Percutaneous treatment of mitral regurgitation with MitraClip device

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Postep Kardiol Inter 2013; 9, 4 (34): 383–389
DOI: 10.5114/pwki.2013.38869

Abstract

The percutaneous edge-to-edge repair of mitral regurgitation with a MitraClip device has been recently approved in Europe. The results of the randomized EVEREST II study showed a favourable safety profile of the technique. However, the efficacy in terms of regurgitation reduction in a population with predominantly degenerative mitral disease was inferior as compared to the results of conventional open heart surgery. Nevertheless, up to 50% of symptomatic heart failure patients with severe mainly functional mitral regurgitation are not treated surgically because of very high procedural risk. The registry data suggest that the minimally invasive and generally well-tolerated MitraClip procedure reduces symptoms and need for recurrent hospitalization and improves left ventricular function in inoperable subjects. The ongoing randomized clinical trials with clinical endpoints will further define the current role of percutaneous edge-to-edge repair in heart failure patients with mitral regurgitation.

Key words: MitraClip, mitral regurgitation.

Introduction

Mitral regurgitation is the second most frequent valve disease requiring surgical treatment in Europe [1]. Open heart surgery with valve repair is the gold standard for the correction of mitral regurgitation, especially in patients with degenerative valve disease [2]. However, up to 50% of patients with heart failure symptoms and severe mitral regurgitation are not treated surgically because of prohibitive procedural risk related to numerous comorbidities in this population [3]. Therefore, several minimally invasive devices were introduced or are currently being tested clinically in order to develop the optimal technique minimizing the procedure-related risk of mitral valve repair. The most advanced project of minimally invasive percutaneous mitral valve repair is based on the concept of the cardiac surgeon Ottavio Alfieri, who developed the technique of edge-to-edge valve repair [4, 5]. Briefly, the middle scallops of anterior and posterior leaflets (A2 and P2) are sutured together to reduce regurgitation and create a double orifice mitral valve during diastole. Following positive results of Alfieri's technique in selected patients, the percutaneously deployed mechanical implant MitraClip was designed [6–8]. The MitraClip system mirrors the surgical procedure in permanent approximation of valve leaflets. A detailed description of the MitraClip system was published previously [6–9]. The implant is introduced through the guide catheter (24 Fr) using the femoral vein access. After transseptal puncture the system is positioned in the left atrium and left ventricle to adequately grasp the leaflets with the clip. The procedure is performed in general anaesthesia under fluoroscopy with continuous transoesophageal echocardiography guidance and requires close cooperation between the operator and the echocardiographers. Images of the whole system, the clip and typical echocardiographic projections are presented in Figures 1 and 2.

The aim of the current paper is to review the current evidence on safety and efficacy of percutaneous edge-to-edge mitral valve repair with use of the MitraClip system.

Initial experience

Following positive results of the preclinical animal studies a phase I trial (EVEREST: Endovascular Valve Edge-to-Edge Repair Study) was conducted [9]. The EVEREST I study included 27 patients with moderate to severe mitral regurgitation (93% of patients with degenerative valve disease) who were either symptomatic or had depressed left ventricular systolic function (ejec-

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Received: 20.08.2013, **accepted:** 10.10.2013.

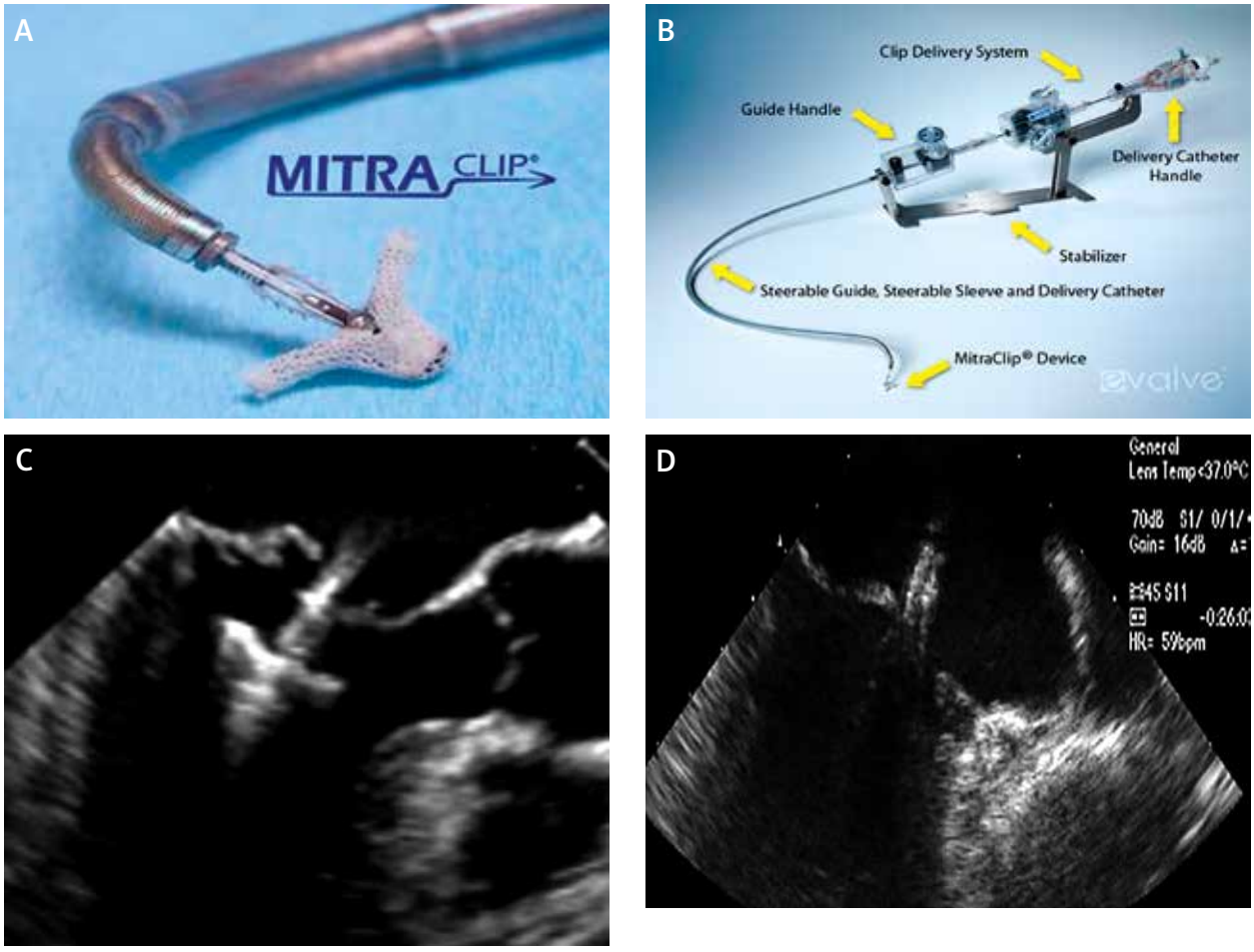

Fig. 1. MitraClip device – echocardiographic images recorded during the procedure (by courtesy of Abbott); **A** – the clip, **B** – the MitraClip delivery system, **C** – TEE LVOT projection showing the clip, **D** – TEE intercommissural projection showing the clip

tion fraction > 30% and < 60% or left ventricular end systolic diameter > 45 mm and < 55 mm). All the patients enrolled were potential candidates for surgical repair and fulfilled the detailed echocardiographic criteria (i.e. central regurgitation jet, lack of leaflet cleft or calcifications, flail segment width < 1.5 cm). The primary safety end-point assessed at 30 days after clip deployment was freedom from acute procedure-related complications (death, myocardial infarction, cardiac tamponade, cardiac surgery, clip detachment, stroke, or septicaemia). The efficacy goal of the procedure was a reduction of regurgitation to at least grade 2+. The MitraClip device was eventually implanted in 24 out of 27 enrolled subjects. The results of the study were encouraging as 85% of patients were at 30 days free from events defined in the safety end-point. Overall, there were no deaths, 1 patient developed stroke likely to hypotension following the procedure, and in 3 patients partial clip detachments occurred. At 30 days and at 6 months areduction in mitral regurgitation to ≤ 2+ was observed in 14 patients (58%). It should be noted that the protocol allowed implantation of more than one clip in case of unsatisfactory results only after the first 10 patients were enrolled. The success of the EVEREST I trial provided a stimulus for the design of the phase II EVEREST II study in which 279 patients with moderate to severe mitral regurgitation were randomized 2 : 1 either to MitraClip implantation or open heart surgical valve repair [10]. As in the EVEREST I trial most patients had degenerative disease and preserved left ventricular function. All the participants were eligible for surgery. The acute procedural results were worse in the MitraClip group with 41 (23%) patients with persistent grade 3+ or 4+ mitral regurgitation prior to discharge as compared to grade ≤ 2+ in all 80 patients treated surgically. Out of 41 patients with significant persistent regurgitation after clip implantation in 28 the surgical procedure was eventually performed (around 50% were treated with valve repair). During the first year following the procedure in the percutaneous repair group 20% of subjects underwent surgical mitral valve repair while in the surgical arm the rate

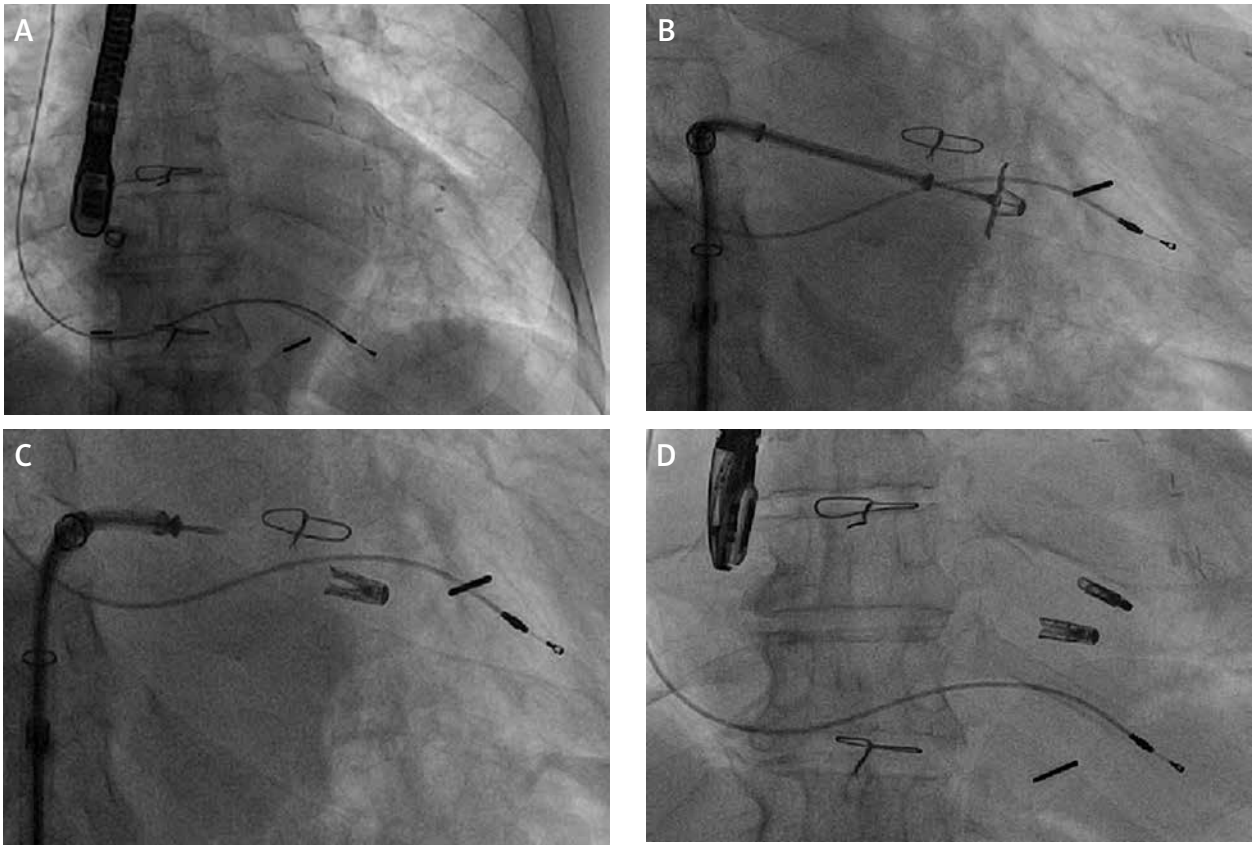

Fig. 2. Angiographic images of the MitraClip device recorded during the procedure. **A** – The TEE probe, **B** – the MitraClip system during positioning in the left ventricle, **C** – the clip immediately after implantation, still connected by a tiny line to the delivery system, **D** – two clips implanted, final effect of the procedure

was only 2.2%. At 12 months follow-up 55% of patients in the MitraClip arm were free from death, surgery or grade 3+ and 4+ mitral regurgitation as compared to 73% of patients in the surgery group (p = 0.007) (Figure 3). Interestingly, at 12 months follow-up 13% of surgical patients were in functional NYHA class III or IV as compared to only 2% from the MitraClip group (p = 0.002). At two years the mortality rate was 11%, equal for both study arms. The left ventricular volumes and dimensions were significantly decreased according to echocardiographic examination in both study arms, although the magnitude of change was larger in surgical patients. However, there was also observed significant reduction (7% in absolute values) in ejection fraction in the surgical group. Looking at the safety end-points assessed at 30 days, there were more major adverse events in the surgery group (48% vs. 15%; p < 0.001) (Figure 4). The difference in adverse events was mainly driven by the lower rate of blood transfusions and prolonged mechanical ventilation in patients treated percutaneously. The authors of the EVEREST II trial concluded that MitraClip implantation although less effective in regurgitation reduction was safer and resulted in a similar clinical outcome as conventional surgery.

Current utilization of MitraClip device in clinical practice

The initial experience with the MitraClip system based on the EVEREST I and II studies comes mostly from patients with degenerative regurgitation, who were also good candidates for surgery, because of low incidence of comorbidities and preserved left ventricular systolic function. However, in this low-risk population good long-term results in terms of improved symptoms and survival and the repair durability can be achieved at low risk with open heart surgery. On the other hand, there is a growing population of heart failure patients with functional mitral regurgitation and extensive comorbidities for whom the surgery carries a substantial mortality risk. The minimally invasive MitraClip system has been evaluated in several observational studies in these subjects. The third arm of the EVEREST II study (EVEREST High Risk Study – EVEREST-HRS) had an observational prospective design and included patients who fulfilled the echocardiographic eligibility criteria for a MitraClip procedure and for whom estimated surgical mortality risk was ≥ 12% (> 50% had prior cardiac surgery) [11]. Overall, 78 patients predominantly with functional regurgitation were treated with MitraClip implantation. The procedural suc-

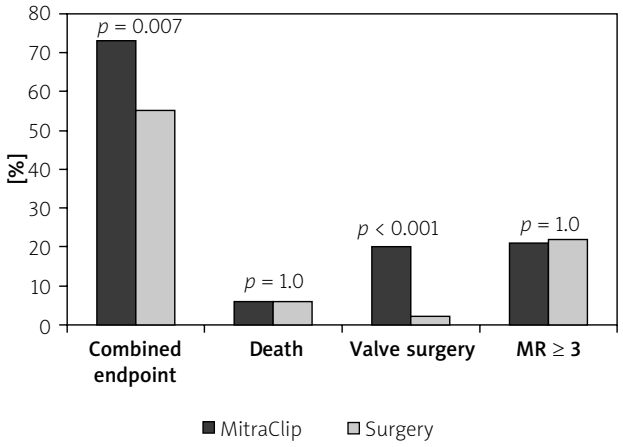

Fig. 3. Efficacy endpoints assessed at 1 year after the procedure in patients enrolled inthe EVEREST II study

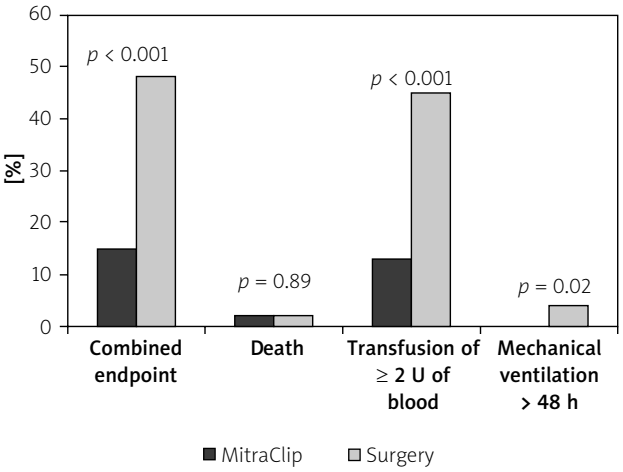

Fig. 4. Safety endpoints assessed at 1 month after the procedure in patients enrolled inthe EVEREST II study

Table 1. Baseline characteristics and clinical outcome in high-risk patients with mitral regurgitation treated with implantation of the MitraClip device. Summary of the representative studies

	Baseline characteristics					Follow-up		
Study	Number of patients	Functional MR [%]	Predicted surgical mortality [%]	Age [years]	NYHA III–IV [%]	30 days or in-hospital mortality [%]	NYHA III–IV at follow-up (different length of follow-up – from 1 month to over 1 year) [%]	MR ≤ 2+ At 1 month or 1 year
Everest II High Risk study	78	59	18.2	77	89	7.7	26	78
TRAMI registry (Baldus *et al.*)	486	66	11.0	75	93	2.5	36	–
GRASP registry (Grasso *et al.*)	117	76	12	72	80	0.9	–	85
ACCESS-EU registry (Maisano *et al.*)	567	69	23.0	74	84.9	3.4	29	78
Auricchio *et al.*	51	100	30	70	98	4.2	22	–

MR – mitral regurgitation

cess of device implantation was achieved in 96% of patients with a 30-day mortality rate of 7.7%. At 12 months follow-up mitral regurgitation ≤ 2+ was present in 78% of surviving patients. Moreover, there was a significant improvement in left ventricular diastolic and systolic volumes. Importantly, at one year follow-up 74% of patients were in NYHA functional class I/II while before intervention 89% of subjects suffered from moderate to severe heart failure symptoms (NYHA III/IV). Also, the annual rate of hospitalization for heart failure was reduced after device implantation as compared to the period before the intervention. The control group in the EVEREST-HRS study comprised 36 concurrently screened patients of similar clinical characteristics who did not receive any intervention. The 12 months mortality rate was 24% in the intervention group and 45% in control patients ($p = 0.047$). Similar results were obtained by the authors of the TRAMI (Transcatheter Mitral Valve Interventions) registry involving the patients treated with MitraClip in Germany between 2009 and 2011 [12]. The TRAMI registry data come from one of the largest populations treated with MitraClip implantation (486 patients) described so far. The median age of patients enrolled was 75 years. The majority (93%) were in NYHA class III or IV before the intervention. The aetiology of regurgitation was functional in 66% of patients (80% ischaemic cardiomyopathy) and the majority (> 70%) of subjects had a reduced ejection fraction (< 50%). The median logistic EuroSCORE was 23% and median STS mortality score 11%. The major reasons for percutaneous intervention were high surgical risk, age, frailty and patient's wish. Interestingly, in 9% of patients in the TRAMI registry the

implantation of MitraClip was an emergency procedure. Overall, procedural success was achieved in 94% of cases and after the clip implantation 89% of patients had no more than moderate mitral regurgitation. The procedure was safe. The peri-procedural major complications included severe bleeding (3.9%), vascular complications requiring surgery (2.8%), pericardial effusion (0.9%), transient ischaemic attacks (1.3%) and stroke (0.4%). The in-hospital mortality was low at 2.5%. However, 34 (12.5%) patients died after discharge at a median of 3 months; in 20 patients the cause of death was cardiovascular. This high mortality rate most likely reflects the advanced stage of disease and number of comorbidities in patients currently treated with a MitraClip device in Germany. Another prospective national registry – GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) was performed in Italy [13]. The study population comprised 117 patients predominantly with functional regurgitation and at high risk (mean logistic EuroSCORE = 12%) of conventional surgery. Acute success defined as mitral regurgitation < 3+ was achieved in all patients. No procedural mortality was observed. At one month following clip implantation 1 patient died from gastrointestinal bleeding, there was one stroke and in one patient transfusion of ≥ 2 U of blood was required. Similarly to the results of the TRAMI registry, the late mortality was high – 14% at 1 year (cardiovascular cause in 45%)– which reflects the disease stage in enrolled subjects. The durability of repair was better in patients with functional origin of regurgitation; in 25% of patients with degenerative disease, deterioration to grade ≥ 3+ occurred, versus 7% of patients with functional regurgitation. Recently the acute and mid-term results of the large registry ACCESS-EU were published [14]. Over 500 patients treated with MitraClip implantation in 14 European centres were prospectively included. Their baseline clinical characteristics were similar to those in previously described groups: the majority of subjects (69%) with functional regurgitation, depressed left ventricular systolic function (53% of patients with EF ≤ 40%) and very high surgical risk (logistic EuroSCORE = 23.0%). It should be underlined that 5% of patients were in cardiogenic shock at the time of the procedure. The device was implanted in 99.6% of patients; 60% received one clip, 37% two clips, and in 3% more than 2 clips were necessary. All the patients survived the procedure. The incidence of cardiac tamponade was 0.9% and need for periprocedural resuscitation 1.1%. The hemodynamic measurements revealed increase in cardiac output and reduction in pulmonary capillary wedge pressure following MitraClip implantation. Satisfactory mitral regurgitation reduction to ≤ 2+ was achieved in 91% of patients. Overall, at one year there were only 12% of patients in whom no improvement in mitral regurgitation from baseline was noted. The one month mortality rate was 3.4% and one year mortality was 18.8%, which is very similar to previously cited reports. Also, similarly to previous studies, significant improvement in heart failure symptoms was recorded.

MitraClip implantation in non-responders to cardiac resynchronization therapy

According to the large (800 subjects) study by Di Biase *et al*., moderate to severe (grade 3+ to 4+) functional mitral regurgitation is present in around 35% of potential cardiac resynchronization therapy (CRT) recipients [15]. In 45% of patients after CRT implantation the regurgitation improvement ≥ 1+ was achieved. However, in 43% of subjects no change was observed and in 12% the regurgitation increased. Auricchio *et al*. conducted a study to test if MitraClip implantation may correct regurgitation and improve symptoms in CRT non-responders [16]. Fifty-one CRT non-responders with significant (≥ 2+) mitral regurgitation received a MitraClip device. There were two deaths during the procedure including one caused by device-related chordal rupture. However, in most of the remaining subjects significant regurgitation reduction was achieved. The improvement in clinical symptoms at one month and one year follow-up was similar to that previously reported and progressively increased over time. Serial echocardiographic examinations revealed reverse left ventricular remodelling and increase in left ventricular ejection fraction. The 30-day mortality was 4.2% but during 1 year follow-up 9 (18%) patients died, the majority from cardiovascular causes.

Ongoing randomized studies

There are currently two ongoing large scale randomized clinical trials designed for patients with heart failure and significant functional mitral regurgitation:

RESHAPE-HF study – *A Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation*

The primary endpoint is a hierarchical composite of all-cause mortality and recurrent heart failure hospitalization within two-year follow-up. The estimated number of 800 subjects with heart failure and functional mitral regurgitation will be randomized 1 : 1 either to MitraClip implantation or optimal standard of care therapy. The anticipated study completion date is August 2016. The study protocol with detailed inclusion and exclusion criteria is registered at www.clinicaltrial.org (NCT01772108). Briefly, the key inclusion criteria include:

- moderate-to-severe functional mitral regurgitation as defined by the European Association of Echocardiography,
- NYHA III or IV heart failure despite optimal standard of care,

- at least one acute care admission/emergency room visit or significant elevation of BNP or NT-proBNP,
- left ventricular EF ≥ 15% and ≤ 40% and left ventricular end diastolic diameter ≥ 55 mm.

COAPT study– *Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk Patients*

The primary effectiveness endpoint is recurrent heart failure hospitalization and the primary safety endpoint is a composite of all-cause death, stroke, new onset or worsening of kidney dysfunction, left ventricular assist device implant, or heart transplant. The estimated number of 420 patients with heart failure and moderate-to-severe functional mitral regurgitation will be randomized 1 : 1 either to MitraClip repair or to non-surgical management based on standard clinical practice. The estimated primary completion date is January 2017. The study protocol with detailed inclusion and exclusion criteria is registered at www.clinicaltrial.org (NCT 01626079). The key inclusion criteria are as follows:

- symptomatic functional mitral regurgitation ≥ 3+ secondary to ischaemic or non-ischaemic cardiomyopathy; the severity and aetiology of regurgitation to be confirmed by the Echo Core Lab,
- NYHA functional class II, III or ambulatory IV,
- extremely high risk of mitral valve surgery due to comorbidities,
- history of at least one hospitalization for heart failure within previous year or elevated levels of BNP or NT-proBNP.

Percutaneous edge-to-edge repair in current European guidelines on management of valvular heart disease and congestive heart failure

Surgical repair of the mitral valve is the current treatment of choice for the vast majority of patients with severe primary regurgitation. However, MitraClip implantation may be considered in symptomatic inoperable/high surgical risk patients, who fulfil echocardiographic criteria and have a life expectancy > 1 year (class IIb, level of evidence C) [2]. In patients with secondary regurgitation the indications for isolated mitral valve surgery without concomitant coronary revascularization are limited. However, there is an option for percutaneous edge-to-edge repair for secondary regurgitation in patients symptomatic despite optimal medical therapy including CRT, with appropriate valve anatomy, who are judged inoperable or are at high surgical risk and have a life expectancy > 1 year (class IIb, level of evidence C) [2]. Also the guidelines for management of heart failure state that in patients with secondary mitral regurgitation with indication for valve repair but judged inoperable or at unacceptably high surgical risk, MitraClip therapy may be considered in order to improve symptoms [17].

Conclusions

Current experience with the MitraClip device is limited, based on a single randomized trial and several registries that comprised a different population of patients than that enrolled in the randomized study. The available evidence suggests that:

1. The percutaneous edge-to-edge treatment of mitral regurgitation is a minimally invasive, reasonably effective and safe technique that may reduce symptoms and improve left ventricular function in echocardiographically selected patients at high risk of surgical repair.
2. The procedure is less effective than surgery in reducing mitral regurgitation and in up to 20% significant regurgitation persists. This may be related either to the failure of the procedure (the learning curve) or presence of regurgitation mechanisms that cannot be corrected solely by valve leaflets approximation.
3. The MitraClip device cannot replace the surgical procedure in patients with low surgical risk and preserved left ventricular function.
4. The ongoing clinical trials will evaluate the durability of valve repair with the MitraClip system and its impact on clinical outcomes in high-risk patients with functional mitral regurgitation.

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