six months follow-up, MR severity was graded according to the technique described by Foster et al.[17] Severity scale of 1 to 4 using color flow Doppler (color flow mapping) and color flow jet area (MR-jet area/ LA area) appeared to be the best reproducible parameters. Vena contracta and regurgitant orifice were recorded if possible but not included as parameters for MR assessment because they have not been validated for a double-orifice valve. The MV orifice area was assessed using the pressure half-time method.

Other echocardiographic parameters included LV ejection fraction (LVEF), LV end-systolic and end-diastolic diameters (LVESD, LVEDD) and volumes (LVESV, LVEDV) using the biplane Simpson's method, LA dimension and volume, right ventricular systolic pressure (RVSP) using tricuspid regurgitation flow velocity, and right atrial (RA) pressure using vena cava inferior dimensions. Two expert observers performed the endpoint analysis.

Statistical analysis

Descriptive statistics were used to report patients' characteristics. Continuous variables with normal distribution are reported by mean ± standard deviation. Median and range were used when normal distribution was absent. Percentages were used to report categorical variables. Patients' data before and after the procedure were compared with Chi-square or Fisher exact test for nominal variables and independent Student's *t*-test for continuous variables. Paired samples *t*-test was used for within patient comparison of continuous variables. All tests were two sided and $p<0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS software (SPSS Inc., version 14.0 for Windows).

Results

Patient characteristics

A total of 52 patients (mean age 73.2 ± 10.1 years, 69.2% male) underwent percutaneous MV repair. Demographic and clinical characteristics are summarized in Table I. Overall, 81% of the study population had congestive heart failure with advanced NYHA class and high log NT-pro-BNP values (mean 7.9 ± 1.0 pg/ml). Moreover, the vast majority of patients had several co-morbidities which contributed to high logistic EuroSCORES (mean 27.1 ± 17.0%). All patients presented with moderate-to-severe (46.2%) or severe (53.8%) MR, mainly secondary to cardiomyopathy (90.4%). Only 5 patients (9.6%) were treated because of primary degenerative MR.

Table I. Baseline characteristics

Number	52
Age (y)	73.2 ± 10.1
Age > 75 y	24 (46.2)
Male gender	36 (69.2)
BMI (kg/m^2)	26.5 ± 4.9
Comorbidities	
Diabetes	11 (21.2)
Hypertension	34 (65.4)
COPD	14 (26.9)
Renal insufficiency*	36 (69.2)
Congestive heart failure	42 (80.8)
Coronary artery disease	35 (67.3)
Atrial fibrillation	25 (48.1)
Logistic Euroscore (%)	27.1 ± 17.0
NYHA Funtional Class	
II	1 (1.9)
III	39 (75.0)
IV	12 (23.1)
QoL index score	56.7 ± 22.3
6-MWT distance (m)	277 ± 129
Medication	
Loop diuretics	49 (94.2)
Aldosterone-antagonists	33 (63.5)
ACEI/ARB	42 (80.8)
Beta-blockers	29 (55.8)
Oral anticoagulation	34 (65.4)
Aspirin	20 (38.5)
Laboratory findings	
Haemoglobine (mmol/l)	7.9 ± 1.0
Creatinine (µmol/l)	135.0 ± 52.5
Log NT-pro-BNP (pg/ml)	7.9 ± 1.0
ECG	
Rhythm (SR/AF/PM), %	46.2/28.8/25.0
QRS width (ms)	137.1 ± 31.9
LBBB	13 (25.0)
MR severity	
3+ (moderate-to-severe)	24 (46.2)
4 (severe)	28 (53.8)
MR aetiology	
functional	47 (90.4)
Ischaemic	31 (59.6)
Non-ischaemic	16 (30.8)
degenerative	5 (9.6)

Data are presented as n (%) or mean ± SD.
*Defined as estimated glomerular filtration rate < 60ml/min/1.73m^2
y, years; BMI, Body Mass Index; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; QoL, Quality of life; 6-MWT, Six-minute walk test; ACEI, angiotensin-converting enzyme Inhibitor; ARB, angiotensin-II receptor blocker; SR, sinus rhythm; AF, atrial fibrillation; PM, pacemaker rhythm; LBBB, left bundle branch block; MR, mitral regurgitation.

Procedural and in-hospital outcome

Clip implantation was successful in 53/55 procedures (96.4%). One clip was placed in 46 patients (83.6%), 2 clips in six patients (10.9%), and 3 clips in one patient (1.8%). Three patients underwent re-intervention to have a second clip implanted. In two patients the procedure was initially unsuccessful. In the first patient, the heart appeared to be rotated in the thorax after pneumectomy. As a consequence, visualization of the septum was challenging, transseptal puncture was unsuccessful and the procedure was abandoned after puncturing the LA wall. This patient was treated successfully one month later after anatomical assessment with MRI (suspicion of triatrial heart). In a second patient, no clip was placed because the MR-jet was located too far medial to accomplish a satisfactory leaflet apposition. He was treated conservatively. One patient died in the course of a so called “rescue-clip” procedure due to cardiogenic shock and acute heart failure. This 66-year-old male with a LV ejection fraction of 15%, underwent the second clip procedure four months after the first, because of severe MR with heart failure after a non-ST-segment elevation myocardial infarction. Another patient with dilated cardiomyopathy and pulmonary hypertension died eight days after the procedure due to end-stage heart failure. In this patient, a total of three clips were implanted, of which one partially detached from the posterior leaflet during the procedure. Partial clip detachment occurred in another patient before discharge, a second clip was placed successfully one week later. One patient developed cardiac tamponade a few hours after the procedure, requiring subxiphoidal drainage. Two patients suffered from femoral bleeding at the puncture site, one needed surgery. In another patient an iatrogenic pharyngeal bleeding (requiring blood transfusion) occurred due to TEE-probe manipulation. Procedural characteristics and in-hospital complications are listed in Table II.

Table II. Procedural and in-hospital characteristics

Procedures, n	55*
Successful clip implantation, n (%)	53 (96.4)
Clips per procedure, n (%)	
0	2 (3.6)
1	46 (83.6)
2	6 (10.9)
3	1 (1.8)
Procedure time (min ± SD)	147.7 ± 69.9
Radiation time (min ± SD)	42.3 ± 21.9
Radiation dose (Gy/cm^2 ± SD)	185.7 ± 116.9
Length of hospital stay (days)	5 (3-15)†
Length of intensive care stay (days)	1 (1-6)†
In-hospital complications, n (%)	
Death	2 (3.6)‡
Cardiac	2 (3.6)
Non-cardiac	0
Cardiac tamponade	1 (1.8)
Transseptal complications	1 (1.8)
Procedure related surgical intervention	1 (1.8)
Bleeding requiring transfusion	2 (3.6)
Partial clip detachment	2 (3.6)‡
Clip embolization	0

* in 52 patients.
† data presented as median (range).
‡ one death and one partial clip detachment occurred in the same patient.
n, number; Gy, Gray.

Mid-term clinical outcome

Clinical follow-up data were available in 48 patients. One patient moved abroad and was lost to follow-up. Overall 6-month mortality was 11.5%. In addition to the two in-hospital deaths, four other patients died during follow-up. One patient died of non-cardiac cause. All others died due to progressive heart failure. Six other patients (12.5%) were rehospitalized because of worsened heart failure, needing intravenous diuretic and/or inotropic therapy. Two of these patients received a cardiac resynchronization device with defibrillator (CRT-D) during this admission. Another patient presented with ventricular fibrillation originating from an old myocardial scar, a CRT-D was implanted. Complications during follow-up are shown in Table III.

Table III. Clinical events during 6-month follow-up (n=48*), n (%)

Death	4 (8.3)
Cardiac	3 (6.3)
Non-cardiac	1 (2.1)
Mitral valve surgery	0
Stroke	0
Mitral valve endocarditis	0
Partial clip detachment	1 (2.1)
Clip embolization	0
Rehospitalization for heart failure	6 (12.5)

* Two patients died in hospital, one patient was lost to follow up, and in one patient no clip was placed.

Paired clinical data at baseline and follow-up could be obtained in the majority of patients (Table IV). NYHA functional class diminished significantly from 3.2 ± 0.4 to 2.0 ± 0.8 (p<0.001), and 84% of the patients with clinical follow-up was in NYHA class I or II (Figure 1). Five patients (11.4%) did not improve in NYHA class. A QoL index score reduction from 56.5 ± 21.9 to 39.4 ± 20.5 (p<0.001) was observed. Furthermore, log NT-pro-BNP decreased from 7.7 ± 1.0 pg/ml to 7.1 ± 1.2 pg/ml (p<0.001). As a result of the improved functional capacity, 6-MWT distances increased from 300 ± 108 to 339 ± 120 meters (p=0.02).

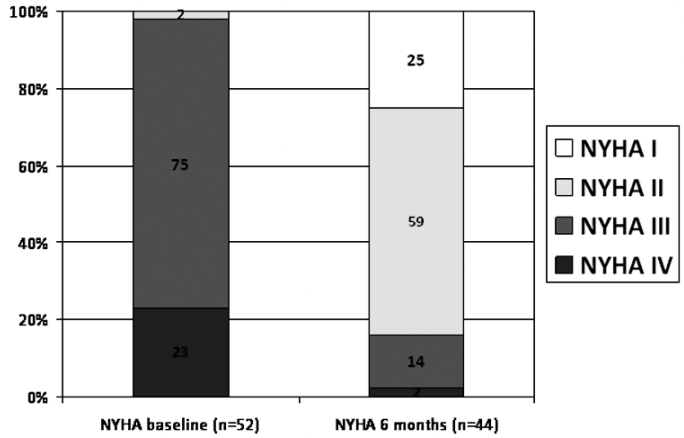

Figure 1. Change in NYHA functional class.

At baseline, 98% of the patients was in NYHA class III or IV. Six months after clip repair, 84% of the patients was in NYHA class I or II.

Table IV. Paired comparison of baseline and 6-month functional and echocardiographic characteristics

	n	Baseline	6 months	p-value
NYHA functional class	44	3.2 ± 0.4	2.0 ± 0.8	<0.001
QoL index score	44	56.5 ± 21.9	39.4 ± 20.5	<0.001
6-MWT distance (m)	31	300 ± 108	339 ± 120	0.02
Log NT-pro-BNP (pg/ml)	38	7.7 ± 1.0	7.1 ± 1.2	<0.001
Echocardiographic parameters	42			
LVEDD (mm)		63.9 ± 10.3	61.9 ± 10.2	0.01
LVESD (mm)		54.0 ± 12.8	52.9 ± 13.0	0.35
LVEDV (ml)		184.0 ± 72.4	172.9 ± 83.9	0.08
LVESV (ml)		123.2 ± 65.3	114.4 ± 74.7	0.07
LVEF (%)		36.6 ± 14.1	39.3 ± 14.2	0.05
LA volume index (ml/BSA)		62.6 ± 23.8	49.8 ± 20.1	0.001
LA dimension (mm)		49.4 ± 6.3	49.0 ± 7.9	0.7
MR grade		3.5 ± 0.5	1.7 ± 0.8	<0.001
MR/LA area (%)		50.7 ± 15.5	26.4 ± 13.1	<0.001
RVSP (mmHg)		38.8 ± 13.1	31.1 ± 10.9	0.001
RA pressure (mmHg)		7.9 ± 3.8	5.0 ± 3.8	0.005
Mean transmitral gradient (mmHg)		-	3.8 ± 2.0	
Mitral valve orifice area (cm^2)		-	2.9 ± 0.8	

Data are presented as mean ± standard deviation.
NYHA, New York Heart Association; QoL, Quality of life; 6-MWT, six-minutes walking test; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, Left ventricular ejection fraction; LA, left atrial; MR, mitral regurgitation; RVSP, right ventricular systolic pressure; RA, right atrial.

Impact on mitral regurgitation and LV remodelling

Echocardiographic follow-up could be performed in 42 patients (80.8%). Data are summarized in Table III. Overall, 40/42 patients (95.2%) had a reduction in MR with ≥ 1 grade. Only two patients did not improve and remained at grade 3+ MR. In 79% of the patients, a reduction in MR grade to ≤ 2 was achieved (Figure 2). Subsequently, RA pressure en RVSP dropped significantly. No clinical or echocardiographic signs of MV stenosis were observed during follow-up.

Compared with baseline, LVEF improved significantly from 36.6 ± 14.1% to 39.3 ± 14.2% (p=0.05). LVEDD decreased from 63.9 ± 10.3mm to 61.9 ± 10.2mm (p=0.01). The LV volumes decreased non-significantly.

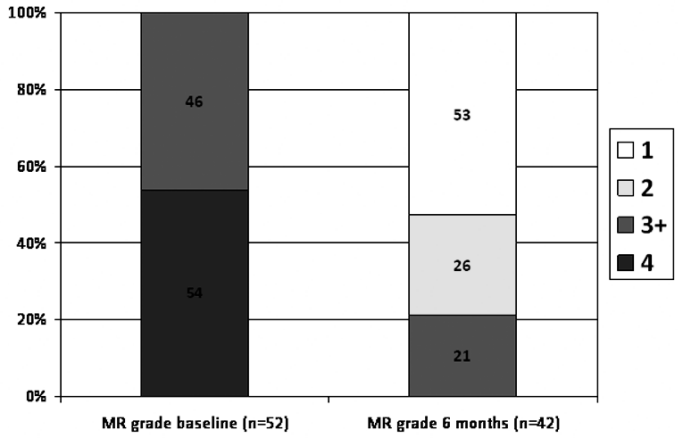

Figure 2. Change in mitral regurgiation (MR) grade.

At baseline, all patients had moderate-to-severe (grade 3+) or severe (grade 4) MR. Six months after clip implantation, 79% of the patients had MR grade ≤ 2.

Discussion

We report the largest single-centre experience for percutaneous edge-to-edge MV repair in a high-surgical-risk population. Our results indicate that this technique can be accomplished with favourable mid-term outcomes with an increase in functional capacity and improvement in echocardiographic parameters.

Patients with severe symptomatic MR might develop progressive heart failure, which is often refractory to medical therapy. Without intervention, these patients have an annual rate of death of 5% or more.[18] Especially for patients with functional MR and poor LV function, there are no widely accepted indications for surgery other than as a concomitant procedure at the time of bypass surgery, but its benefits have been variable and outcomes suboptimal.[4, 5, 19, 20] The peri-procedural mortality rates described in surgical series varies between 2.1% and 11% in patients with depressed LV function, and as high as 25% in very high-risk or elderly patients.[21, 22] In our study, including high-risk patients with poor LV function, we report an in-hospital mortality of 3.8%. Two patients who were treated in our early experience phase died in-hospital

due to end-stage heart failure. Reviewing those cases we must conclude that the risk-benefit ratio for percutaneous repair was suboptimal. Therefore, a stringent selection process is mandatory, including a guideline-supported indication for intervention and extensive pre-procedural echocardiographic assessment. In the presence of myocardial fibrosis and irreversible LV adverse remodelling, MR reduction may not provide any benefit.[19, 23] Therefore gadolinium-enhanced and dobutamine stress magnetic resonance imaging might be helpful for patient selection.

In the recent published EVEREST II trial (Endovascular Valve Edge-to-Edge Repair Study II), 279 patients were randomized in a 2:1 ratio to undergo clip therapy or open MV surgery and showed no difference in mortality (6% in both groups) at 12-month follow-up.[24] Noteworthy, in this trial, MR of degenerative origin was predominant (73%) and mean LVEF was 60.0 ± 10.1% in the clip group. In the present study, the overall six-month mortality rate was 11.5 %. However, the mean LVEF was 37% with a predicted peri-procedural mortality rate of 27%.

Recently, Franzen et al. showed the effectiveness of MV clip therapy in an end-stage heart failure population.[25] In this multi-centre study, 50 patients (LVEF ≤ 25%, mean logistic Euroscore 34%) with functional MR were included, and at six months follow-up MR ≤ 2+ was present in 87% of the patients. In the EVEREST II trial, surgery appeared to be more effective in reducing MR compared to percutaneous repair. However, in the subgroup with functional MR (27% in both groups) surgery was not superior.[24] In our study population, including 90% functional MR, a reduction in MR of ≥ 1 grade was achieved in 95% and 79% of the patients had MR grades ≤ 2, six months after the procedure.[11-13] Despite the LV geometric distortion with concomitant annular dilatation in the majority of our patients, clip placement was successful in 96%, which is comparable with the report by Franzen et al.[25] Taken together, patients with functional MR can be treated successfully and seem to benefit most from this new technique. Moreover, Maisano et al. reported that isolated surgical edge-to-edge repair has acceptable outcomes for both degenerative and functional MR with a 5-year freedom from recurrent MR ≥2+ and reoperation of 90%.[26]

As a result of MR reduction we observed diminished plasma NT-pro-BNP levels, accompanied with significant improvements in QoL and functional capacity, which maybe the primary goal in this challenging high-risk population. The improvement

in objective parameters shows that the observed clinical effect can be attributed to improvements beyond a placebo. NYHA functional class improved in 89% of our population, which is in line with previous reports.[11, 25] The EVEREST II trial showed similar improvements in NYHA functional class and QoL in both the clip and surgery subgroups at 12 months.[24]

Of note, percutaneous MV repair seems to be associated with positive reverse LV remodelling. We report a significant increase in LVEF, decrease in LVEDD, and obvious improvements in LV volumes. The question remains if this will affect long-term prognosis, as recent reports showed no evidence that surgery for functional MR prolongs life, despite LV reverse remodelling.[27, 28]

Our findings underline the growing understanding that percutaneous approaches become a valuable treatment option for an important number of patients with severe (especially functional) MR who can not undergo surgery.[29] In the future, the field of percutaneous transcatheter MV repair will undoubtedly evolve exponentially. In our opinion, as functional MR is primary a disease of the LV, a combination of the edge-to-edge repair with other percutaneous techniques addressing the annulus and the LV itself will be necessary to provide durable correction and satisfactory long-term outcomes.[30]

Limitations

First, we acknowledge the observational, non-randomized nature of the study and the relative small number of patients. However, we continue to treat patients, not eligible for surgery, and will perform long-term follow-up to determine the true value of this new approach. Another limitation is that the follow-up echocardiograms could not be reviewed in a blinded or independent way. Furthermore, we assessed MR severity after clip placement only by MR jet-area and the MR/LA jet ratio. However, comparing these parameters pre- and post-procedure should provide a reliable perception of MR reduction.

Conclusions

Percutaneous edge-to-edge MV repair seems to be a valuable alternative for patients with severe, symptomatic MR who or no candidates for open MV surgery. We observed important reductions in MR grade in the majority of patients which contributed to positive LV remodelling with improvement of QoL and functional capacity. However, careful patient selection seems obligatory, especially in case of advanced heart failure.

Reference List

(1) Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. *Lancet* 2009 April 18;373(9672):1382-94.

(2) Agricola E, Ielasi A, Oppizzi M et al. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. *Eur J Heart Fail* 2009 June;11(6):581-7.

(3) Carabello BA. The current therapy for mitral regurgitation. *J Am Coll Cardiol* 2008 July 29;52(5):319-26.

(4) Bonow RO, Carabello BA, Kanu C et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006 August 1;114(5):e84-231.

(5) Vahanian A, Baumgartner H, Bax J et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007 January;28(2):230-68.

(6) Mirabel M, Iung B, Baron G et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J* 2007 June;28(11):1358-65.

(7) Enriquez-Sarano M, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. *Circulation* 1995 February 15;91(4):1022-8.

(8) Haan CK, Cabral CI, Conetta DA, Coombs LP, Edwards FH. Selecting patients with mitral regurgitation and left ventricular dysfunction for isolated mitral valve surgery. *Ann Thorac Surg* 2004 September;78(3):820-5.

(9) Tribouilloy CM, Enriquez-Sarano M, Schaff HV et al. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. *Circulation* 1999 January 26;99(3):400-5.

(10) Alfieri O, Maisano F, De Bonis M. et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg* 2001 October;122(4):674-81.

(11) Feldman T, Kar S, Rinaldi M et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol* 2009 August 18;54(8):686-94.

(12) Franzen O, Baldus S, Rudolph V et al. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. *Eur Heart J* 2010 June;31(11):1373-81.

(13) Tamburino C, Ussia GP, Maisano F et al. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. *Eur Heart J* 2010 June;31(11):1382-9.

(14) Van den Branden BJ, Post MC, Swaans MJ et al. Percutaneous mitral valve repair using the edge-to-edge technique in a high-risk population. *Neth Heart J* 2010 September;18(9):437-43.

(15) Swaans MJ, Van den Branden BJ, Van der Heyden JA et al. Three-dimensional transoesophageal echocardiography in a patient undergoing percutaneous mitral valve repair using the edge-to-edge clip technique. *Eur J Echocardiogr* 2009 December;10(8):982-3.

(16) Zoghbi WA, Enriquez-Sarano M, Foster E et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003 July;16(7):777-802.

(17) Foster E, Wasserman HS, Gray W et al. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. *Am J Cardiol* 2007 November 15;100(10):1577-83.

(18) Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol* 2003 March 1;91(5):538-43.

(19) Pierard LA, Carabello BA. Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment. *Eur Heart J* 2010 December;31(24):2996-3005.

(20) Mihaljevic T, Lam BK, Rajeswaran J et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. *J Am Coll Cardiol* 2007 June 5;49(22):2191-201.

(21) Geidel S, Lass M, Krause K et al. Early and late results of restrictive mitral valve annuloplasty in 121 patients with cardiomyopathy and chronic mitral regurgitation. *Thorac Cardiovasc Surg* 2008 August;56(5):262-8.

(22) Nowicki ER, Birkmeyer NJ, Weintraub RW et al. Multivariable prediction of in-hospital mortality associated with aortic and mitral valve surgery in Northern New England. *Ann Thorac Surg* 2004 June;77(6):1966-77.

(23) Di Salvo TG, Acker MA, Dec GW, Byrne JG. Mitral valve surgery in advanced heart failure. *J Am Coll Cardiol* 2010 January 26;55(4):271-82.

(24) Feldman T, Foster E, Glower DG et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011 April 14;364(15):1395-406.

(25) Franzen O, Van der Heyden JA, Baldus S et al. MitraClip(R) therapy in patients with end-stage systolic heart failure. *Eur J Heart Fail* 2011 May;13(5):569-76.

(26) Maisano F, Vigano G, Blasio A, Colombo A, Calabrese C, Alfieri O. Surgical isolated edge-to-edge mitral valve repair without annuloplasty: clinical proof of the principle for an endovascular approach. *EuroIntervention* 2006 August;2(2):181-6.

(27) Diodato MD, Moon MR, Pasque MK et al. Repair of ischemic mitral regurgitation does not increase mortality or improve long-term survival in patients undergoing coronary artery revascularization: a propensity analysis. *Ann Thorac Surg* 2004 September;78(3):794-9.

(28) Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2005 February 1;45(3):381-7.

(29) Bach DS, Awais M, Gurm HS, Kohnstamm S. Failure of guideline adherence for intervention in patients with severe mitral regurgitation. *J Am Coll Cardiol* 2009 August 25;54(9):860-5.

(30) Chiam PT, Ruiz CE. Percutaneous transcatheter mitral valve repair: a classification of the technology. *JACC Cardiovasc Interv* 2011 January;4(1):1-13.

9.1

Re-do mitral valve clipping after partial clip detachment

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JACC Cardiovasc Interv **2010 February;3(2):251-2**

A 45-year-old male patient, with a history of an ischaemic cardiomyopathy, peripheral arterial disease, and renal dysfunction, was admitted for percutaneous mitral valve repair. Cardiac magnetic resonance imaging showed an ejection fraction of 18% without viability. Severe mitral regurgitation (MR) occurred due to left ventricular annular dilatation and restriction of the posterior leaflet (Figure 1). Consequently, an important reduction in functional capacity (New York Heart Association class 3) was present. He was declined for surgery because of a predicted operative mortality rate of 36% (logistic EuroSCORE) and accepted for the percutaneous approach.

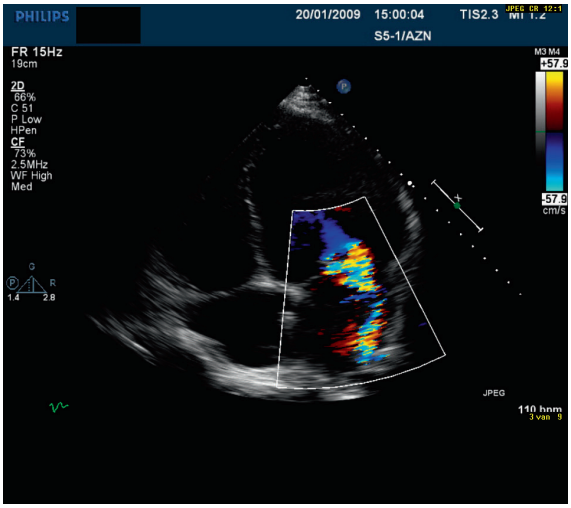

Figure 1. Two-dimensional 4-chamber transthoracic echocardiographic image showing a severe, eccentric MR jet.

There is an important mitral regurgitation (MR) (color jet), due to left ventricular annular dilation and restriction of the posterior mitral valve leaflet. Consequently, the MR jet is orientated to the posterolateral wall of the left atrium and almost reaches the right upper pulmonary vein.

The procedure was performed under general anaesthesia and guided with fluoroscopy and transesophageal echocardiography (3D-TEE, Philips probe, transducer X7-2t, Philips Healthcare, Best, the Netherlands). Access was gained using the right femoral vein, and after transseptal puncture the clip delivery system was advanced into the

left atrium. The clip was successfully delivered into the left ventricle just below the mitral valve annulus and retrieved in the center of the maximal jet of the MR, which was located medial to the center of the annulus. After grasping the mitral valve leaflet edges, the clip was closed and released, creating a double mitral valve orifice. Unfortunately, 24 h later, transthoracic echocardiography showed clip detachment from the anterior mitral leaflet (Figure 2A) without reduction in MR (Figure 2B).

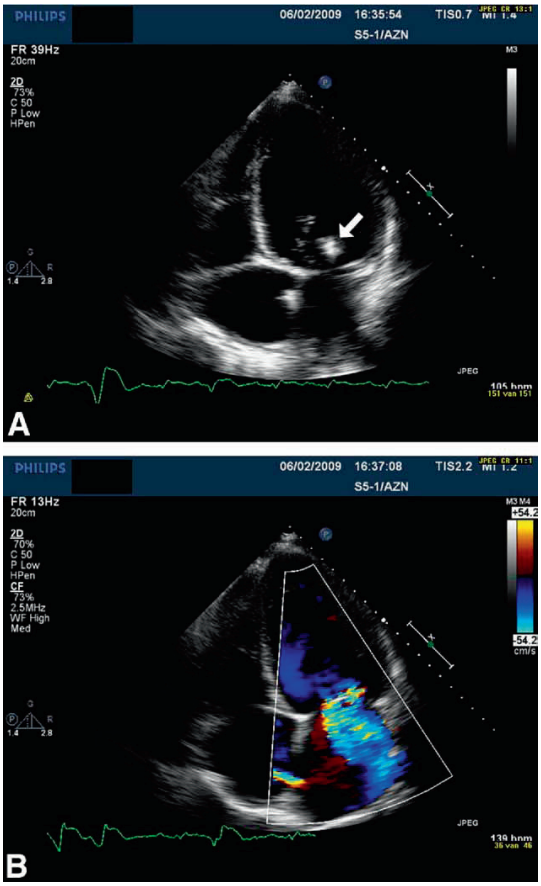

Figure 2. Two-dimensional 4-chamber TTE image after partial clip detachment.

(A) *This image shows clip detachment from the anterior mitral valve leaflet. The clip (arrow) is only attached to the posterior mitral valve leaflet.* ***(B)*** *With color Doppler imaging, an even more important MR is recognized, with an MR jet area accounting for more than one-half of the left atrium area. An iatrogenic atrial septum defect is seen after transseptal puncture. Abbreviations as in Figure 1.*

A second clip was placed more centrally to maintain a better coaptation of the two leaflets (Figure 3).

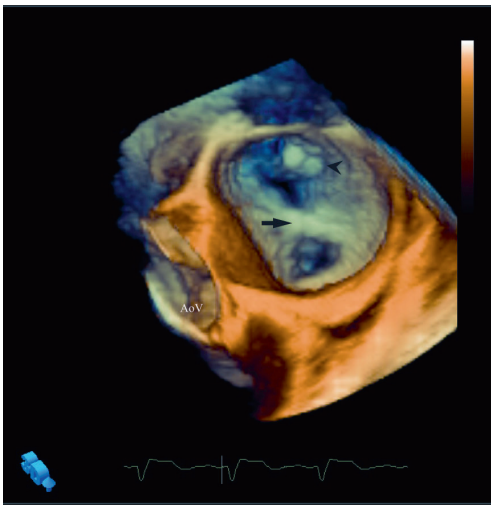

Figure 3. Three-dimensional transesophageal echocardiography image after successful placement of the second clip.
The first clip (arrowhead) is only attached to the posterior mitral valve leaflet. The second clip (arrow) was placed more centrally, creating a double-orifice mitral valve.

The procedure was uneventful, and echocardiography confirmed adequate positioning of the second clip with substantial reduction in MR (Figure 4). Reviewing the echocardiographic studies, the first clip was positioned too far to the medial (P1-A1) coaptation line. The selection of this position was guided upon what we assumed to be the maximum jet of regurgitation. Obviously, the real maximum jet was originating more lateral. Most probably, favoring the medial site, insufficient leaflet insertion was obtained. The patient was discharged 5 days later without clinical events related to the clip detachment. At one month, echocardiography showed mild MR (grade 2), unfortunately without clinical improvement. Because of persistent heart failure, he received a biventricular implantable cardioverter-defibrillator 3 months later.

Theoretically, partial clip detachment holds an increased risk of endocarditis, thrombus formation, and clip dislodgment with embolization. Therefore, we treated the patient with warfarine and clopidogrel. Furthermore, lifelong endocarditis prophylaxis was advised. At six months follow-up no such complications did occur, which is in line with recent findings of the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) trial investigators.[1]

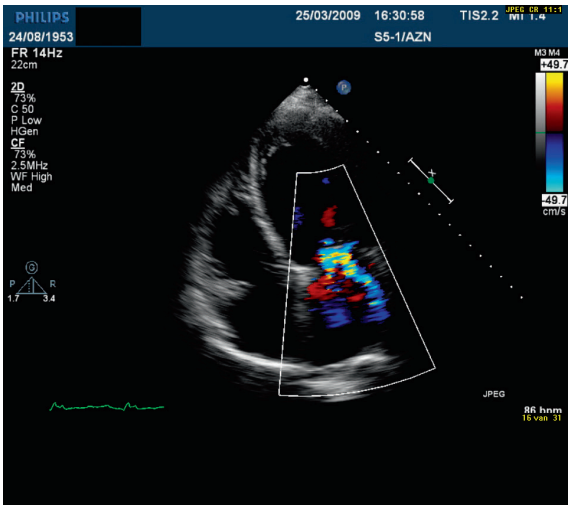

Figure 4. Two-dimensional 4-chamber TTE image shows reduction in MR after second clip placement.

This figure shows the final result in a 4-chamber TTE view. There is an obvious reduction in MR. Placement of the second clip has resulted in a central coaptation of the leaflets with a double orifice, creating two small MR jets.

Abbreviations as in Figure 1.

Reference List

(1) Feldman T, Kar S, Rinaldi M et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol* 2009 August 18;54(8):686-94.

9.2

Three-dimensional transesophageal echocardiography in a patient undergoing percutaneous mitral valve repair using the edge-to-edge clip technique

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Eur J Echocardiogr **2009 December;10(8):982-3**

Abstract

We report a case of percutaneous mitral valve repair, using the Mitraclip® device, in which we show that application of real-time three-dimensional transesophageal echocardiography (3D-TEE) is extremely helpful for the guidance of this procedure. Because of its excellent visualization capacities, 3D-TEE simplifies the transseptal puncture, the positioning of the clip above the mitral valve orifice, the grasping of the mitral valve leaflets, and the evaluation of the final result. Therefore, we conclude that 3D-TEE has the potential to increase the safety and efficacy of this new technique to treat mitral regurgitation in patients who cannot undergo conventional valve surgery.

Surgical mitral valve repair is the preferred therapy for severe mitral regurgitation (MR). In cases of unacceptable high peri-operative risk, percutaneous mitral repair using a clip (Mitraclip™, Evalve Inc., Menlo Park, USA) may be an alternative approach.[1, 2] The first phase I clinical trial showed safety and feasibility of this technique.[3] The clip device system is delivered to the left atrium via a transseptal puncture and enables placement of a clip on the mitral valve leaflets, resulting in permanent leaflet approximation similar to the approximation achieved with the suture-based edge-to-edge repair technique to create a double-orifice mitral valve.[4] Correct positioning of the clip device over the mitral orifice, perpendicular to the line of leaflet coaptation, is mandatory to prevent clip disengagement and to obtain an acceptable MR reduction. Therefore, guiding with fluoroscopy and both transthoracic (TTE) and transesophageal echocardiography (TEE) are required. We added three-dimensional TEE (3D-TEE, Philips probe, transducer X7-2t, Philips Healthcare, Best, the Netherlands) imaging to optimize the guiding during the procedure and to evaluate the anatomic result and residual MR.

A 82-year-old female patient was admitted for elective percutaneous mitral valve repair. She was known with a dilated cardiomyopathy due to chronic, severe MR. Left ventricular ejection fraction was estimated at 35%. Echocardiography revealed a left ventricular end-diastolic diameter of 70 mm with significant annular dilatation. She had developed pulmonary hypertension with a mean pulmonary artery pressure of 35 mmHg and consequently experienced an important and progressive reduction in functional capacity (New York Heart Association class 4). Her predicted operative mortality rate was 27%, using the logistic EuroSCORE. She was declined for surgery.

The procedure was performed under general anaesthesia. At the beginning of the procedure, color Doppler 2D-TEE showed a severe central MR due to annular dilatation (Figure 1).

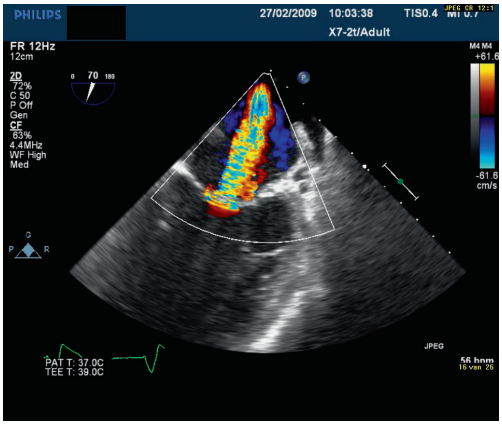

Figure 1. Mid-commissural 2D-TEE view showing the severe, central MR-jet due to left ventricular annular dilatation.

After transseptal puncture, the clip delivery system was centred above the mitral orifice and advanced into the left ventricle, just below the free edges of the leaflets (Figure 2). Correct positioning was improved using live 3D-TEE guidance. While the clip was retracted, the leaflets were grasped during systole.

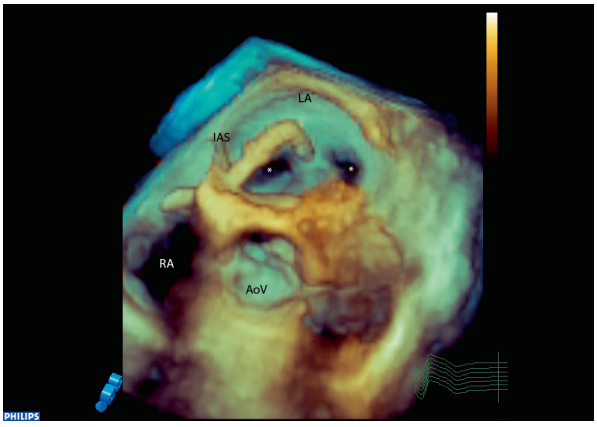

Figure 2. 3D-TEE full-volume view showing the advancement of the clip delivery system from the right atrium (RA) to the left atrium (LA) via transseptal puncture and the creation of the double mitral valve orifice (asterisks) after grasping the mitral valve leaflets. The clip is still attached to the catheter. IAS, interatrial septum; AoV, aortic valve.

When correct positioning was confirmed by echocardiography, the clip was closed, creating a double mitral valve orifice (Figure 3).

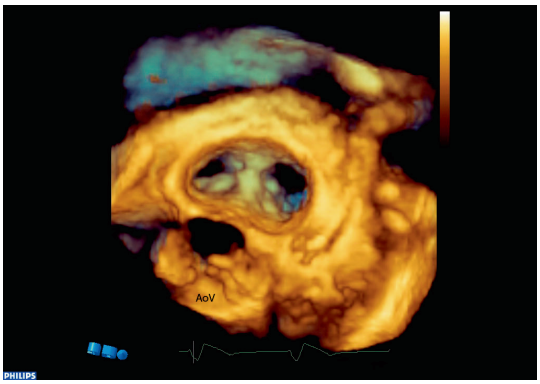

Figure 3. 3D-TEE image after successful clip placement with achievement of a double orifice. AoV, aortic valve.

Color Doppler echocardiography showed an adequate reduction in MR at the end of the procedure (Figure 4). The patient was discharged in improved condition four days later.

This case demonstrates that adding 3D-TEE for percutaneous mitral valve repair simplifies the guiding procedure and should contribute to a higher success rate of this new technique.

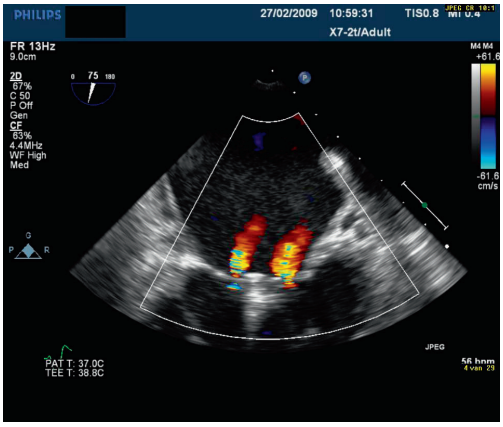

Figure 4. Mid-commissural 2D-TEE view showing a significant reduction in MR after successful clip placement.

Reference List

(1) Fann JI, St Goar FG, Komtebedde J et al. Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: efficacy and healing response. *Circulation* 2004 August 24;110(8):988-93.

(2) St Goar F, Fann JI, Komtebedde J et al. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. *Circulation* 2003 October 21;108(16):1990-3.

(3) Feldman T, Wasserman HS, Herrmann HC et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol* 2005 December 6;46(11):2134-40.

(4) Maisano F, Torracca L, Oppizzi M et al. The edge-to-edge technique: a simplified method to correct mitral insufficiency. *Eur J Cardiothorac Surg* 1998 March;13(3):240-5.

Part five

General discussion

10

General discussion

Patent foramen ovale management

Despite extensive diagnostic evaluation, the cause of ischaemic stroke remains undefined in approximately 40% of patients, referred to as cryptogenic stroke.[1, 2] After the initial reports by Lechat et al. and Webster et al. in 1988, numerous observational studies, but not all, have suggested the association between cryptogenic stroke due to a paradoxical embolism and PFO.[3-8] Therefore, the question remains whether this is an association by chance or a true cause-and-effect relationship. Although the combination of cryptogenic stroke and PFO has been more convincingly demonstrated in patients less than 55 years of age, in patients with an atrial septal aneurysm (ASA), and in patients with a large PFO, these associations have not been observed consistently.[9-11] For example, Handke et al. demonstrated the association of cryptogenic stroke and PFO in older patients.[12] In support of PFO as a conduit for paradoxical embolization, there are numerous case reports demonstrating venous thrombi trapped within the PFO.[13, 14]

Because in healthy people with a PFO, embolic events are not more frequent than in control subjects (only 2% of all PFOs become symptomatic), no primary prevention is currently recommended.[15] However, once a thromboembolic event occur in patients with PFO, the risk of recurrence is substantial (annual rates varying from 1.5% to 12% depending on the population studied) and secondary prevention becomes an issue.[16] Treatment choices include medical therapy with antiplatelet agents or anticoagulants, percutaneous device closure or open surgical repair. Surgical closure has lost its indication as an isolated procedure, but is still performed during cardiac surgery for another reason.[17, 18] The choice between medical therapy and percutaneous closure has been the subject of intense debate over the past several years. The risk of the treatment has to be weighed against the risk of stroke recurrence in the individual patient. The Lausanne study reported a TIA/stroke recurrence of 3.8% in 140 patients with a PFO irrespective of treatment type (antiplatelet, anticoagulant or closure).[19] In the PFO/ASA study, Mas et al. prospectively studied 581 cryptogenic stroke patients, 37% had a PFO, 1.7% had an ASA, and 9% had both.[20] All patients were treated with 300 mg aspirin daily. There were no differences in annual stroke and death rate between patients with PFO (1.5%) and patients without PFO (1.8%), but

the risk of stroke recurrence was significantly higher in case of an associated ASA. The authors concluded that patient with PFO and ASA were insufficiently protected by aspirin alone. In the prospective PICSS (Patent Foramen Ovale in Cryptogenic Stroke Study), a substudy of the randomized WARSS (Warfarin-Aspirin Recurrent Stroke Study), 250 patients with cryptogenic stroke (39% with PFO) were treated with aspirin or warfarin.[21] During follow-up of two years, neither the presence or the size of the PFO, nor the coincidence of an ASA was found to adversely affect the rate of recurrent stroke or death. In patients with cryptogenic stroke and PFO, there was a trend toward primary event reduction with warfarin compared with aspirin (9.5% vs. 17.9%, relative risk=0.52; 95% CI 0.16-1.67, p=0.3), though the study was not adequately powered for this specific comparison. Cujec et al. retrospectively analyzed 90 cryptogenic stroke patients and reported higher recurrence rates of cerebral ischaemic events in patients with PFO compared to those without PFO (12% vs. 5%).[22] Interestingly, warfarin appeared to be more effective than aspirin for secondary stroke prevention.

On the other hand, major bleeding risk, particularly from the use of warfarin, is estimated at 1% to 2% annually and minor bleeding risk 10% to 20%, higher in those on warfarin compared with aspirin.[23, 24] Other limitations of medical treatment are the lack of compliance and the contraindication in certain circumstances. Reviewing the aformentioned trials, the American Academy of Neurology concluded that PFO alone is not associated with an increased risk of subsequent stroke or death in patients who have had a cryptogenic stroke and are treated medically.[25] Furthermore they stated that both PFO and ASA possibly increase the risk of recurrent stroke in medically treated patients younger than 55 years and that the evidence is insufficient to determine if warfarin or aspirin is superior in preventing recurrent stroke. Both the American Heart Association/American Stroke Association (AHA/ASA) and American College of Chest Physicians (ACCP) guidelines recommend antiplatelet therapy for patients with ischaemic stroke or TIA and PFO (AHA/ASA Class IIa, Level of Evidence B; ACCP grade 1A).[26, 27] There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin (AHA/ASA Class IIb, Level of Evidence B) unless other indications exist for anticoagulant therapy (AHA/ASA Class IIa, Level of Evidence C; ACCP grade 1C).[28, 29]

Effectiveness of percutaneous PFO closure

Percutaneous PFO closure is suggested as an alternative or an additive to medical therapy for secondary prevention of recurrent stroke. The use of a double-umbrella device was first described by Bridges et al. in 1992.[30] Since then, interest in PFO closure is rising, and numerous reports have shown the feasibility and efficacy of this technique. In one of the largest series to date, Wahl et al. reported an annual recurrence rate of thromboembolic events of 1.1% in 525 patients.[31] Our group found a 2.5% yearly recurrence rate of embolic events in 83 patients using two different devices (Amplatzer® and Cardioseal/Starflex®).[32] In a multicenter study published by Luermans et al., the recurrence rate of neurologic events was 3% per year in 430 patients treated with the Intrasept® device.[33] Wöhrle summarized the outcomes of 8 studies comprising 998 patients treated medically and 12 studies comprising 2016 patients who underwent percutaneous closure.[34] The annual rate of TIA/stroke was lower after percutaneous closure compared with medically treated patients (1.3% vs. 5.2%). Khairy et al. performed a systematic review of 10 studies of percutaneous closure (1355 patients) and 6 studies of medical therapy (895 patients).[35] They found a 1-year rate of recurrent neurologic thromboembolism during medical treatment of 3.8% to 12% compared to 0% to 4.9% after device closure. However, this review was limited because the treatment in de “medical” arm was not uniform and this arm contained older patients with a higher cardiovascular risk profile. In another report, Windecker et al. compared the risk of recurrent stroke in 308 patients with PFO and showed a strong trend in favour of percutaneous PFO closure compared to medical therapy (7.8% vs. 22.2% after 4 years, p=0.08).[36] When percutaneous closure was compared with aspirin alone, differences became significant (8.5% vs. 28.3%, p=0.03). In addition, percutaneous closure was superior to medical treatment in patients with complete PFO occlusion and in patients with more than one neurologic event at baseline. Schuchlenz et al. studied 280 patients treated with antiplatelets (n=66), anticoagulation (n=47), or percutaneous closure (n=167). The annual rate of recurrent TIA/stroke was lowest after percutaneous closure (0.6%) compared with anticoagulation (5.6%) and antiplatelets (13%).[37] The only randomized data so far were presented in 2010 by Furlan.[38] In the CLOSURE I trial, 909 patients were randomized equally to PFO closure using the Starflex® device (as well as six months aspirin and

clopidogrel) or the best medical therapy (aspirin or warfarin or a combination). At two years, the primary endpoint of stroke or TIA did not differ between the device group and the medically treated group (3.1% vs. 3.4% for stroke and 3.3% vs. 4.6% for TIA). Major vascular complications and atrial fibrillation were significantly more common in the device group (3.2% vs. 0% for vascular complications ($p<0.001$) and 5.7% vs. 0.7% for atrial fibrillation ($p<0.001$) respectively). Because the trial has not been published until now, the data are not incorporated in the current guidelines who still state that "There are insufficient data to make a recommendation regarding PFO closure in patients with a first stroke and PFO" and "PFO closure may be considered for patients with recurrent stroke despite optimal medical therapy (Class IIb; Level of Evidence C)".[39] Several other randomized trial are ongoing (CLOSE, PC, Gore-REDUCE and RESPECT) and will hopefully provide powerful evidence for the optimal treatment of patients with cryptogenic stroke and PFO in the future.

Except from the recurrence of thromboembolic events, residual shunting after percutaneous PFO closure can be another expression of the incomplete closure after device implantation. Residual shunting has been reported between 0-20%, and even up to 49% in some studies.[40-47] The variability is undoubtedly due to differences in imaging techniques for shunt detection, definitions of residual shunting, follow-up time and the use of different closure devices. After device implantation, most PFOs will be closed completely within the expected endothelialisation period of two to three months, but a minority close between six and twelve months post-procedure.[48] Large PFOs, large closure devices and an ASA have been proposed as predictors for the occurrence of residual shunt.[49-51] Small defects do not appear to have any clinical significance and may close late.[52] Continuation of antiplatelet therapy is recommended in case of residual shunt. Moderate-to-severe residual shunts have been associated with an increased risk of recurrent thromboembolic events.[53, 54] Currently, the residual shunt subgroup represents a specific challenge. Recently, Majunke et al. presented their experience with repeat PFO closure.[55] Forty patients with a moderate-to-severe residual shunt on TEE had a second device implanted with a success rate of 98%. Complete closure was achieved in 69% of the patients during a mean follow-up of 36 ± 29 months, but only three patients had a residual shunt which was more than mild. One patient who received three devices died due to cardiac

tamponade. Diaz et al. treated 20 patients for the same indication.[56] The procedure was successful in 95% of the cases and all but one patient showed complete defect closure after six months.

Safety of percutaneous PFO closure

Growing experience with better materials and devices has decreased the complication rate of this technique. Major complications such as death, emergent surgery, severe bleeding, tamponade or fatal pulmonary embolism occur in about 1.5% of the patients.[57] Minor complications such as supraventricular arrhythmias, device embolization, device thrombosis, minor bleeding, ECG changes, and arteriovenous fistula are reported in approximately 8%.[58] Thrombus formation on the device seems to be device-specific and has become rare (< 0.5%) in newer generation devices.[59] New-onset atrial arrhythmias are reported in 7% to 15% of the patients and tend to occur in the first months after the procedure and are usually transient with spontaneous conversion to sinus rhythm.[60] A potential additional long-term adverse effect of an implanted device containing nitinol (nickel and titanium), is nickel allergy and hypersensitivity which can occur in up to 15% of the population.[61] However, this seems not to be a relevant clinical issue.

New devices in percutaneous PFO closure : the old and the beautiful?

To further improve the safety of percutaneous PFO closure and to overcome some of the potential complications, conventional closure devices are continuously improved and as the PFO has a tunnel-like anatomy, more "PFO-specific" devices and techniques are under investigation. The objective is to close the PFO-tunnel without leaving bulky material in the right and left atrium potentiating thrombus formation, erosion, and arrhythmias. Another benefit might include long-term retention of transseptal access for ablative therapy and treatment of mitral valve disease.

Bioabsorbable device

Jux ea. introduced the BioSTAR® closure device (NMT Medical, Boston, USA), which consists of a totally biodegradable matrix (porcine acellular collagen), accelerating rapid neo-endothelialization and a natural healing of the defect.[62] The matrix is

mounted on the Starflex® framework and is the only part of the device which stays behind. The idea is to beget "septal defect repair" instead of "septal defect occlusion". Mullen et al. described the first clinical application in the prospective, multicenter BioSTAR® evaluation study (BEST).[63] The bioabsorbable device was implanted in 54 patients with PFO and in four patients with a small ASD. They reported no major complications, five patients (9%) developed a supraventricular tachycardia (SVT), and one patient developed a mobile thrombus which resolved after treatment with oral anticoagulation. The closure rate at six months assessed by cTTE was 96%, but they did not incorporate small shunts. In a report by Ussia ea., 23 patients were treated with the bioabsorbable device.[64] In one patient (4%) the device had to be retrieved because of malpositioning. During follow-up, one patient (4.5%) suffered haemorrhagic stroke related to double antiplatelet therapy and two patients (9%) had atrial arrhythmias. At six months, 21% had residual shunting using contrast transcranial Doppler. We described the largest single-centre series of PFO closure with the bioabsorbable device.[65] Although we found an acceptable safety profile (3.2% major complications, 12.9% new-onset SVT's) this was not excelling the aforementioned results of first generation devices.[66] Regarding the efficacy of the device, we observed 3.2% recurrent TIAs and 23.7% residual shunts (including small shunts) after six months. Moreover, in a direct head-to-head comparison with the Cardioseal® device, we found no differences regarding safety and efficacy, with a non-significant higher percentage of moderate shunts in the bioabsorbable device group (11% vs. 2%, p=0.17).[67] We concluded that the natural healing induced by the bioabsorbable device in human may take more time than initially observed in animal models.[68] Recently, Duong-Hong et al. reported about a double umbrella septal occluder which is made of totally bioabsorbable polymers.[69] Two devices were inserted in pigs by open thoracotomy and showed complete endothelialization without residual shunt after one month. Examination of the explanted devices however, revealed moderate inflammatory response and thrombus formation in de gaps between the two disks. Another concept tested in a swine model, is the Biodisk® (Cook Medical, Bloomington, IN, USA), consisting of two nitinol wire components covered with a platinum coil, a flexible ring (single disk) with a cross bar covered by porcine small intestinal submucosa and an anchor with delivery bar.[70]

The self-expanding disk is deployed in the left atrium and pulled back against the interatrial septum, then the delivery catheter is withdrawn to expand the anchor in the right atrium. Device implantation was successful in all 12 animals and histological examination showed appropriate endothelialization and neo-intima formation. At four months, the matrix was nearly completely remodelled with only minimal foreign body reaction.

Occlutech Figulla device

The Occlutech Figulla® PFO occluder (Occlutech GmbH., Jena, Germany) was launched as a modification of the Amplatzer® PFO occluder (AGA Medical, Plymouth, Minnesota, USA). The novelty is the use of a unique braiding technology which allows a 50% reduction of meshwork material (in a single layer) on the left atrial disk.[71, 72] This should contribute to greater flexibility, better property of self-centring in the defect and a reduced risk of thrombus formation at the left atrial side. We analyzed 48 patients who received an Occlutech Figulla® device in our centre.[73] We observed no periprocedural complications. In-hospital, 8.3% of the patients developed an inguinal haematoma. During 6-month follow-up, no major complications did occur and 13.3% of the patients experienced an atrial arrhythmia. Most striking was the high percentage of residual shunting (total 30.2%, minimal 25.6%, moderate 4.6%). Our results are in line with recent data by Saguner et al. who reported 39% residual shunting in 20 patients who underwent PFO closure with the Occlutech Figulla® device.[74] We agree with their presumption that the single flat layer left atrial disk may unfold incompletely with suboptimal positioning at the septum as it is folded in a “tulip-like” fashion in the delivery sheath. The lower risk of thrombus formation with this device should be assessed by TEE in a larger population with longer follow-up. A trial overview of PFO closure using the bioabsorbable device and the Occlutech Figulla® device is summarized in Table I.

Table I. Outcome, complications and efficacy using the BioSTAR and the Occlutech device for PFO closure.

Author	Year	Device	N	FU (mo)	Complications (%)		Residual Shunt (%)	TE (%)
					Total	Major		
Mullen[75]	2006	BioSTAR	58	6	10.3	0	4	0
Ussia[76]	2009	BioSTAR	23	8	17.4	4.5	21	0
Vd Branden[77]	2010	BioSTAR	62	6	27.4	3.2	23.7	3.2
Krizanic[78]	2008	Occlutech	36	6	5.6	2.8	11.8	2.9
Krizanic[79]	2010	Occlutech	29	6	0	0	3.7	0
Vd Branden[80]	2010	Occlutech	48	6	20.8	0	30.2	0
Saguner[81]	2011	Occlutech	20	6	15	10	39	0

N, number; FU, follow-up; mo, months; TE, thromboembolism after PFO closure.

Other devices

Beside the modification of first generation devices, three new "in-tunnel" PFO closure techniques have been proposed: the SeptRX® device (Nitinol Devices and Components, Fremont, CA, USA) and the Coherex Flat stent® (Coherex Medical, Salt Lake City, UT, USA) are both advanced in the PFO tunnel and stabilized with anchors. The PFx closure system (Cierra, Redwood City, CA, USA) uses radiofrequency energy to close the PFO without leaving behind any foreign material. The SeptRX® device is designed to fit directly into the PFO tunnel and consists of a self-expanding nitinol frame with flexible anchors at the top, surrounding a fine-wired nitinol mesh which should stimulate the natural adhesion response. In the first-in-man trial, 13 patients underwent device implantation, of which two were unsuccessful due to the anatomy of the PFO.[82] In the other patients full closure was observed at six months without adverse events. The Coherex Flatstent® consists of a nitinol frame covered with polyurethane foam and is also anchored within the PFO tunnel where it expands to bring the septum primum and septum secundum into contact. Experimental studies showed its feasibility.[83] In 2009 the results of 49 successfully treated patients were presented. Embolization of the device occurred in three patients and at six months, complete closure was achieved in 94% of the patients (non-published data). The PFx closure system employs monopolar radiofrequency thermal energy to effectuate PFO closure by welding the tissues of the septum primum and septum secundum together

without leaving a permanent implant in the heart. Preclinical animal studies showed excellent scar formation with formation of collagen and normal tissue remodelling at four weeks.[84] Sievert et al. published a prospective multicenter study, in which 144 patients with an indication for PFO closure were included.[85] Successful application of radiofrequency energy was achieved in 130 patients (90%). There were no device-related complications. Unfortunately, the overall closure rate was only 55% at six-month follow-up. In small diameter PFOs (< 8mm), the closure rate was 72%. During the study, modifications were made to the catheter to improve device positioning which resulted in higher closure rates with the second generation catheters. In two patients with residual shunt, a TIA occurred during follow-up. The authors stated that the radiofrequency-based closure technique is safe but that closure rates are lower compared with implant devices which necessitates further refinements in material and procedural aspects. Another new transcatheter PFO closure strategy is the suture-based technique, mimicking the standard surgical method of closing a PFO. A catheter is introduced to puncture, capture, and suture the septum primum and septum secundum. The suture is made of nonabsorbable polypropylene and a clip is used to fix the suture. The first-in-human procedures showed feasibility and safety of this new approach.[86, 87] However, despite a decrease in right-to-left shunt in all 11 patients, complete closure was achieved in only one patient.[88]

Conclusions and future directions

In our opinion, available evidence and common sense strongly favour causation rather than association between PFO and the risk of stroke. One could even question the attribute “cryptogenic” to a stroke that occurs without another identifiable aetiology. Percutaneous closure represents a valuable treatment option, particularly in high-risk patients, because it addresses the cause of paradoxical embolization. Available data from observational studies, registries, and systematic reviews show lower event rates after PFO closure, compared to medical therapy. The only randomized trial reported similar reoccurrences of TIA and stroke, but was, in our opinion, underpowered. Therefore, we have to await the results of the ongoing

randomized studies. We propose a very careful evaluation and selection of patients who can benefit from PFO closure. For example, we believe that there is no doubt to close the PFO in a young patient who has suffered a major stroke, has no vascular risk factors, but has a PFO with ASA and an underlying coagulopathy.
New techniques for percutaneous PFO closure are under extensive investigation with varying success up till now. Although "device-free" PFO closure is theoretically desirable, from a practical point of view there are some obstacles to overcome. Further modifications of these techniques will hopefully lead to more durable results. Finally, randomized trails will be required to compare new strategies with the implantation of permanent devices.

Atrial septal defect management

The indications for closure and the choice of treatment are much more clear for the secundum type atrial septal defect (ASD) compared to PFO. According to the current European guidelines, percutaneous device closure is the method of choice whenever applicable (Class I, Level of evidence C).[89] Morphologic characteristics amenable for device closure includes a stretched diameter < 38 mm and sufficient rim of tissue of at least 5 mm except towards the aorta. This is the case in about 80% of patients.

Effectiveness of percutaneous ASD closure
Currently, the Amplatzer® septal occluder (ASO) is one of the most frequently used devices worldwide with high procedural success (>90%) and favourable long-term results.[90-92] In comparative studies, the ASO performed generally better than the Cardioseal/Starflex® device with a higher percentage of complete ASD closure during follow-up.[93-95] The overall residual shunt rate after ASD closure varies between 0% and 46%, and for the ASO between 0% and 23%.[96-101] Percutaneous ASD closure results in improvements of right and left ventricular functions, symptoms and exercise capacity.[102-105]

Safety of percutaneous ASD closure

Studies comparing surgical and transcatheter closure have reported similar mortality, but morbidity was lower and hospital stay shorter after percutaneous closure.[106, 107] The possible complications during and after percutaneous ASD closure are mostly the same as those in percutaneous PFO closure. Two large studies from the early days demonstrated complication rates from 4% to 8%, mainly attributed to device embolization and arrhythmias.[108, 109] More recent reports showed lower and probably more realistic major complication rates below 2%.[110, 111] Device malposition or embolization appear to be device-related and are the most frequent reasons for surgical intervention.[112-114] Erosion of the atrial wall or the aorta as well as thromboembolic events appear to be very rare.[115, 116] Post-procedure arrhythmias occur early and are mostly self-limiting.[117] The incidence of conduction abnormalities and heart block is low.[118, 119]

New devices in percutaneous ASD closure

In contrast to PFO closure, innovations in ASD treatment are less obvious because the hole has to be closed mechanically, so one will probably always need a patch or a closure device. In the past years a few new devices have been proposed, mainly modifications of existing devices, in order to lower the complication risk. The BioSTAR® device was introduced by Jux et al. who stated that the bioabsorbable matrix of the device is an attractive concept, especially for ASD closure in the pediatric age group.[120] They showed an accelerated healing response with higher early closure rates using the bioabsorbable device (n=26) compared with the Starflex® device (n=10) after ASD closure in sheep.[121] Hoehn et al. presented there experience with the biodegradable device, implanted in nine children with an ASD and in one child with a fenestrated Fontan baffle.[122] Mean defect size was 10.2 mm using balloon inflation for size assessment. They reported no adverse events and complete closure of all defects after 30 days. Morgan et al. reported comparable closure rates for the bioabsorbable device and the ASO in children with ASD diameters < 16 mm.[123] In our opinion, the bioabsorbable device could be of value in a pediatric population with small defects, but the achievement of adequate closure of larger defects in adults is unlikely.

Another new device for ASD closure is the Occlutech Figulla® ASD occluder (FSO). The construction technique and the objectives are the same as for the aforementioned Occlutech Figulla® PFO Occluder.[72] The appearance and the implantation technique are similar to those of the ASO, but again there is an important reduction of material on the left atrial side. As summarized in Table II, most reports showed favourable results regarding efficacy and safety.[124-127] In our first description of 34 ASD patients we also found a very acceptable safety profile with 100% implantation success, no major complications, 8.8% atrial arrhythmias, 1.2% transient ST elevation and 14.7% groin haematomas.[128] On the other hand, a relatively high percentage of residual shunts was observed (total 32.5%, moderate 14.7%, large 2.9%). Compared to the ASO, the FSO should theoretically be associated with less device related complications such as thrombus formation and atrial rhythm disturbances. Therefore we retrospectively compared both devices (ASO, n=132; FSO, n=53) and found slightly more new-onset rhythm disturbances in the FSO group (7.5% vs. 3.8%).[129] Furthermore, there were more femoral haematomas in the FSO group (9.4% vs. 2.3%), probably because the FSO requires a larger delivery catheter and because we used more intracardiac echocardiography to guide the procedure, which requires bilateral vein puncture. An important finding was the excess of residual shunts (mainly small) in the FSO group after six months (39.5% vs. 10.6%) which could be related to the smaller right atrial disc of the FSO device. Another explanation might be that the FSO device has only 15 different available sizes compared to 27 different sizes for the ASO, making the selection of the appropriate size more difficult, with a higher probability of undersizing. Other studies found residual shunt rates between 0% and 1.5% with the important limitation that they only used the color Doppler technique, which could lead to underdiagnosis.[130-133] On the other hand, the most important goal in an ASD with right heart volume overload is to eliminate the left-to-right shunt, except in case of cryptogenic stroke. Only in the FSO treated patient with a large residual shunt on contrast-TTE, a left-to-right shunt was observed using color Doppler. We did not observe any thrombus formation on both device types. The risk of thrombus formation on the ASO in known to be very low (<1%), so it will be a challenge for the FSO to perform better.[134, 135] Hence, we are not convinced that the FSO is ready to replace the ASO in percutaneous ASD closure. A prospective randomized trial with larger groups and longer follow-up is needed to draw definite conclusions.

Table II. Outcome, complications and efficacy using the Occlutech device in ASD closure.

Author	Year	N	FU (mo)	Complications (%)		Residual Shunt (%)	TE (%)
				Total	Major		
Pac[136]	2009	33	6	15	3	0*	0
Ilkay[137]	2010	28	6	14.3	0	0*	0
Krizanic[138]	2010	12	6	0	0	0*	0
Cansel[139]	2011	68	6	2.9	0	1.5*	0
Vd Branden[129]	2011	53	6	22.6#	3.8	39.5	0

N, number; FU, follow-up; mo, months; TE, thromoboembolism after ASD closure.
*using Color Doppler; #including 9.5% minimal femoral haematomas

Conclusions and future directions

Nowadays, percutaneous closure is the treatment of choice in secundum type ASDs. Available data provide enough evidence that this procedure can be performed with a high success rate, low complication rate and that it results in improvement of functional capacity and cardiac function. The ASO is associated with the best clinical outcomes until now. Future device designs should focus on a combination of reliable defect closure and minimization of the amount of material in the right and the left atrium.

Transcatheter treatment of mitral valve regurgitation

Patients with severe symptomatic mitral regurgitation (MR) have a poor prognosis with an annual mortality rate of 5% without surgical intervention.[140, 141] Moreover, mortality can be as high as 60% at 5 years when associated with significant heart failure.[142] Medical management of MR is limited to controlling symptoms of heart failure. Mitral valve (MV) surgery is still the treatment of choice, but has been associated with high operative mortality in patients with advanced age, co-morbidities, and reduced left ventricular (LV) function.[143] As a result, the vast majority of these patients currently do not undergo surgery and are treated conservatively.[144] Importantly, many of such patients are repeatedly hospitalized for heart failure and they experience a poor quality of life. This underserved group of patients opens the

door for a variety of less invasive transcatheter concepts.[145] Most of these techniques parallel surgical approaches and target the various components of the MV complex.

Percutaneous edge-to-edge mitral valve repair

Of all available percutaneous techniques, the edge-to-edge repair using the MitraClip® (Abbott Vascular, Santa Clara, California, USA) is most advanced in terms of clinical investigation. The technique mimics the surgical procedure introduced by O. Alfieri approximately 15 years ago, which creates a double MV orifice by means of a few stitches securing the leaflets together at their mid-part.[146] In most patients, annuloplasty is performed in conjunction with leaflet repair. However, Maisano et al. published a 12-year follow-up report of patients treated with isolated edge-to-edge repair, which suggested the feasibility of a transcatheter application and proof of principle for this technique.[147] The MitraClip® system uses a tri-axial catheter system with a clip device at its distal tip. After transseptal puncture, the clip is advanced in the LV and retracted to grasp both MV leaflets. After echocardiographic confirmation of adequate positioning and sufficient MR reduction, the clip is released. The safety and feasibility of the clip technique was shown in a porcine model.[148, 149]

Efficacy of the edge-to-edge technique

The initial clinical experience was reported by Feldman et al. in the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) phase I safety and feasibility trial.[150] Reductions in MR were achieved in most patients: 64% of patients were discharged with MR ≤ 2+ after one month and 93% of these patients had sustained MR reduction after six months. Thereafter, data on 107 patients (55 patients from the EVEREST I and 52 roll-in patients from the EVEREST II study) demonstrated acute MR reduction ≤ 2+ at discharge in 74% of the patients.[151] At 12 months, clinical symptoms were improved in 74% of the patients. The composite primary efficacy endpoint (freedom from MR ≥ 2+, MV surgery and death at 12 months) was 66%. The recently published EVEREST II trial randomized 279 patients in a 2:1 ratio to undergo percutaneous repair or conventional surgery.[152] Clip therapy appeared to be less effective compared to surgery: the rate of surgery for MV dysfunction was 20% vs. 2.2% ($p<0.001$) and there was a greater improvement in MR reduction in the surgery group ($p<0.001$).

Interestingly, age ≥ 70 years and functional MR were identified as parameters for patients in which surgery was not superior with regard to efficacy. Furthermore, in the intention-to-treat analysis, clinical outcomes (NYHA class, quality of life and LV dimensions) improved in a similar way in both groups. Noteworthy, patients included in the EVEREST trials had a low-risk profile for surgery with a mean LV ejection fraction (LVEF) of 60-62% and low rates of associated co-morbidities. In addition, only 21% of the patients in EVEREST I and 27% of the patients in EVEREST II had functional MR.

First reports of clip therapy in high-surgical-risk patients came from two European groups, who presented their short-term outcomes. Tamburino et al., implanted a clip in 31 patients (81% male, median age 71 years, mean logistic EuroSCORE 14.3 ± 11.9%) of which 58% presented with functional MR.[153] Acute MR reduction ≤ 2+ was achieved in 96.8% of the patients. At 30 days, all patients were at NYHA functional class I/II with significant improvements in pulmonary artery pressures and LV dimensions. Franzen et al. selected 51 patients (67% male, mean age 73±10 years) who were judged as high-risk for conventional surgery.[154] The mean logistic EuroSCORE was 28 ± 22%, mean LVEF 36 ± 17% and 69% had functional MR. In two-thirds of the patients a reduction in MR by two or three grades was observed which resulted in NYHA class I or II. In our first short-term follow-up report we described the effects of clip therapy in 9 high-risk patients (78% male, mean age 75.9 ± 9.0 years and mean logistic EuroSCORE 33.8 ± 9.0%) and found similar outcomes.[155] At 30 days, 78% of the patients had sustained reduction of MR ≤ 2+ with significant improvements in pulmonary artery pressure and NYHA functional class.

Franzen et al. recently showed the effectiveness of MV clip therapy in an end-stage heart failure population.[156] In this multi-centre registry (including our centre), 50 patients (76% male, mean age 70 ± 11 years, mean logistic EuroSCORE 34%, mean LVEF 19 ± 5%) with functional MR were included and 94% of them were treated successfully. Six months after the procedure, a reduction in MR to ≤ 2+ was seen in 27/31 patients (87%) in association with significant improvements in functional capacity (assessed with 6-minutes walking tests), NT-pro-BNP levels and LV geometry. Of the 32 patients with clinical follow-up, 23 (72%) had improved to NYHA class I or II. Our second follow-up study of 52 high-risk patients (mean logistic EuroSCORE 27.1 ± 17.0%, 90.4% functional MR) demonstrated efficacy results which were in line with

the report by Franzen et al. Procedural success was 96.4%. Reduction in MR of ≥ 1 grade was achieved in 95.2% of the patients and 79% had MR grades ≤ 2 after six months.[157] Furthermore, significant improvements in 6-minutes walking distances, NT-pro-BNP, systolic pulmonary artery pressures and LV function were noticed.
To summarize, the percutaneous edge-to-edge technique is a valuable treatment option in high-risk patients who are denied for open heart surgery. Successful clip placement can be achieved in the majority of patients and is associated with improvements in quality of life and functional capacity. Furthermore, the adequate MR reduction seems to be associated with positive LV remodelling, which is regarded as a major determinant of long-term prognosis.

Safety of the edge-to-edge technique

In the EVEREST I, there was no procedural mortality and the in-hospital mortality was < 1% (one patient on mechanical ventilation subsequently died).[151] Kaplan-Meier freedom from death was 96%, 94%, and 90% at 1, 2, and 3 years, respectively. Ten patients (9%) experienced a major adverse event (MAE) at 30 days, including a nonprocedural death. Three patients had a transseptal complication of which one required blood transfusion and two required surgery. After 30 days, partial clip detachment had occurred in 10 patients (9%), none of them was associated with urgent intervention. Despite the lower efficacy, clip therapy demonstrated superior safety compared with surgery in the EVEREST II trial.[152] At 30 days, MAE had occurred in 15% of the clip patients and in 48% of the operated patients ($p<0.001$). These differences were mainly driven by the lower incidence of blood transfusions in the clip arm.
Tamborino et al. reported a cardiac tamponade after transseptal puncture and a non-cardiac death, resulting in a primary safety endpoint of 93.6%.[153] Franzen et al. did not observe any periprocedural complications.[154] Thirty-day mortality was 2% (one patient died of pneumonia, another of end-stage heart failure). During follow-up they reported two partial clip detachments, two ruptures of a minor chorda, and two groin haematomas (all 3.9%). In the heart failure report by Franzen et al., the Kaplan-Meier freedom from death was 81.2% and 76.9% at six months, and at ten months respectively.[156] The deceased patients tended to be older and in a more advanced

stage of heart failure (the cumulative survival at six months was only 64.2% in NYHA IV patients). Of 38 successfully treated patients, 58% were re-hospitalized for heart failure. In our analysis of 52 patients, overall survival was 88.5% at six months.[157] All six patients, except from one, died of progressive heart failure. Two patients (3.6%) experienced partial clip detachment and were successfully treated with a second clip.[158] One patient (1.8%) suffered from cardiac tamponade, one needed surgery for a femoral bleeding (1.8%), and two other patients required blood transfusion (3.6%). Outcomes of the several trials are listed in Table III.

Conclusions and future directions

Various minimal invasive technologies are emerging in interventional cardiology and cardiac surgery. The desire for less invasive approaches, coupled with the fact that a significant proportion of patients with co-morbidities or advanced age are not referred for surgery, has driven the field of transcatheter valve therapy. However, percutaneous techniques for the treatment of MR remain largely investigational. The most supportive evidence to date comes from the edge-to-edge clip technique. Procedural safety of this technique has been demonstrated. Most complications are primarily related to either cardiac catheterization in general or the transseptal puncture. The most important device-related complication is partial clip detachment. No association with clip embolization, endocarditis or thrombus formation has been observed until now. The randomized EVEREST II trial showed superior safety for clip therapy compared to surgery. Nevertheless, careful patient selection seems obligatory, especially in advanced heart failure. We have to await long-term follow-up results to reveal whether this technique will offer an effective and durable repair. Several other techniques, including various direct and indirect annuloplasty and LV remodelling devices, have achieved first-in-human results. Especially the annuloplasty technique, which use the coronary sinus to “push” the posterior annulus anteriorly, seems attractive because of the simplicity of the approach, but is also subject to several potential limitations. Though, this technique can certainly be of value in patients with an appropriate anatomic relation between coronary sinus, circumflex coronary artery and MV annulus. In direct annuloplasty, the annulus is reshaped directly via the left atrium or LV with anchors which are pulled together or with radiofrequency energy

to cause constriction of the annulus. A fundamental problem for the treatment of functional MR is the associated LV geometric distortion. Therefore, techniques are currently tested to remodel the LV, for example by introducing a transventricular bridge between pads which are placed anterior and posterior and drawn together. Other novel concepts are in the earliest stages of development, like beating heart chordal replacement and percutaneous MV replacement.

Most likely, a combination of percutaneous techniques (for example the edge-to-edge technique and annuloplasty), will be required for satisfactory and durable results. Furthermore, it will be necessary to evaluate new interventions separately in degenerative and functional MR, as these are two different entities. Overall, it is unlikely that these techniques will reproduce the results of surgical repair, but they will provide a good alternative for the growing population who cannot undergo surgery.

An intense collaboration between interventional cardiologists, cardiac imaging experts, and cardiac surgeons will become more imperative in the future to succeed. Ultimately, these new techniques should be carefully compared with conventional surgery and conservative medical treatment. Only than we can offer the individual patient the appropriate treatment.

Table III. Outcomes, safety and efficacy of percutaneous edge-to-edge mitral valve repair.

Author	Year	N	FU (mo)	Age (y)	Logistic EuroSCORE (%)	Procedural success (%)	MR reduction* ≤ 2+ (%)	NYHA class improvement (%)	LV remodelling	Complications (%) Total	Complications (%) Major	Mortality* (%)
Feldman[108]	2009	107	12	71	-	90	66	74	-	18	9	4.1
Franzen[111]	2010	51	1	73	28.0	96	94[#]	90[#]	-	18	0	2.0
Tamburino[110]	2010	31	1	71	14.3	100	97	100	Yes	6.4	3.2	3.2
Franzen[113]	2011	50	6	70	34.0	94	87	72	Yes	-	-	16.0
Feldman[109]	2011	184	12	67	-	-	82	90	Yes	-	15.0[¶]	6.0
Vd Branden[114]	2011	52	6	73	27.1	96	79	84	Yes	13.5	7.7	11.5

* at maximal follow-up duration; [#] at discharge; [¶] at one month
N, number; FU, follow-up; mo, months; y, years; MR, mitral regurgitation; NYHA, New York Heart Association; LV, left ventricle.

Reference List

(1) Hart RG, Miller VT. Cerebral infarction in young adults: a practical approach. *Stroke* 1983 January;14(1):110-4.

(2) Sacco RL, Ellenberg JH, Mohr JP et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol* 1989 April;25(4):382-90.

(3) Lechat P, Mas JL, Lascault G et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988 May 5;318(18):1148-52.

(4) Webster MW, Chancellor AM, Smith HJ et al. Patent foramen ovale in young stroke patients. *Lancet* 1988 July 2;2(8601):11-2.

(5) Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000 October 24;55(8):1172-9.

(6) Petty GW, Khandheria BK, Meissner I et al. Population-based study of the relationship between patent foramen ovale and cerebrovascular ischemic events. *Mayo Clin Proc* 2006 May;81(5):602-8.

(7) Meissner I, Khandheria BK, Heit JA et al. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. *J Am Coll Cardiol* 2006 January 17;47(2):440-5.

(8) Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002 June 4;105(22):2625-31.

(9) Bonati LH, Kessel-Schaefer A, Linka AZ et al. Diffusion-weighted imaging in stroke attributable to patent foramen ovale: significance of concomitant atrial septum aneurysm. *Stroke* 2006 August;37(8):2030-4.

(10) Steiner MM, Di Tullio MR, Rundek T et al. Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. *Stroke* 1998 May;29(5):944-8.

(11) Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000 October 24;55(8):1172-9.

(12) Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med* 2007 November 29;357(22):2262-8.

(13) Hust MH, Staiger M, Braun B. Migration of paradoxic embolus through a patent foramen ovale diagnosed by echocardiography: successful thrombolysis. *Am Heart J* 1995 March;129(3):620-2.

(14) Nellessen U, Daniel WG, Matheis G, Oelert H, Depping K, Lichtlen PR. Impending paradoxical embolism from atrial thrombus: correct diagnosis by transesophageal echocardiography and prevention by surgery. *J Am Coll Cardiol* 1985 April;5(4):1002-4.

(15) Kraywinkel K, Jauss M, Diener HC, Weimar C. [Patent foramen ovale, atrial septum aneurysm, and stroke. An examination of the status of recent evidence]. *Nervenarzt* 2005 August;76(8):935-42.

(16) Sacco RL, Adams R, Albers G et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Circulation* 2006 March 14;113(10):e409-e449.

(17) Dearani JA, Ugurlu BS, Danielson GK et al. Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events. *Circulation* 1999 November 9;100(19 Suppl):II171-II175.

(18) Homma S, Di Tullio MR, Sacco RL, Sciacca RR, Smith C, Mohr JP. Surgical closure of patent foramen ovale in cryptogenic stroke patients. *Stroke* 1997 December;28(12):2376-81.

(19) Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van MG. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. Lausanne Stroke with Paradoxal Embolism Study Group. *Neurology* 1996 May;46(5):1301-5.

(20) Mas JL, Arquizan C, Lamy C et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001 December 13;345(24):1740-6.

(21) Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002 June 4;105(22):2625-31.

(22) Cujec B, Mainra R, Johnson DH. Prevention of recurrent cerebral ischemic events in patients with patent foramen ovale and cryptogenic strokes or transient ischemic attacks. *Can J Cardiol* 1999 January;15(1):57-64.

(23) Go AS, Hylek EM, Chang Y et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 2003 November 26;290(20):2685-92.

(24) Mohr JP, Thompson JL, Lazar RM et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001 November 15;345(20):1444-51.

(25) Kizer JR, Devereux RB. Clinical practice. Patent foramen ovale in young adults with unexplained stroke. *N Engl J Med* 2005 December 1;353(22):2361-72.

(26) Sacco RL, Adams R, Albers G et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Circulation* 2006 March 14;113(10):e409-e449.

(27) Salem DN, O'Gara PT, Madias C, Pauker SG. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008 June;133(6 Suppl):593S-629S.

(28) Furie KL, Kasner SE, Adams RJ et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011 January;42(1):227-76.

(29) Salem DN, O'Gara PT, Madias C, Pauker SG. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008 June;133(6 Suppl):593S-629S.

(30) Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. *Circulation* 1992 December;86(6):1902-8.

(31) Wahl A, Kunz M, Moschovitis A et al. Long-term results after fluoroscopy-guided closure of patent foramen ovale for secondary prevention of paradoxical embolism. *Heart* 2008 March;94(3):336-41.

(32) Luermans JG, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Complications and mid-term outcome after percutaneous patent foramen ovale closure in patients with cryptogenic stroke. *Neth Heart J* 2008 October;16(10):332-6.

(33) Luermans JG, Post MC, Schrader R et al. Outcome after percutaneous closure of a patent foramen ovale using the Intrasept device: a multi-centre study. *Catheter Cardiovasc Interv* 2008 May 1;71(6):822-8.

(34) Wohrle J. Closure of patent foramen ovale after cryptogenic stroke. *Lancet* 2006 July 29;368(9533):350-2.

(35) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003 November 4;139(9):753-60.

(36) Windecker S, Wahl A, Nedeltchev K et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J Am Coll Cardiol* 2004 August 18;44(4):750-8.

(37) Schuchlenz HW, Weihs W, Berghold A, Lechner A, Schmidt R. Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale. *Int J Cardiol* 2005 May 11;101(1):77-82.

(38) Furlan A. CLOSURE I Trial: a prospective, multicenter, randomized, controlled trial to evaluate the safety and efficacy of the STARFlex septal closure system versus best medical therapy in patients with stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale. *Presented at: American Heart Association Scientific Sessions 2010, Nov 13-17, Chicago* 2010;(Abstract 21572).

(39) Furie KL, Kasner SE, Adams RJ et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011 January;42(1):227-76.

(40) Braun M, Gliech V, Boscheri A et al. Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. *Eur Heart J* 2004 March;25(5):424-30.

(41) Harms V, Reisman M, Fuller CJ et al. Outcomes after transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Am J Cardiol* 2007 May 1;99(9):1312-5.

(42) Luermans JG, Post MC, Schrader R et al. Outcome after percutaneous closure of a patent foramen ovale using the Intrasept device: a multi-centre study. *Catheter Cardiovasc Interv* 2008 May 1;71(6):822-8.

(43) Luermans JG, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Complications and mid-term outcome after percutaneous patent foramen ovale closure in patients with cryptogenic stroke. *Neth Heart J* 2008 October;16(10):332-6.

(44) Martin F, Sanchez PL, Doherty E et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation* 2002 August 27;106(9):1121-6.

(45) Post MC, Van DK, Budts W. Percutaneous closure of a patent foramen ovale: single-centre experience using different types of devices and mid-term outcome. *Acta Cardiol* 2005 October;60(5):515-9.

(46) Wahl A, Krumsdorf U, Meier B et al. Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. *J Am Coll Cardiol* 2005 February 1;45(3):377-80.

(47) Windecker S, Wahl A, Chatterjee T et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000 February 29;101(8):893-8.

(48) Harms V, Reisman M, Fuller CJ et al. Outcomes after transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Am J Cardiol* 2007 May 1;99(9):1312-5.

(49) Greutmann M, Greutmann-Yantiri M, Kretschmar O et al. Percutaneous PFO closure with Amplatzer PFO occluder: predictors of residual shunts at 6 months follow-up. *Congenit Heart Dis* 2009 July;4(4):252-7.

(50) Shafi NA, McKay RG, Kiernan FJ, Silverman IE, Ahlquist M, Silverman DI. Determinants and clinical significance of persistent residual shunting in patients with percutaneous patent foramen ovale closure devices. *Int J Cardiol* 2009 November 12;137(3):314-6.

(51) Wahl A, Kunz M, Moschovitis A et al. Long-term results after fluoroscopy-guided closure of patent foramen ovale for secondary prevention of paradoxical embolism. *Heart* 2008 March;94(3):336-41.

(52) Spies C, Strasheim R, Timmermanns I, Schraeder R. Patent foramen ovale closure in patients with cryptogenic thrombo-embolic events using the Cardia PFO occluder. *Eur Heart J* 2006 February;27(3):365-71.

(53) Wahl A, Meier B, Haxel B et al. Prognosis after percutaneous closure of patent foramen ovale for paradoxical embolism. *Neurology* 2001 October 9;57(7):1330-2.

(54) Windecker S, Wahl A, Chatterjee T et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000 February 29;101(8):893-8.

(55) Majunke N, Wallenborn J, Baranowski A, Wunderlich N, Sievert H. Device closure of residual shunt after percutaneous closure of patent foramen ovale. *EuroIntervention* 2010 February;5(7):833-7.

(56) Diaz T, Cubeddu RJ, Rengifo-Moreno PA et al. Management of residual shunts after initial percutaneous patent foramen ovale closure: a single center experience with immediate and long-term follow-up. *Catheter Cardiovasc Interv* 2010 July 1;76(1):145-50.

(57) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003 November 4;139(9):753-60.

(58) Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003 November 4;139(9):753-60.

(59) Krumsdorf U, Ostermayer S, Billinger K et al. Incidence and clinical course of thrombus formation on atrial septal defect and patient foramen ovale closure devices in 1,000 consecutive patients. *J Am Coll Cardiol* 2004 January 21;43(2):302-9.

(60) Alaeddini J, Feghali G, Jenkins S, Ramee S, White C, bi-Samra F. Frequency of atrial tachyarrhythmias following transcatheter closure of patent foramen ovale. *J Invasive Cardiol* 2006 August;18(8):365-8.

(61) Wertman B, Azarbal B, Riedl M, Tobis J. Adverse events associated with nickel allergy in patients undergoing percutaneous atrial septal defect or patent foramen ovale closure. *J Am Coll Cardiol* 2006 March 21;47(6):1226-7.

(62) Jux C, Wohlsein P, Bruegmann M, Zutz M, Franzbach B, Bertram H. A new biological matrix for septal occlusion. *J Interv Cardiol* 2003 April;16(2):149-52.

(63) Mullen MJ, Hildick-Smith D, De Giovanni JV et al. BioSTAR Evaluation STudy (BEST): a prospective, multicenter, phase I clinical trial to evaluate the feasibility, efficacy, and safety of the BioSTAR bioabsorbable septal repair implant for the closure of atrial-level shunts. *Circulation* 2006 October 31;114(18):1962-7.

(64) Ussia GP, Cammalleri V, Mule M et al. Percutaneous closure of patent foramen ovale with a bioabsorbable occluder device: single-centre experience. *Catheter Cardiovasc Interv* 2009 October 1;74(4):607-14.

(65) Van den Branden BJ, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Patent foramen ovale closure using a bioabsorbable closure device: safety and efficacy at 6-month follow-up. *JACC Cardiovasc Interv* 2010 September;3(9):968-73.

(66) Van den Branden BJ, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Patent foramen ovale closure using a bioabsorbable closure device: safety and efficacy at 6-month follow-up. *JACC Cardiovasc Interv* 2010 September;3(9):968-73.

(67) Van den Branden BJ, Luermans JG, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. The BioSTAR(r) device versus the CardioSEAL(r) device in patent foramen ovale closure: comparison of mid-term efficacy and safety. *EuroIntervention* 2010 September;6(4):498-504.

(68) Jux C, Bertram H, Wohlsein P, Bruegmann M, Paul T. Interventional atrial septal defect closure using a totally bioresorbable occluder matrix: development and preclinical evaluation of the BioSTAR device. *J Am Coll Cardiol* 2006 July 4;48(1):161-9.

(69) Duong-Hong D, Tang YD, Wu W et al. Fully biodegradable septal defect occluder-a double umbrella design. *Catheter Cardiovasc Interv* 2010 November 1;76(5):711-8.

(70) Pavcnik D, Takulve K, Uchida BT et al. Biodisk: a new device for closure of patent foramen ovale: a feasibility study in swine. *Catheter Cardiovasc Interv* 2010 May 1;75(6):861-7.

(71) Krizanic F, Sievert H, Pfeiffer D, Konorza T, Ferrari M, Figulla HR. Clinical evaluation of a novel occluder device (Occlutech) for percutaneous transcatheter closure of patent foramen ovale (PFO). *Clin Res Cardiol* 2008 December;97(12):872-7.

(72) Krizanic F, Sigler M, Figulla HR. Transvenous closure of patent foramen ovale: preliminary results with a new self-expanding nitinol wire mesh in a Swine model. *Cardiol Res Pract* 2009;2009:943453.

(73) Van den Branden BJ, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Percutaneous atrial shunt closure using the novel occlutech figulla device: 6-month efficacy and safety. *J Interv Cardiol* 2011 June;24(3):264-70.

(74) Saguner AM, Wahl A, Praz F et al. Figulla PFO occluder versus Amplatzer PFO occluder for percutaneous closure of patent foramen ovale. *Catheter Cardiovasc Interv* 2011 April 1;77(5):709-14.

(75) Mullen MJ, Hildick-Smith D, De Giovanni JV et al. BioSTAR Evaluation STudy (BEST): a prospective, multicenter, phase I clinical trial to evaluate the feasibility, efficacy, and safety of the BioSTAR bioabsorbable septal repair implant for the closure of atrial-level shunts. *Circulation* 2006 October 31;114(18):1962-7.

(76) Ussia GP, Cammalleri V, Mule M et al. Percutaneous closure of patent foramen ovale with a bioabsorbable occluder device: single-centre experience. *Catheter Cardiovasc Interv* 2009 October 1;74(4):607-14.

(77) Van den Branden BJ, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Patent foramen ovale closure using a bioabsorbable closure device: safety and efficacy at 6-month follow-up. *JACC Cardiovasc Interv* 2010 September;3(9):968-73.

(78) Krizanic F, Sievert H, Pfeiffer D, Konorza T, Ferrari M, Figulla HR. Clinical evaluation of a novel occluder device (Occlutech) for percutaneous transcatheter closure of patent foramen ovale (PFO). *Clin Res Cardiol* 2008 December;97(12):872-7.

(79) Krizanic F, Sievert H, Pfeiffer D et al. The Occlutech Figulla PFO and ASD occluder: a new nitinol wire mesh device for closure of atrial septal defects. *J Invasive Cardiol* 2010 April;22(4):182-7.

(80) Van den Branden BJ, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Percutaneous atrial shunt closure using the novel occlutech figulla device: 6-month efficacy and safety. *J Interv Cardiol* 2011 June;24(3):264-70.

(81) Saguner AM, Wahl A, Praz F et al. Figulla PFO occluder versus Amplatzer PFO occluder for percutaneous closure of patent foramen ovale. *Catheter Cardiovasc Interv* 2011 April 1;77(5):709-14.

(82) Zimmermann WJ, Heinisch C, Majunke N et al. Patent foramen ovale closure with the SeptRx device initial experience with the first "In-Tunnel" device. *JACC Cardiovasc Interv* 2010 September;3(9):963-7.

(83) Ruygrok PN. The Coherex FlatStent: an advance in patent foramen ovale closure. *Expert Rev Med Devices* 2010 March;7(2):193-9.

(84) Hara H, Jones TK, Ladich ER et al. Patent foramen ovale closure by radiofrequency thermal coaptation: first experience in the porcine model and healing mechanisms over time. *Circulation* 2007 August 7;116(6):648-53.

(85) Sievert H, Ruygrok P, Salkeld M et al. Transcatheter closure of patent foramen ovale with radiofrequency: acute and intermediate term results in 144 patients. *Catheter Cardiovasc Interv* 2009 February 15;73(3):368-73.

(86) Majunke N, Baranowski A, Zimmermann W et al. A suture not always the ideal solution: problems encountered in developing a suture-based PFO closure technique. *Catheter Cardiovasc Interv* 2009 February 15;73(3):376-82.

(87) Ruiz CE, Kipshidze N, Chiam PT, Gogorishvili I. Feasibility of patent foramen ovale closure with no-device left behind: first-in-man percutaneous suture closure. *Catheter Cardiovasc Interv* 2008 June 1;71(7):921-6.

(88) Majunke N, Baranowski A, Zimmermann W et al. A suture not always the ideal solution: problems encountered in developing a suture-based PFO closure technique. *Catheter Cardiovasc Interv* 2009 February 15;73(3):376-82.

(89) Baumgartner H, Bonhoeffer P, De Groot NM et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010 December;31(23):2915-57.

(90) Knepp MD, Rocchini AP, Lloyd TR, Aiyagari RM. Long-term follow up of secundum atrial septal defect closure with the amplatzer septal occluder. *Congenit Heart Dis* 2010 January;5(1):32-7.

(91) Majunke N, Bialkowski J, Wilson N et al. Closure of atrial septal defect with the Amplatzer septal occluder in adults. *Am J Cardiol* 2009 February 15;103(4):550-4.

(92) Masura J, Gavora P, Podnar T. Long-term outcome of transcatheter secundum-type atrial septal defect closure using Amplatzer septal occluders. *J Am Coll Cardiol* 2005 February 15;45(4):505-7.

(93) Post MC, Suttorp MJ, Jaarsma W, Plokker HW. Comparison of outcome and complications using different types of devices for percutaneous closure of a secundum atrial septal defect in adults: a single-center experience. *Catheter Cardiovasc Interv* 2006 March;67(3):438-43.

(94) Butera G, Carminati M, Chessa M et al. CardioSEAL/STARflex versus Amplatzer devices for percutaneous closure of small to moderate (up to 18 mm) atrial septal defects. *Am Heart J* 2004 September;148(3):507-10.

(95) Luermans JG, Post MC, ten Berg JM, Plokker HW, Suttorp MJ. Long-term outcome of percutaneous closure of secundum-type atrial septal defects in adults. *EuroIntervention* 2010 November;6(5):604-10.

(96) Chessa M, Carminati M, Butera G et al. Early and late complications associated with transcatheter occlusion of secundum atrial septal defect. *J Am Coll Cardiol* 2002 March 20;39(6):1061-5.

(97) Fischer G, Stieh J, Uebing A, Hoffmann U, Morf G, Kramer HH. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients. *Heart* 2003 February;89(2):199-204.

(98) Luermans JG, Post MC, ten Berg JM, Plokker HW, Suttorp MJ. Long-term outcome of percutaneous closure of secundum-type atrial septal defects in adults. *EuroIntervention* 2010 November;6(5):604-10.

(99) Pedra CA, Pihkala J, Lee KJ et al. Transcatheter closure of atrial septal defects using the Cardio-Seal implant. *Heart* 2000 September;84(3):320-6.

(100) Post MC, Suttorp MJ, Jaarsma W, Plokker HW. Comparison of outcome and complications using different types of devices for percutaneous closure of a secundum atrial septal defect in adults: a single-center experience. *Catheter Cardiovasc Interv* 2006 March;67(3):438-43.

(101) Spies C, Timmermanns I, Schrader R. Transcatheter closure of secundum atrial septal defects in adults with the Amplatzer septal occluder: intermediate and long-term results. *Clin Res Cardiol* 2007 June;96(6):340-6.

(102) Brochu MC, Baril JF, Dore A, Juneau M, De GP, Mercier LA. Improvement in exercise capacity in asymptomatic and mildly symptomatic adults after atrial septal defect percutaneous closure. *Circulation* 2002 October 1;106(14):1821-6.

(103) Giardini A, Donti A, Formigari R et al. Determinants of cardiopulmonary functional improvement after transcatheter atrial septal defect closure in asymptomatic adults. *J Am Coll Cardiol* 2004 May 19;43(10):1886-91.

(104) Luermans JG, Post MC, ten Berg JM, Plokker HW, Suttorp MJ. Long-term outcome of percutaneous closure of secundum-type atrial septal defects in adults. *EuroIntervention* 2010 November;6(5):604-10.

(105) Salehian O, Horlick E, Schwerzmann M et al. Improvements in cardiac form and function after transcatheter closure of secundum atrial septal defects. *J Am Coll Cardiol* 2005 February 15;45(4):499-504.

(106) Du ZD, Hijazi ZM, Kleinman CS, Silverman NH, Larntz K. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol* 2002 June 5;39(11):1836-44.

(107) Losay J, Petit J, Lambert V et al. Percutaneous closure with Amplatzer device is a safe and efficient alternative to surgery in adults with large atrial septal defects. *Am Heart J* 2001 September;142(3):544-8.

(108) Chessa M, Carminati M, Butera G et al. Early and late complications associated with transcatheter occlusion of secundum atrial septal defect. *J Am Coll Cardiol* 2002 March 20;39(6):1061-5.

(109) Fischer G, Stieh J, Uebing A, Hoffmann U, Morf G, Kramer HH. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients. *Heart* 2003 February;89(2):199-204.

(110) Majunke N, Bialkowski J, Wilson N et al. Closure of atrial septal defect with the Amplatzer septal occluder in adults. *Am J Cardiol* 2009 February 15;103(4):550-4.

(111) Masura J, Gavora P, Podnar T. Long-term outcome of transcatheter secundum-type atrial septal defect closure using Amplatzer septal occluders. *J Am Coll Cardiol* 2005 February 15;45(4):505-7.

(112) Amanullah MM, Siddiqui MT, Khan MZ, Atiq MA. Surgical rescue of embolized amplatzer devices. *J Card Surg* 2011 May;26(3):254-8.

(113) Luermans JG, Post MC, ten Berg JM, Plokker HW, Suttorp MJ. Long-term outcome of percutaneous closure of secundum-type atrial septal defects in adults. *EuroIntervention* 2010 November;6(5):604-10.

(114) Post MC, Suttorp MJ, Jaarsma W, Plokker HW. Comparison of outcome and complications using different types of devices for percutaneous closure of a secundum atrial septal defect in adults: a single-center experience. *Catheter Cardiovasc Interv* 2006 March;67(3):438-43.

(115) Anzai H, Child J, Natterson B et al. Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. *Am J Cardiol* 2004 February 15;93(4):426-31.

(116) El-Said HG, Moore JW. Erosion by the Amplatzer septal occluder: experienced operator opinions at odds with manufacturer recommendations? *Catheter Cardiovasc Interv* 2009 June 1;73(7):925-30.

(117) Johnson JN, Marquardt ML, Ackerman MJ et al. Electrocardiographic changes and arrhythmias following percutaneous atrial septal defect and patent foramen ovale device closure. *Catheter Cardiovasc Interv* 2011 May 11.

(118) Al-Anani SJ, Weber H, Hijazi ZM. Atrioventricular block after transcatheter ASD closure using the Amplatzer septal occluder: risk factors and recommendations. *Catheter Cardiovasc Interv* 2010 April 1;75(5):767-72.

(119) Johnson JN, Marquardt ML, Ackerman MJ et al. Electrocardiographic changes and arrhythmias following percutaneous atrial septal defect and patent foramen ovale device closure. *Catheter Cardiovasc Interv* 2011 May 11.

(120) Jux C, Wohlsein P, Bruegmann M, Zutz M, Franzbach B, Bertram H. A new biological matrix for septal occlusion. *J Interv Cardiol* 2003 April;16(2):149-52.

(121) Jux C, Bertram H, Wohlsein P, Bruegmann M, Paul T. Interventional atrial septal defect closure using a totally bioresorbable occluder matrix: development and preclinical evaluation of the BioSTAR device. *J Am Coll Cardiol* 2006 July 4;48(1):161-9.

(122) Hoehn R, Hesse C, Ince H, Peuster M. First experience with the BioSTAR-device for various applications in pediatric patients with congenital heart disease. *Catheter Cardiovasc Interv* 2010 January 1;75(1):72-7.

(123) Morgan G, Lee KJ, Chaturvedi R, Benson L. A biodegradable device (BioSTAR) for atrial septal defect closure in children. *Catheter Cardiovasc Interv* 2010 August 1;76(2):241-5.

(124) Cansel M, Pekdemir H, Yagmur J et al. Early single clinical experience with the new Figulla ASD Occluder for transcatheter closure of atrial septal defect in adults. *Arch Cardiovasc Dis* 2011 March;104(3):155-60.

(125) Halabi A, Hijazi ZM. A new device to close secundum atrial septal defects: first clinical use to close multiple defects in a child. *Catheter Cardiovasc Interv* 2008 May 1;71(6):853-6.

(126) Ilkay E, Kacmaz F, Ozeke O et al. The efficiency and safety of percutaneous closure of secundum atrial septal defects with the Occlutech Figulla device: initial clinical experience. *Turk Kardiyol Dern Ars* 2010 April;38(3):189-93.

(127) Krizanic F, Sievert H, Pfeiffer D et al. The Occlutech Figulla PFO and ASD occluder: a new nitinol wire mesh device for closure of atrial septal defects. *J Invasive Cardiol* 2010 April;22(4):182-7.

(128) Van den Branden BJ, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Percutaneous atrial shunt closure using the novel occlutech figulla device: 6-month efficacy and safety. *J Interv Cardiol* 2011 June;24(3):264-70.

(129) Van den Branden BJ, Mulder TBJM, Post MC, ten Berg JM, Suttorp MJ. The Occlutech Figulla device versus the Amplatzer device in percutaneous atrial septal defect closure. *Submitted* 2011.

(130) Cansel M, Pekdemir H, Yagmur J et al. Early single clinical experience with the new Figulla ASD Occluder for transcatheter closure of atrial septal defect in adults. *Arch Cardiovasc Dis* 2011 March;104(3):155-60.

(131) Ilkay E, Kacmaz F, Ozeke O et al. The efficiency and safety of percutaneous closure of secundum atrial septal defects with the Occlutech Figulla device: initial clinical experience. *Turk Kardiyol Dern Ars* 2010 April;38(3):189-93.

(132) Krizanic F, Sievert H, Pfeiffer D et al. The Occlutech Figulla PFO and ASD occluder: a new nitinol wire mesh device for closure of atrial septal defects. *J Invasive Cardiol* 2010 April;22(4):182-7.

(133) Pac A, Polat TB, Cetin I, Oflaz MB, Balli S. Figulla ASD occluder versus amplatzer septal occluder: a comparative study on validation of a novel device for percutaneous closure of atrial septal defects. *J Interv Cardiol* 2009 December;22(6):489-95.

(134) Anzai H, Child J, Natterson B et al. Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. *Am J Cardiol* 2004 February 15;93(4):426-31.

(135) Krumsdorf U, Ostermayer S, Billinger K et al. Incidence and clinical course of thrombus formation on atrial septal defect and patient foramen ovale closure devices in 1,000 consecutive patients. *J Am Coll Cardiol* 2004 January 21;43(2):302-9.

(136) Pac A, Polat TB, Cetin I, Oflaz MB, Balli S. Figulla ASD occluder versus amplatzer septal occluder: a comparative study on validation of a novel device for percutaneous closure of atrial septal defects. *J Interv Cardiol* 2009 December;22(6):489-95.

(137) Ilkay E, Kacmaz F, Ozeke O et al. The efficiency and safety of percutaneous closure of secundum atrial septal defects with the Occlutech Figulla device: initial clinical experience. *Turk Kardiyol Dern Ars* 2010 April;38(3):189-93.

(138) Krizanic F, Sievert H, Pfeiffer D et al. The Occlutech Figulla PFO and ASD occluder: a new nitinol wire mesh device for closure of atrial septal defects. *J Invasive Cardiol* 2010 April;22(4):182-7.

(139) Cansel M, Pekdemir H, Yagmur J et al. Early single clinical experience with the new Figulla ASD Occluder for transcatheter closure of atrial septal defect in adults. *Arch Cardiovasc Dis* 2011 March;104(3):155-60.

(140) Agricola E, Ielasi A, Oppizzi M et al. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. *Eur J Heart Fail* 2009 June;11(6):581-7.

(141) Alvarez JM, Deal CW, Loveridge K et al. Repairing the degenerative mitral valve: ten- to fifteen-year follow-up. *J Thorac Cardiovasc Surg* 1996 August;112(2):238-47.

(142) Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol* 2003 March 1;91(5):538-43.

(143) Mirabel M, Iung B, Baron G et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J* 2007 June;28(11):1358-65.

(144) Vahanian A, Baumgartner H, Bax J et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007 January;28(2):230-68.

(145) Masson JB, Webb JG. Percutaneous treatment of mitral regurgitation. *Circ Cardiovasc Interv* 2009 April;2(2):140-6.

(146) Fucci C, Sandrelli L, Pardini A, Torracca L, Ferrari M, Alfieri O. Improved results with mitral valve repair using new surgical techniques. *Eur J Cardiothorac Surg* 1995;9(11):621-6.

(147) Maisano F, Vigano G, Blasio A, Colombo A, Calabrese C, Alfieri O. Surgical isolated edge-to-edge mitral valve repair without annuloplasty: clinical proof of the principle for an endovascular approach. *EuroIntervention* 2006 August;2(2):181-6.

(148) Fann JI, St Goar FG, Komtebedde J et al. Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: efficacy and healing response. *Circulation* 2004 August 24;110(8):988-93.

(149) St GF, Fann JI, Komtebedde J et al. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. *Circulation* 2003 October 21;108(16):1990-3.

(150) Feldman T, Wasserman HS, Herrmann HC et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol* 2005 December 6;46(11):2134-40.

(151) Feldman T, Kar S, Rinaldi M et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol* 2009 August 18;54(8):686-94.

(152) Feldman T, Foster E, Glower DG et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011 April 14;364(15):1395-406.

(153) Tamburino C, Ussia GP, Maisano F et al. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. *Eur Heart J* 2010 June;31(11):1382-9.

(154) Franzen O, Baldus S, Rudolph V et al. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. *Eur Heart J* 2010 June;31(11):1373-81.

(155) Van den Branden BJ, Post MC, Swaans MJ et al. Percutaneous mitral valve repair using the edge-to-edge technique in a high-risk population. *Neth Heart J* 2010 September;18(9):437-43.

(156) Franzen O, Van der Heyden JA, Baldus S et al. MitraClip(R) therapy in patients with end-stage systolic heart failure. *Eur J Heart Fail* 2011 May;13(5):569-76.

(157) Van den Branden BJ, Swaans MJ, Post MC et al. Percutaneous edge-to-edge mitral valve repair in high-surgical-risk patients: do we hit the target? *Submitted* 2011.

(158) Van den Branden BJ, Swaans MJ, Post MC et al. Redo mitral valve clipping after partial clip detachment. *JACC Cardiovasc Interv* 2010 February;3(2):251-2.

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Summary

This thesis reports on the application of several new devices for percutaneous treatment of structural heart disease. A patent foramen ovale (PFO) is a tunnel-like communication between the right and the left atrium and has been associated with the occurrence of cryptogenic stroke. PFO closure has proven its efficacy in preventing recurrent TIA or stroke. An atrial septal defect (ASD) occurs when a part of the interatrial septum is missing and is characterized by a left-to-right shunt, resulting in volume overload of the right heart. Percutaneous closure has become common practice. New devices for PFO and ASD closure are being constructed to facilitate the procedure and to lower the complication rate.
Mitral valve regurgitation (MR) is an important clinical issue. Less invasive transcatheter techniques are proposed as an alternative treatment option in high-surgical-risk patients.
The aims of this thesis were to study the safety and the efficacy if this new devices and techniques.

Part one of this thesis, encapsulating **Chapter 1**, offers an introduction to the anatomy, pathophysiology, diagnosis, and treatment of PFO, ASD and MR.

Part two of this thesis concerns the effectiveness and the safety of PFO closure, using a new bioabsorbable device.

Chapter 2 attends the short-term results of 35 consecutive patients who underwent percutaneous PFO closure with the bioabsorbable device (BioSTAR®, NMT Medical, Boston, USA) between November 2007 and July 2008. The only in-hospital complication was a surgical device retrieval from the femoral vein. Four patients developed a minimal femoral haematoma. At one month follow-up (n=33), one patient (3%) developed a TIA and three patients (9%) suffered from paroxysmal atrial fibrillation. One day after closure, residual shunting (assessed with contrast transthoracic echocardiography (cTTE)) was present in 56% of the patients (minimal 27%, moderate 23%, and severe 6%) and at one month, a residual shunt was present in 45% of the patients (minimal 30%, moderate 12%, and severe 3%). We concluded that percutaneous PFO closure using the bioabsorbable closure device is safe. However, a high rate of residual shunting is present at one month follow-up.

In **Chapter 3** we compared the mid-term efficacy and safety of percutaneous PFO closure using the bioabsorbable BioSTAR® device (NMT Medical, Boston, USA) with the non-bioabsorbable CardioSEAL® device from the same manufacturer. We included 37 patients who received the bioabsorbable device and 44 patients who received the non-bioabsorbable device between June 2003 and July 2008. We observed no significant differences in short-term complications between both groups. Within six months, two patients who received the bioabsorbable device developed a recurrent TIA. Overall, atrial arrhythmias occurred in 19%, with no difference between both groups. At six months, a residual shunt was present in 29% (27% minimal, 2% moderate) using the non-bioabsorbable device compared to 28% (17% minimal, 11% moderate) using the bioabsorbable device (p=0.18). A predictor for residual shunt could not be found. In conclusion, there is no difference in safety and efficacy at six months between the non-bioabsorbable and bioabsorbable device used for PFO closure. However, the bioabsorbable device tends to be associated with a higher percentage of moderate shunting.

In **Chapter 4** we describe the 6-month outcome of 62 patients after PFO closure with the bioabsorbable device. There were two major in-hospital complications: in one patient (1.6%) the device embolized to the aorta, was retracted to the femoral artery and surgically removed. In another patient (1.6%) the device was pulled through the PFO, could not be retracted into the sheath and required femoral vein incision. Furthermore, there was a device reposition in one patient (1.6%), and a minimal groin haematoma in six patients (9.7%). During 1-month follow-up (n=60), one patient developed a TIA in the presence of a residual shunt and seven patients (11.3%) suffered from new-onset supraventricular tachycardia. At 6-month follow-up (n=60), one patient without residual shunt developed a TIA and one developed atrial fibrillation. A mild or moderate residual shunt was noted in 51.7%, 33.9%, and 23.7% after one day, one month, and six months follow-up, respectively. A large shunt was present in 8.3%, 3.4%, and 0% after one day, one month, and six months follow-up. In conclusion, closure of PFO using the bioabsorbable device is associated with a low complication rate and a low recurrence rate of embolic events despite a relatively high percentage of mild or moderate residual shunting after six months.

In **Part three** of this thesis, the results of atrial shunt closure using the novel Occlutech Figulla® device are discussed.

In **Chapter 5** the results of percutaneous PFO (n=48) and ASD (n=34) closure with the Occlutech Figulla® device (Occlutech GmbH., Jena, Germany) are reported. All patients were treated between October 2008 and October 2009. Implantation success was 100%. The in-hospital complications were two new-onset supraventricular tachycardias (2.4%, both ASD patients), nine patients developed a minimal groin haematoma (11.0%, 4 PFO and 5 ASD patients), and one transient ST-segment elevation during the procedure (1.2%, ASD patient). During 6-month follow-up (n=79), no major complications or reoccurrences of cerebral thromboembolic events were reported. Seven patients (8.9%, 6 PFO and 1 ASD patient) experienced a new arrhythmia. Using contrast transthoracic echocardiography six months after PFO closure (n=45), a residual shunt was present in 30.2% of the patients (small 25.6%, moderate 4.6%, severe 0%). In the ASD group (n=34), a residual shunt was observed in 32.5% (small 17.7%, moderate 14.7%, severe 2.9%). We concluded that the Occlutech Figulla® device appears to be easy to use, effective, and safe for percutaneous closure of PFO and ASD. We observed a low complication rate but a relative high percentage of small residual shunts six months after closure.

The aim of **Chapter 6** was to compare the safety and efficacy of percutaneous ASD closure between the Occlutech Figulla® septal occluder (FSO) and the Amplatzer® septal occluder (ASO) (AGA Medical, Plymouth, Minnesota, USA). Between October 2000 and December 2010, a total of 185 patients (FSO, n=53; ASO, n=132) underwent percutaneous ASD closure and completed the 6-month follow-up. In-hospital, two devices embolized in each group (3.8% vs. 1.5% for the FSO and ASO group, respectively). Similar rates of new-onset supraventricular tachycardias were observed in-hospital (1.9% vs. 1.5%). During 6-month follow-up, three patients (5.9%) in the FSO group and four patients (3.1%) in the ASO group reported a new supraventricular tachycardia. At six months, the residual shunt rate was significantly higher in the FSO group (total 39.5%, 25.6% minimal, 11.6% moderate, 2.3% large) compared to the ASO group (total 10.6%, 7.9% minimal, 1.8% moderate, 0.9% large) ($p<0.001$).

In conclusion, the use of the FSO for percutaneous ASD closure is associated with a comparable safety profile as the ASO. Despite the structural innovations of the FSO, we observed more residual shunts during follow-up.

Part four encompasses studies on the percutaneous treatment of mitral regurgitation (MR) with the edge-to-edge clip technique in patients who are no candidates for conventional surgery.

In **Chapter 7** we evaluated the MitraClip® system (Abbott Vascular, Santa Clara, California, USA) in the first nine patients and report the short-term results. All nine high-risk patients (78% male, age 75.9 ± 9.0 years, logistic EuroSCORE 33.8 ± 9.0%) were treated at our hospital between January 2009 and August 2009. One patient (10%) developed an inguinal bleeding and needed surgery. In one patient (10%) partial clip detachment occurred, a second clip was implanted successfully. The MR grade before repair was ≥3 in 100%, one month after repair a reduction in MR grade to ≤2 was present in 78% (p=0.001). Right ventricular systolic pressure decreased from 43.9 ± 12.1 to 31.6 ± 11.7 mmHg (p=0.009), NYHA functional class improved from median 3 (range 3 to 4) to 2 (range 1 to 4) (p=0.04), and Quality of life (QoL) index (using the Minnesota questionnaire) improved from 62.9 ± 16.3 to 49.9 ± 30.7 (p=0.12). We concluded that transcatheter mitral valve (MV) repair using the MitraClip® seems to be safe in a high-risk population. A reduction in MR can be achieved in most patients, resulting in a short-term improvement of functional capacity and QoL.

In **Chapter 8** we describe the 6-month outcome of a larger high-risk population treated with the percutaneous edge-to-edge MV repair technique. Fifty-five procedures were performed in 52 patients (69.2% male, age 73.2 ± 10.1 years, logistic EuroSCORE 27.1 ± 17.0%). In three patients partial clip detachment occurred, a second clip was placed successfully. One patient experienced cardiac tamponade, requiring subxiphoidal drainage. Two patients developed an inguinal bleeding, of whom one needed surgery. Six patients (11.5%) died during six months follow-up (five patients due to progressive heart failure and one non-cardiac death). The MR

grade before repair was ≥ 3 in 100%, after six months a reduction in MR grade to ≤ 2 was present in 79% of the patients. Left ventricular (LV) end-diastolic diameter, LV ejection fraction and systolic pulmonary artery pressure improved significantly. Accompanied improvements in NYHA functional class, QoL-index, 6-minutes walking test distances and log NT-pro-BNP were observed. In conclusion, MR reduction can be achieved by percutaneous edge-to-edge repair in the majority of patients, resulting in LV remodelling with improvement of functional capacity after six months.

Chapter 9 provides 2 case-reports regarding the edge-to-edge MV repair. In the first case we present a patient who experienced partial clip detachment and therefore required a redo-procedure. In the second case we demonstrate the implementation of three-dimensional transesophageal echocardiography to guide the percutaneous edge-to-edge repair procedure.

Chapter 10, the general discussion, describes the different treatment options for PFO, ASD, and MR. We provide an overview of the literature with implementation of our study results, highlighting new techniques with recommendations for further investigation.

11

Samenvatting

In dit proefschrift wordt de toepassing van verscheidene nieuwe devices voor de behandeling van structurele hartziekten beschreven. Een patent foramen ovale (PFO) is een tunnelvormige verbinding tussen het rechter en het linker atrium en wordt geassocieerd met het optreden van het cryptogeen herseninfarct. Het sluiten van het PFO is effectief gebleken in het voorkomen van een hernieuwd herseninfarct. Een atriumseptum defect (ASD) ontstaat wanneer een deel van het interatriale septum ontbreekt en wordt gekenmerkt door een links-rechts shunt, wat leidt tot een volume overbelasting van de rechter hartshelft.
Het percutaan sluiten van een ASD wordt tegenwoordig veelvuldig toegepast. Om de procedure te vergemakkelijken en de kans op complicaties te verlagen worden nieuwe devices voor PFO en ASD sluiting ontwikkeld.
Mitralisklepinsufficientie (MI) is een belangrijk klinisch probleem. Minimaal invasieve transkatheter technieken kunnen als alternatief dienen voor de behandeling van patiënten met een hoog operatierisico.
De doelstelling van dit proefschrift betreft het onderzoek naar de veiligheid en de effectiviteit van deze nieuwe devices en technieken.

Deel één van het proefschrift omvat **hoofdstuk 1**, de inleiding, waarin de anatomie, de pathofysiologie, de diagnosestelling en de behandelingsmogelijkheden van het PFO, het ASD en MI worden uiteengezet.

In **Deel twee** van het proefschrift wordt de effectiviteit en de veiligheid van PFO sluiting onderzocht, gebruik makende van een bioabsorbeerbaar sluitingsdevice.

Hoofdstuk 2 omvat de korte termijn resultaten van 35 patiënten die een PFO sluiting ondergingen met het bioabsorbeerbare device (BioSTAR®, NMT Medical, Boston, USA) tussen november 2007 en juli 2008. De enige complicatie in het ziekenhuis was een embolisatie van een device wat chirurgisch verwijderd diende te worden uit de liesader. Vier patiënten ontwikkelden een klein lieshematoom. Tijdens de eerste maand na sluiting (n=33), kreeg 1 patient een TIA en 3 patienten (9%) paroxysmaal atriumfibrilleren. Eén dag na sluiting was een residuele shunt aanwezig in 45% van de patiënten (minimaal 30%, matig 12%, ernstig 3%). Concluderend kon worden gesteld

dat percutane PFO sluiting met het bioabsorbeerbare device veilig is, ondanks een hoog percentage residuele shunts, 1 maand na de procedure.

In **hoofdstuk 3** worden de effectiviteit en de veiligheid van percutane PFO sluiting met het bioabsorbeerbare BioSTAR® device (NMT Medical, Boston, USA) en het niet bioabsorbeerbare CardioSEAL® device (NMT Medical, Boston, USA) vergeleken. We includeerden 37 patiënten die behandeld werden met het bioabsorbeerbare device en 44 patiënten die behandeld werden met het niet bioabsorbeerbare device tussen juni 2003 en juli 2008. We vonden geen significante verschillen in het optreden van complicaties op korte termijn tussen beide groepen. Tijdens de eerste 6 maanden na sluiting, ontwikkelden twee patiënten, behandeld met het BioSTAR® device, een recidief TIA. Atriale ritmestoornissen traden op bij 19% van de patiënten, zonder verschil tussen beide groepen. Zes maanden na sluiting was een residuele shunt aanwezig in 29% (27% minimale shunt, 2% matige shunt) van de patiënten met een CardioSEAL® device en in 28% (17% minimale shunt, 11% matige shunt) van de patiënten met een BioSTAR® device (p=0.18). Een voorspeller voor het optreden van residuele shunt werd niet aangetoond. Concluderend vonden wij geen verschillen tussen het bioabsorbeerbare device en het niet bioabsorbeerbare device wat betreft de effectiviteit en veiligheid na 6 maanden. Echter, het gebruik van het bioabsorbeerbare device lijkt geassocieerd te zijn met een hoger percentage matige residuele shunts.

In **hoofdstuk 4** beschrijven we de uitkomst na 6 maanden van 62 patiënten die een percutane PFO sluiting ondergingen met het bioabsorbeerbare device. Er traden twee belangrijke complicaties op in het ziekenhuis: bij 1 patiënt (1.6%) emboliseerde het device naar de aorta, werd teruggetrokken tot in de arteria femoralis en werd chirurgisch verwijderd. Bij een andere patiënt (1.6%) werd het device door het PFO getrokken, kon niet meer in de sheath gerecupereerd worden en diende chirurgisch verwijderd te worden uit de vena femoralis. Voorts was er een device repositie bij 1 patiënt (1.6%) en een klein lieshematoom bij 6 patiënten (9.7%). Tijdens de eerste maand na sluiting (n=60), ontwikkelde 1 patient een TIA in de aanwezigheid van een residuele shunt en zeven patiënten (11.3%) ontwikkelden een

nieuwe supraventriculaire tachycardie. In de eerste 6 maanden na sluiting (n=60), ontwikkelde 1 patiënt een TIA zonder de aanwezigheid van een residuele shunt en 1 patiënt ontwikkelde atriumfibrilleren. Een geringe tot matige residuele shunt werd geconstateerd bij 51.7%, 33.9% en 23.7% van de patiënten na respectievelijk 1 dag, 1 maand en 6 maanden follow-up. Een ernstige shunt was aanwezig bij 8.3%, 3.4% en 0% van de patiënten na respectievelijk 1 dag, 1 maand en 6 maanden follow-up. Concluderend blijkt PFO sluiting met het bioabsorbeerbare device gepaard te gaan met een lage kans op complicaties en een lage kans op het heroptreden van thromboembolische events ondanks een relatief hoog percentage van geringe en matige residuele shunts na 6 maanden.

Deel 3 van het proefschrift omvat de resultaten betreffende PFO en ASD sluiting gebruik makende van het nieuwe Occlutech Figulla® device.

In **hoofdstuk 5** beschrijven we de resultaten van percutane PFO (n=48) en ASD (n=34) sluiting met het Occlutech Figulla® device (Occlutech GmbH., Jena, Germany). Alle patiënten werden behandeld tussen oktober 2008 en oktober 2009. Alle devices werden succesvol geïmplanteerd. In het ziekenhuis trad een supraventriculaire tachycardie op in twee patiënten (2.4%, allebei ASD patiënten), een beperkt lieshematoom in negen patiënten (11%, 4 PFO patiënten en 5 ASD patiënten) en een voorbijgaande ST-segment elevatie tijdens de procedure in 1 patiënt (1.2%, ASD patiënt). Tijdens de eerste 6 maanden na de procedure (n=79) traden geen belangrijke complicaties of hernieuwde cerebrale thromboembolische events op. Zeven patiënten (8.9%, 6 PFO patiënten en 1 ASD patiënt) kregen een nieuwe supraventriculaire ritmestoornis. Gebruik makende van contrast transthoracale echocardio-grafie 6 maanden na PFO sluiting (n=45), vonden we een residuele shunt bij 30.2% van de patiënten (gering 25.6%, matig 4.6%, ernstig 0%). In de ASD groep (n=34) werd een residuele shunt gedetecteerd in 32.5% van de patiënten (gering 17.7%, matig 14.7%, ernstig 2.9%). We concludeerden dat het Occlutech Figulla® device makkelijk hanteerbeer is en veilig en effectief blijkt voor het percutaan sluiten van een PFO en een ASD. Wij registreerden een laag complicatie percentage maar een relatief hoog percentage van geringe residuele shunts, 6 maanden na sluiting.

In **hoofdstuk 6** worden de veiligheid en de effectiviteit van percutane ASD sluiting met de Occlutech Figulla® septal occluder (FSO) en de Amplatzer® septal occluder (ASO) (AGA Medical, Plymouth, Minnesota, USA) vergeleken. Tussen oktober 2000 en december 2010, ondergingen in totaal 185 patiënten (FSO, n=53; ASO, n=132) een percutane ASD sluiting en vervolledigden de 6 maanden follow-up. Tijdens het ziekenhuisverblijf emboliseerden twee devices in elke groep (3.8% vs. 1.5% voor respectievelijk de FSO en de ASO groep). In beide groepen kwamen vergelijkbare aantallen supraventriculaire tachycardieën voor rondom de procedure (1.9% vs. 1.5%). Gedurende 6 maanden follow-up ontwikkelden drie patiënten (5.9%) in de FSO groep en vier patiënten (3.1%) in de ASO groep een nieuwe supraventriculaire tachycardie. Na 6 maanden bleek de hoeveelheid residuele shunts in de FSO groep (totaal 39.5%, 25.6% gering, 11.6% matig, 2.3% ernstig) hoger in vergelijking met de ASO groep (totaal 10.6%, 7.9% gering, 1.8% matig, 0.9% ernstig) ($p<0.001$). Concluderend kunnen we stellen dat het gebruik van de FSO voor percutane ASD sluiting geassocieerd is met een vergelijkbaar veiligheidsprofiel als de ASO. Ondanks de structurele innovaties van de FSO constateerden we meer residuele shunts tijdens de follow-up periode.

Deel vier behelst het onderzoek van de percutane behandeling van mitraslisklep-insufficiëntie (MI) met de “edge-to-edge” clip techniek bij patiënten die niet in aanmerking komen voor open hartchirurgie.

In **hoofdstuk 7** evalueren we het MitraClip® systeem (Abbott Vascular, Santa Clara, California, USA) in de eerste negen patiënten en rapporteren we de korte termijn resultaten. Alle negen hoogrisico patiënten (78% man, leeftijd 75.9 ± 9.0 jaar, logistische EuroSCORE 33.8 ± 9.0%) werden behandeld in ons ziekenhuis tussen januari 2009 en augustus 2009. Eén patiënt (10%) ontwikkelde een liesbloeding en moest chirurgisch behandeld worden. Bij 1 patiënt (10%) werd een partiële cliploslating vastgesteld, een tweede clip werd succesvol geïmplanteerd. De MI graad voor clipimplantatie was ≥3 in 100% van de patiënten, 1 maand na clipimplantatie werd een reductie van de MI graad naar ≤2 gezien in 78% van de patiënten ($p=0.001$). De rechter ventrikel systolische druk nam af van 43.9 ± 12.1 naar 31.6 ± 11.7 mmHg

(p=0.009), de NYHA functionele klasse verbeterde van mediaan 3 (range 3 to 4) naar 2 (range 1 to 4) (p=0.04), en de Quality of life (QoL) index (gebruik makende van de Minnesota vragenlijst) verbeterde van 62.9 ± 16.3 naar 49.9 ± 30.7 (p=0.12). Concluderend kon worden gesteld dat transkatheter mitralisklepreparatie met de MitraClip® veilig kan worden uitgevoerd in een hoogrisico populatie. Een afname van de MI kan bereikt worden in de meeste patiënten resulterend in een verbetering van de functionele klasse en de kwaliteit van leven op korte termijn.

In **hoofdstuk 8** beschrijven we de uitkomsten na 6 maanden van een grotere groep hoogrisico patiënten, behandeld met de percutane MitraClip® techniek. Vijfenvijftig procedures worden verricht in 52 patiënten (69.2% man, leeftijd 73.2 ± 10.1 jaar, logistische EuroSCORE 27.1 ± 17.0%). In 3 patiënten werd een partiële cliploslating geconstateerd waarvoor succesvol een tweede clip werd geplaatst. Eén patiënt kreeg een tamponade waarvoor subxiphoidale drainage noodzakelijk was. Twee patiënten ontwikkelden een liesbloeding waarvan 1 patiënt een operatie diende te ondergaan. Zes patiënten (11.5%) overleden tijdens de eerste 6 maanden na de ingreep (5 patiënten tgv. progressief hartfalen en 1 patiënt tgv. een niet-cardiale oorzaak). De MI graad voor de behandeling was ≥ 3 in 100%, na 6 maanden was er een reductie in MI graad naar ≤ 2 waarneembaar in 79% van de patiënten. Linker ventrikel (LV) eind-diastolische diameter, LV ejectiefractie en de systolische arteria pulmonalis druk lieten een significante verbetering zien. Tevens werden verbeteringen waargenomen in NYHA functionele klasse, QoL-index, zes-minuten wandeltest afstand en log NT-pro-BNP. Concluderend kan met deze nieuwe techniek in de meerderheid van de patiënten een belangrijke afname in MI worden bereikt, resulterend in LV remodelling met verbetering van de functionele capaciteit na 6 maanden.

Hoofdstuk 9 bevat twee case-reports. In de eerste casus beschrijven we een patiënt bij wie een partiële cliploslating optrad en hierdoor een tweede clipimplantatie diende te ondergaan. In de tweede casus demonstreren we de implementatie van driedimensionale transoesofagale echocardiografie om de percutane MitraClip® techniek te begeleiden.

In **hoofdstuk 10**, de algemene discussie, gaan we dieper in op de verschillende behandelingsmogelijkheden voor het PFO, het ASD en de mitralisklepinsufficientie. Hierbij wordt een overzicht gegeven van de literatuur, met implementatie van onze eigen studieresultaten en wordt de nadruk gelegd op nieuwe technieken en aanbevelingen voor toekomstig onderzoek.

11

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De totstandkoming van dit proefschrift was onmogelijk geweest zonder de “actieve” maar zeker ook de “passieve” medewerking van velen. Bij deze wil ik dan ook de hoofdrolspelers en de niet te onderschatten bijrolspelers persoonlijk danken.

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Evy en Mirte, mijn prinsesjes, papa zal niet meer naar “het kraaiennest” moeten net op het moment dat er een leuk filmpje begint of als er geknutseld moet worden. De tijd is nu voor jullie. Jullie guitige kopjes maken van elke dag een feest en doen me elke keer beseffen wat echt belangrijk is in het leven: jullie dus.

Er rest mij geen mooier einde dan het mooiste einde. Mijn allerliefste Yvette, een Oscar voor de beste bijrol in dit proefschrift, elk jaar een Oscar voor de hoofdrol in mijn leven. Het “gewoon-blij-vrolijk-en-liefdevol-in-het-leven-staan” is een gave die ik zo aan je bewonder. Geen ingewikkelde omwegen, gewoon de snelweg naar het geluk. Oppassen dat we niet geflitst worden. Ik hou van je, de rest van ons leven.

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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 3 maart 1977 in het Middelheim ziekenhuis te Antwerpen. Na het behalen van zijn diploma algemeen secundair onderwijs (Wetenschappen-Wiskunde) in 1995 aan het Koninklijk Atheneum te Schoten, startte hij zijn studie geneeskunde aan de Universiteit van Antwerpen (RUCA/UIA). Op 21 juni 2002 werd het artsdiploma behaald met onderscheiding. Nadat hij als arts-assistent niet-in-opleiding ervaring opdeed op respectievelijk de afdeling cardiologie van het Amphia ziekenhuis te Breda en het St. Antonius ziekenhuis te Nieuwegein, startte hij op 1 maart 2003 met de opleiding tot cardioloog (opleider Dr. W. Jaarsma). De twee jaar durende vooropleiding interne geneeskunde werd gevolgd in het Amphia ziekenhuis te Breda (opleider Dr. G. Wenting). Daarna verbleef hij nog een jaar in het Amphia ziekenhuis voor zijn B-jaar cardiologie (opleider Dr. P. Dunselman). De laatste drie jaar van de opleiding werden volbracht in het St. Antonius ziekenhuis te Nieuwegein. Tijdens zijn hartkatheterisatiestage in het laatste jaar van de opleiding werd zijn interesse gewekt voor de innovatieve ontwikkelingen binnen de interventiecardiologie, wat resulteerde in dit proefschrift. Na de afronding van zijn opleiding tot cardioloog (28 februari 2009), startte hij aansluitend met zijn fellowship interventiecardiologie in Nieuwegein wat zal worden beëindigd op 30 september 2011. Op 1 oktober 2011 zal hij als interventiecardioloog toetreden tot de maatschap cardiologie van het Amphia ziekenhuis te Breda. Op 9 juni 2007 trouwde hij met Yvette Maas. Samen kregen zij twee dochters, Evy (2008) en Mirte (2009).

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List of publications

Spontaneous coronary artery dissection in the postpartum period.
Van den Branden BJ, Bruggeling WA, Corbeij HM, Dunselman PH.
Neth Heart J. 2008 Dec;16(12):412-4.

New bioabsorbable septal repair implant for percutaneous closure of a patent foramen ovale: short-term results of a single-centre experience.
Van den Branden BJ, Post MC, Jaarsma W, ten Berg JM, Suttorp MJ.
Catheter Cardiovasc Interv. 2009 Aug 1;74(2):286-90.

Torsade de pointes with short coupling interval.
Van den Branden BJ, Wever EF, Boersma LV.
Acta Cardiol. 2010 Jun;65(3):345-6.

The BioSTAR® device versus the CardioSEAL® device in patent foramen ovale closure: comparison of mid-term efficacy and safety.
Van den Branden BJ, Luermans JG, Post MC, Plokker HW, ten Berg JM, Suttorp MJ.
EuroIntervention. 2010 Sep;6(4):498-504.

Patent foramen ovale closure using a bioabsorbable closure device: safety and efficacy at 6-month follow-up.
Van den Branden BJ, Post MC, Plokker HW, ten Berg JM, Suttorp MJ.
JACC Cardiovasc Interv. 2010 Sep;3(9):968-73.

Percutaneous mitral valve repair using the edge-to-edge technique in a high-risk population.
Van den Branden BJ, Post MC, Swaans MJ, Rensing BJ, Eefting FD, Plokker HW, Jaarsma W, Van der Heyden JA.
Neth Heart J. 2010 Sep;18(9):437-43.

Re-do mitral valve clipping after partial clip detachment.
Van den Branden BJ, Swaans MJ, Post MC, Rensing BM, Eefting FD, Jaarsma W, Van der Heyden JA.
JACC Cardiovasc Interv. 2010 Feb;3(2):251-2.

Three-dimensional transesophagal echocardiography in a patient undergoing percutaneous mitral valve repair using the edge-to-edge clip technique.
Swaans MJ, Van den Branden BJ, Van der Heyden JA, Post MC, Rensing BM, Eefting FD, Plokker HW, Jaarsma W
Eur J Echocardiogr. 2009 Dec;10(8):982-3.

Percutaneous atrial shunt closure using the novel Occlutech Figulla device: 6-month efficacy and safety.
Van den Branden BJ, Post MC, Plokker HW, ten Berg JM, Suttorp MJ
J Interv Cardiol 2011 June;24(3):264-70.

Early statin treatment prior to primary PCI for acute myocardial infarction: REPERATOR, a randomized placebo controlled pilot trial.
Post S, Post MC, Van den Branden BJ, Eefting FD, Goumans MJ, Bosschaert MA, Stella PR, de Man FH, Wiltberg T, Van Belle E, Rensing BJ, Doevendans PA.
Submitted.

Five-year clinical outcome after primary stenting of totally occluded native coronary crteries : a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions.
Van den Branden BJ, Rahel BM, Laarman GJ, Slagboom T, Kelder JC, ten Berg JM, Suttorp MJ.
Accepted for publication (EuroIntervention).

Percutaneous edge-to-edge mitral valve repair in high-surgical-risk patients: do we hit the target?
Van den Branden BJ, Swaans MJ, Post MC, Rensing BJ, Eefting FD, Jaarsma W, Van der Heyden JA.
Submitted.

The Occlutech Figulla® device versus the Amplatzer® device in percutaneous atrial septal defect closure.
Van den Branden BJ, Mulder TB, Post MC, Plokker HW, ten Berg JM, Suttorp MJ. Submitted.

Primary stenting of totally occluded native coronary arteries III (PRISON III): a randomized comparison of sirolimus-eluting stent implantation with zotarolimus-eluting stent implantation for the treatment of total coronary occlusions.
Van den Branden BJ, Teeuwen K, Koolen JJ, Henriques JP, Tijsen JG, van der Schaaf RJ, Vermeersch PHMJ, Rensing BJ, Suttorp MJ.
Submitted.