Percutaneous mitral valve repair in high-risk patients: initial experience with the Mitraclip® system in Belgium

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Aims Treatment with percutaneous edge-to-edge mitral valve repair (Mitraclip®) has recently been recommended as an alternative to conventional mitral valve repair for high surgical risk patients with symptomatic severe mitral regurgitation (MR). In this study, we report the first use of Mitraclip® therapy in Belgium.

Methods and results This prospective registry includes 41 consecutive patients treated with the Mitraclip® in two Belgian centres from October 2010 to June 2013. Acute procedural success, in-hospital safety end points and clinical status were analysed on an intention-to-treat basis up to one year after the procedure. In addition, determinants of major adverse cardiac events (MACE, death, surgical mitral valve intervention, and rehospitalization for heart failure) were analysed.

Acute procedural success (successful clip placement and reduction of colour Doppler flow MR to ≤ 2) was obtained in 32 patients (78%) and 18 of these patients received two clips. The primary safety end point was reached in 36 pts (88%): one patient died due to intracranial bleeding, there were three urgent surgical interventions and one severe access site bleeding. The MACE rate after one year was 41% (17 patients). There were 11 deaths (27%), six surgical interventions (15%) and 10 rehospitalizations for heart failure (24%). Additional subgroup analysis revealed that the one-year MACE rate was particularly high in patients with left ventricular ejection fraction (LVEF) < 25%: 62% vs. 36% in patients with LVEF ≥ 25% ($P = 0.05$). At one year, MR ≤ 2+ and NYHA class ≤ 2 was present in 83% of the surviving patients

Conclusion In high-risk patients with functional MR, treatment with the Mitraclip®-device is a feasible and safe option resulting in improvement of MR severity and clinical symptoms. However, as MACE is high in some subgroups (e.g. LVEF < 25%), careful patient selection is crucial to ensure the maximum benefit from this new technique.

Keywords *Mitral regurgitation – Mitraclip® – high-risk patients.*

INTRODUCTION

Mitral regurgitation (MR) is the second most frequent valve disease requiring surgery[1]. Surgery, preferably mitral valve repair when feasible, is the standard treatment for severe symptomatic mitral regurgitation[1]. In 1991, Alfieri introduced mitral valve repair which consisted of a surgical suture of both the anterior and posterior mitral valve leaflets, creating a double orifice[2].

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Percutaneous edge-to-edge mitral valve repair using the Mitraclip® device (Abbott Vascular, Santa Clara, CA, USA) has emerged as a therapeutic alternative to mitral valve surgery for high surgical risk patients with severe functional or degenerative mitral regurgitation[3,4]. In the EVEREST II trial, Mitraclip® was associated with a superior safety and clinical outcome when compared with conventional surgery[5]. In ACCESS Europe, high surgical risk patients in NYHA functional class III/IV, patients with a low left ventricular ejection fraction (LVEF < 40%) and those with co-morbidities demonstrated clinical benefit from Mitraclip® therapy[6]. Treatment with Mitraclip® has recently been recommended (level of recommendation IIb) as an alternative to conventional mitral valve repair for high surgical risk patients with symptomatic severe mitral regurgitation[1]. In this

multi-centre, prospective Belgian registry feasibility study, Mitraclip® therapy was used to treat high surgical risk patients with heart failure and severe mitral regurgitation. The effect of this therapy on mitral regurgitation reduction and clinical outcome was assessed.

METHODS

Patient population

This prospective registry includes 41 consecutive patients who were treated with the Mitraclip® system in two Belgian centres (Antwerp University Hospital and Onze-Lieve-Vrouw Hospital of Aalst) from October 2010 to June 2013.

Patients were selected carefully by the local heart team using a multimodality decision-making process. First, the patient had to meet the basic criteria for intervention of MR as specified by the European Society of Cardiology Task Force recommendations on the management of valvular heart disease. Second, patients had to be symptomatic, despite optimal medical treatment. Third, the operative risk had to be deemed too high based on a global clinical assessment, including the evaluation of surgical risk by logistic EuroSCORE (http://www.euroscore.org) as well as adjunctive risk evaluation such as the presence of severe comorbidity or frailty. Finally, the technical feasibility of implanting the Mitraclip® had to be determined using a pre-procedural transoesophageal echocardiography (TOE). The echocardiographic criteria are described extensively in a previous document[7]. Briefly, this includes the presence of a primary regurgitation jet originating from malcoaptation of the A2 and P2 scallops of the mitral valve with sufficient coaptation length (> 2 mm) and with a sufficiently large mitral valve orifice area (> 4.0 cm^2).

This study was approved by the local medical ethics committees. Written informed consent was obtained from all patients after explanation of the issues surrounding the procedure.

Procedure

The procedure was performed under general anaesthesia and using TOE and fluoroscopic guidance. The Mitraclip® system is introduced into the left atrium via the transfemoral venous route and transseptal puncture. The clip has two arms and a "gripper" adjacent to each arm (see figure 1). Following alignment of the system coaxial to the cardiac long axis and rotating it such that the opened arms of the clip are oriented perpendicularly to the line of mitral leaflet coaptation, the system is directed towards the origin of the regurgitant jet and advanced into the left ventricle. Upon slight retraction

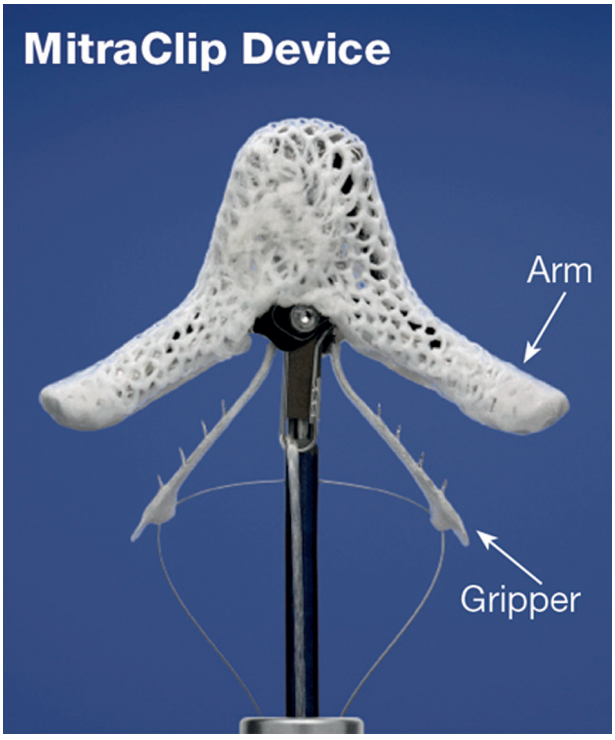

Fig. 1 Mitraclip device with arms and grippers.

of the clip delivery system, the mitral leaflets can be grasped by lowering the grippers onto the clip arms. Once the resulting MR reduction is deemed satisfactory, the clip can be deployed. In case of significant residual MR, despite adequate deployment of the first clip, a second clip can be placed near the first clip if the residual mitral valve orifice is large enough. A comprehensive description of the procedure is reported elsewhere[8].

For all patients, post-procedural pharmacologic management included a three-month prescription of clopidogrel 75 mg daily. In patients without atrial fibrillation, lifelong acetylsalicylic acid 80 mg daily therapy was also prescribed. In patients with atrial fibrillation lifelong oral anticoagulation was prescribed.

The implantation of at least one clip and a reduction of MR to ≤ 2+ was deemed a successful procedure. MR severity was graded according to the guidelines of the American Society of Echocardiography, based on a validated integrative method[9].

Study end points

The primary safety end point was freedom from major adverse events (MAEs), defined as a composite of death, myocardial infarction, urgent cardiac surgery for adverse events, renal failure requiring dialysis, and life-threatening bleeding or bleeding requiring transfusions > 2 units of blood.

The primary clinical efficacy end point was freedom from major adverse cardiac events (MACE) after one year, defined as the combined end point of death, surgical mitral valve intervention, and rehospitalization for heart failure.

Secondary end points were defined as the assessment of clinical status, as reflected by the NYHA functional class and MR severity at 1 month, 6 months and 12 months.

All end points were assessed on an intention-to-treat basis and were obtained from patient records or from telephone calls with the patient.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation or the median plus (interquartile) range, where appropriate. Categorical variables are presented as counts and percentages. Comparisons between categorical variables were performed by the Fisher's exact test. Cumulative event-free survival estimates were plotted using the Kaplan-Meier technique. Differences between survival curves were tested with the log rank test. The Cox proportional hazards model was applied to identify independent predictors of MACE. The following baseline factors were included in the model: age, gender, procedural success, LV ejection fraction as assessed on echocardiography, pre-procedural NYHA functional class, logistic Euroscore and renal function expressed as glomerular filtration rate (GFR). A two-tailed *P*-value < 0.05 was considered statistically significant.

Table 1 Baseline characteristics

Characteristics (n = 41)	
Age (years ± SD)	75 ± 9
Male gender, n (%)	27 (66)
Logistic Euroscore (% ± SD)	22 ± 15
Prior CABG, n (%)	22 (54)
Prior electrical therapy, n (%)	
CRT	9 (22)
ICD	3 (7)
LV ejection fraction (%)	32 ± 10
Cardiomyopathy (LVEF < 40%), n (%)	36 (87)
Glomerular filtration rate (ml/min/1.73 m^2)	54 ± 27
Mitral regurgitation severity, n (%)	
3+ (moderate-to-severe)	24 (59)
4+ (severe)	17 (41)
Mitral regurgitation aetiology, n(%)	
Functional	40 (98)
Degenerative	0 (0)
Mixed	1 (2)
NYHA functional class, n (%)	
II	9 (22)
III	23 (56)
IV	9 (22)
Hospitalization for heart failure in the last two years	30 (73)
Medication, n (%)	
ACE I/ ARB	26 (63)
Beta blocker	30 (73)
Loop diuretic	34 (83)
Aldosterone antagonist	21 (51)

ACE I: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CABG: coronary artery bypass grafting; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter/defibrillator; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association.

RESULTS

Patient characteristics

A total of 41 patients (mean age 75 ± 9) were treated between October 2010 and June 2013. The clinical characteristics are presented in table 1. All patients had an increased surgical mortality risk (average Euroscore 22) and were symptomatic (average NYHA class 3). All patients had functional MR and either cardiomyopathy or annular dilatation. One patient had a mixed aetiology with a moderate prolapse of both leaflets and an annular dilatation. The average LVEF was 32%. A total of 20% of the patients had LVEF < 25%. Previous coronary-artery bypass grafting (CABG) was present in 22 patients and 11 patients received treatment with ICD (n = 8) or CRT (n = 2) or both (n = 1). The majority of patients received optimal medical treatment with ACE I (angiotensin-converting enzyme inhibitor) and/or ARB (angiotensin-II receptor blocker) and/or beta blockers and/or diuretics including aldosterone blocking agents. Almost ¾ of patients had been hospitalized for heart failure within 2 years of the Mitraclip® procedure.

Procedural outcome

The 41 patients underwent a total of 42 interventions, with one repeat procedure performed after six months. Ten patients received a single clip and 29 patients had two clips implanted. In two patients no clip could be implanted, due to an unsuccessful guide insertion in the left atrium in one patient and a puncture-related cardiac tamponade requiring urgent surgery in the other patient.

Acute procedural success (successful clip placement and reduction of colour Doppler flow MR to ≤ 2+) was achieved in 32 patients (78%), with a residual MR of 1+ in 14 patients and 2+ in 18 patients. Procedural failure (n = 9) was due to the following reasons: inability to implant either a first clip (n = 2) or a second clip (n = 3), partial detachment of the clip (n = 2), perforation of the leaflet (n = 1), and an inability to dismount the deployed clip from the guide requiring surgery (n = 1). The total device time, i.e. the time from the septal puncture to withdrawal of the guide catheter from the left atrium, averaged 128 ± 84 min. The median hospital stay post Mitraclip® procedure was five days (IQR 5).

Safety end point

Major adverse in-hospital events occurred in five patients, resulting in a primary safety end point of 88%. There was one in-hospital death due to intracranial bleeding which occurred one week after the procedure. There were two additional major bleeding occurrences, one related to femoral access and another to pericardial bleeding with tamponade requiring urgent surgery. Two other patients needed to undergo urgent cardiac surgery due to detachment of the mitral valve (n = 1) or when it was not possible to dismount the deployed Mitraclip® (n = 1).

Clinical efficacy end point

The MACE rate after one year was 41% (17 patients). There were 11 deaths (27%), six surgical interventions (15%) and 10 rehospitalizations for heart failure (24%). The Kaplan-Meier curves of freedom from MACE and their individual components are depicted in figure 2.

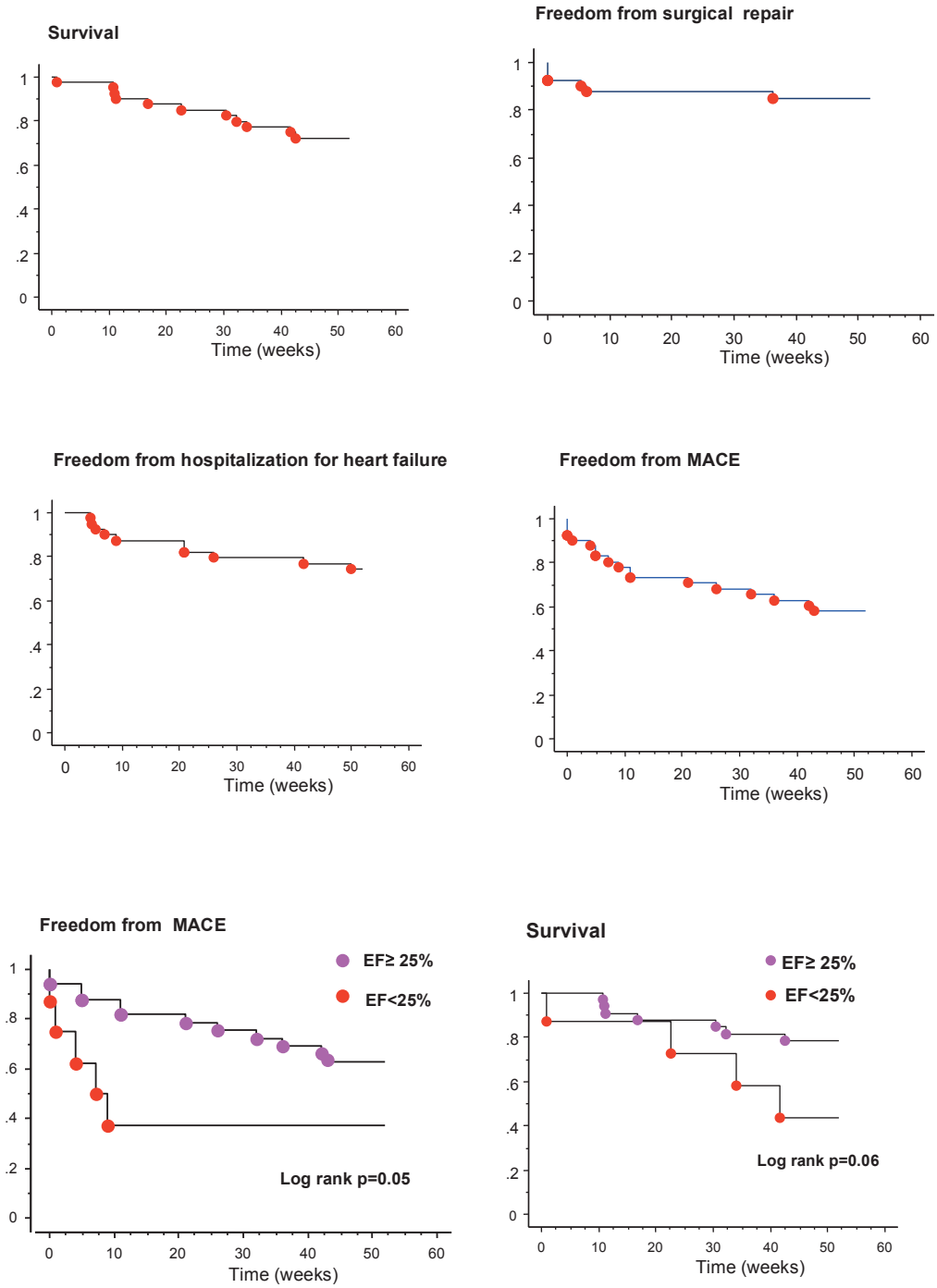

Fig. 2 Kaplan-Meier survival curves for major adverse cardiac events.

Additional analysis revealed that LVEF was the most important determinant of mortality, whereas LVEF and procedural success were the most important determinants for MACE (see table 2). In patients with LVEF < 25%, the one-year mortality and MACE rates were 50% and 62%, respectively. In patients with LVEF ≥ 25%, the one-year mortality and MACE rates were 21% and 36%, respectively (see figure 2).

MR severity decreased significantly with colour Doppler flow MR 1 or 2 after one year in 83% of the surviving patients (see figure 3). The NYHA functional class improved strongly with NYHA class 1 or 2 at one year in 83% of the surviving patients (figure 4).

Table 2 Determinants of mortality and MACE

	RR (95% CI) for mortality	RR (95% CI) for MACE
Female gender	0.31 (0.06-1.5)	0.66 (0.2-2.0)
Unsuccessful procedure	1.85 (0.4-8.5)	4.6 (1.5-14.2)
Age	1.04 (0.9-1.16)	1.06 (0.98-1.15)
Glomerular filtration rate	0.98 (0.9-1.03)	1.02 (0.98-1.04)
Euroscore	1.01 (0.98-1.05)	1.01 (0.98-1.04)
LV ejection fraction	0.88 (0.8-0.96)	0.93 (0.86-0.99)
NYHA class	1.90 (0.8-4.6)	1.7 (0.85-3.5)

LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association.

DISCUSSION

This study describes the authors' initial experience using the Mitraclip® in Belgium. Our data show that this method is safe, even in high surgical risk patients, and our results revealed a clinical improvement in the majority of patients.

The minimally invasive nature of the Mitraclip® significantly reduces operative complications such as blood loss and major infections, in addition to decreasing hospital mortality compared to conventional mitral valve surgery in patients with functional MR[5,10]. Moreover, the majority of the patients who underwent Mitraclip® implantation recovered more quickly and could be discharged earlier. On the other hand, surgical repair with annuloplasty creates a more complete and sustained reduction of MR[11].

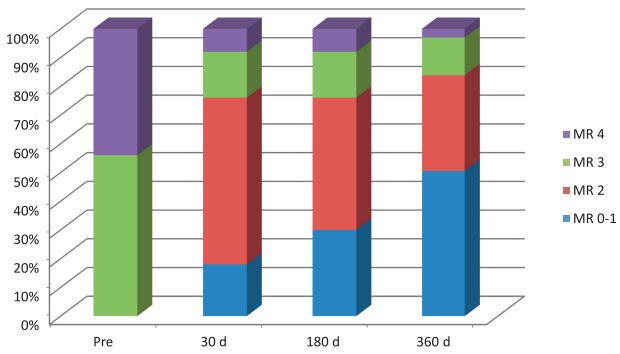

Fig. 3 Mitral regurgitation (MR) grade at baseline, 1 month, 6 months and one year.

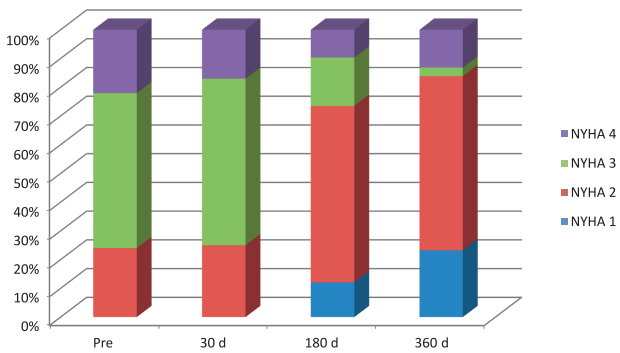

Fig. 4 NYHA, New York Heart Association at baseline, 1 month, 6 months and one year.

The current safety and efficacy of the Mitraclip® system for high surgical risk candidates were recently discussed in a systematic review of available prospective observational studies[12]. Immediate procedural success ranged from 72-100% and there was a weighted mean one-month mortality rate of 3.3% (range 0-8%); the highest success rates were in registries with experience of > 100 procedures. Our 78% success rate and 2.3% mortality rate may fit well in the international experience taking into account the limited experience of about 20 cases/centre.

Other periprocedureal adverse events, such as the early need for surgery, transseptal complications, partial clip detachment and severe bleeding concur with the 0-5% rates reported in the review paper.

The main aim of Mitraclip® implantation in high risk heart failure patients is to improve symptoms by reducing MR. After one year, more than 80% of patients had an MR severity of ≤ 2+ and were in either NYHA class I or II, which is similar to international reports. However, this promising result may partly be due to selection bias which was prompted by a relatively high mortality rate of 27% at one year. The sustained improvements in clinical and echocardiographic results over time may be related to this selection bias, but could also be driven by the positive remodelling effect documented in previous studies[13,14].

The positive effects on morbidity are also reflected in the relatively low rehospitalization rate for heart failure (25%) in this study population with advanced heart failure that had a hospitalization rate of almost 75% in the two years preceding the procedure. The majority of

post-operative mortality within the first year was related to cardiac failure. This mostly occurred beyond 3 months after the procedure. In previously reported cases, one-year mortality ranged from 10-25%. The relatively high mortality rate in our study is most likely related to a more severely depressed left ventricular function, as a substantial proportion of patients had an LVEF below 25%.

Further analysis revealed that LVEF was the most important determinant of both mortality and major adverse cardiac events. In view of the high mortality (up to 50%) in patients with a LVEF below 25% and in view of restricted availability of the Mitraclip® device (due to high cost), the elderly patient with LVEF < 25% might not be the most appropriate candidate at this stage. Careful patient selection remains crucial to ensure maximum benefit from this new technique.

The results of this study should be considered in light of the following limitations. As this is an observational study with a small sample size, the results should be interpreted cautiously. Particularly, identification of predictors of poor clinical response should be the subject of further research in adequately sized studies. This study describes the clinical outcome and does not provide valid data on LV volume evolutions which precludes assessment of the effect of Mitraclip® on LV remodelling.

CONCLUSIONS

In high-risk patients with functional MR, treatment with the Mitraclip® device is a feasible and safe option resulting in improvement of MR severity and clinical symptoms. However, as MACE is high in some subgroups (e.g. LVEF < 25%), careful patient selection is crucial to ensure the maximum benefit from this new technique.

CONFLICTING INTERESTS: none declared.

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