European Journal of Cardio-Thoracic Surgery 50 (2016) 488–494
doi:10.1093/ejcts/ezw093 Advance Access publication 23 March 2016

ORIGINAL ARTICLE

Cite this article as: De Bonis M, Lapenna E, Buzzatti N, La Canna G, Denti P, Pappalardo F *et al*. Optimal results immediately after MitraClip therapy or surgical edge-to-edge repair for functional mitral regurgitation: are they really stable at 4 years? Eur J Cardiothorac Surg 2016;50:488–94.

Optimal results immediately after MitraClip therapy or surgical edge-to-edge repair for functional mitral regurgitation: are they really stable at 4 years?[†]

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Received 15 September 2015; received in revised form 9 January 2016; accepted 25 January 2016

Abstract

OBJECTIVES: Recurrent mitral regurgitation (MR) is common after surgical and percutaneous (MitraClip) treatment of functional MR (FMR). However, the Everest II trial suggested that, in patients with secondary MR and initially successful MitraClip therapy, the results were sustained at 4 years and were comparable with surgery in terms of late efficacy. The aim of this study was to assess whether both those findings were confirmed by our own experience.

METHODS: We reviewed 143 patients who had an initial optimal result (residual MR ≤ 1+ at discharge) after MitraClip therapy (85 patients) or surgical edge-to-edge (EE) repair (58 patients) for severe secondary MR (mean ejection fraction 28 ± 8.5%). Patients with MR ≥ 2+ at hospital discharge were excluded. The two groups were comparable. Only age and logistic EuroSCORE were higher in the MitraClip group.

RESULTS: Follow-up was 100% complete (median 3.2 years; interquartile range 1.8;6.1). Freedom from cardiac death at 4 years (81 ± 5.2 vs 84 ± 4.6%, $P = 0.5$) was similar in the surgical and MitraClip group. The initial optimal MitraClip results did not remain stable. At 1 year, 32.5% of the patients had developed MR ≥ 2+ ($P = 0.0001$ compared with discharge). Afterwards, patients with an echocardiographic follow-up at 2 years (60 patients), 3 years (40 patients) and 4 years (21 patients) showed a significant increase in the severity of MR compared with the corresponding 1 year grade (all $P < 0.01$). Freedom from MR ≥ 3+ at 4 years was 75 ± 7.6% in the MitraClip group and 94 ± 3.3% in the surgical one ($P = 0.04$). Freedom from MR ≥ 2+ at 4 years was 37 ± 7.2 vs 82 ± 5.2%, respectively ($P = 0.0001$). Cox regression analysis identified the use of MitraClip as a predictor of recurrence of MR ≥ 2+ [hazard ratio (HR) 5.2, 95% confidence interval (CI) 2.5–10.8, $P = 0.0001$] as well as of MR ≥ 3 (HR 3.5, 95% CI 0.9–13.1, $P = 0.05$).

CONCLUSIONS: In patients with FMR and optimal mitral competence after MitraClip implantation, the recurrence of significant MR at 4 years is not uncommon. This study does not confirm previous observations reported in the Everest II randomized controlled trial indicating that, if the MitraClip therapy was initially successful, the results were sustained at 4 years. When compared with the surgical EE combined with annuloplasty, MitraClip therapy provides lower efficacy at 4 years.

Keywords: Secondary mitral regurgitation • Mitral valve repair • Percutaneous mitral repair • MitraClip

INTRODUCTION

Residual and recurrent mitral regurgitation (MR) are common after surgical and percutaneous (MitraClip) treatment of functional MR (FMR) and their negative impact on patients' outcome has been documented [1–6]. Most of the studies published so far on MitraClip treatment of secondary MR report only early results [7] and the Everest II is the only randomized controlled trial describing the clinical and echocardiographic outcomes of MitraClip therapy in FMR at 4 years [8]. Interestingly, the Everest II suggested that, in patients with secondary MR and initially successful MitraClip therapy, the results were sustained at 4 years and were most comparable with surgery in terms of late efficacy. This finding is of critical importance when considering this novel approach but, as acknowledged by the Everest II investigators, it has to be considered exploratory and requires further validation. The present study was specifically conceived to assess whether both

[†]Presented at the 29th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Amsterdam, Netherlands, 3–7 October 2015.

those Everest II findings were confirmed by our own experience. By using observational, prospectively collected data, we tried to assess whether optimal results (residual MR ≤ 1+ at hospital discharge) after MitraClip therapy for FMR remain stable at 4 years as previously suggested, particularly in terms of recurrence of MR. In addition, we evaluated the 4-year outcomes of patients with optimal mitral valve (MV) competence after percutaneous and surgical edge-to-edge (EE) repair to assess whether they were comparable at mid-term follow-up.

MATERIALS AND METHODS

Study population

Parts of the methods used in this study were previously described [9]. From 2008 to 2013, 126 patients with severe left ventricular (LV) dysfunction and severe or moderately severe secondary MR were treated with MitraClip therapy in our institution. Out of them, for the purpose of this study, we selected 85 consecutive patients with initial optimal MitraClip results (residual MR ≤ 1+ at hospital discharge). Those patients were compared with the first consecutive 58 patients (out of 65 patients) with FMR who underwent surgical mitral repair with the EE technique combined with annuloplasty between 1999 and 2006 and who were discharged with an initial optimal result (MR ≤ 1+) too. Therefore, the final study population includes 143 patients. In both groups, MR was secondary to both ischaemic or non-ischaemic dilated cardiomyopathy. Patients who died in the hospital, those with MR ≥ 2+ at hospital discharge and patients with primary MV disease, concomitant LV reconstruction or aortic valve procedures were excluded.

The Institutional Ethics Committee approved this study and waived individual consent for this retrospective analysis.

Echocardiography and patient selection

Transthoracic (TTE) and transoesophageal echocardiography (TEE) were routinely performed and an integrative approach was used to define MR severity [10]. A non-linear 4 grade scale was adopted to define MR was as mild (1+/4+), moderate (2+/4+), moderate-to-severe (3+/4+) and severe (4+/4+).

As far as the surgical patients are concerned, those included in this series were treated when the MitraClip system was not yet available. At that time, the most common echocardiographic MV parameters that were considered in patients with secondary MR, were the annular dimensions, the coaptation depth, the tenting area and the site of origin of the regurgitant jet. Moreover, particularly in case of severe LV dysfunction, dobutamine stress echocardiography (DSE) was usually performed unless the patient had atrial fibrillation, sinus tachycardia or inducible ventricular arrhythmias. DSE was used to assess the presence of a contractile reserve, to achieve a better preoperative risk stratification and, in patients with ischaemic dilated cardiomyopathy (DCM), to distinguish those who could benefit from concomitant myocardial revascularization (presence of viability) from those who required only MV surgery (absence of viability) [11].

For MitraClip candidates, the selection was based on the evaluation of the surgical risk by logistic EuroSCORE and by the careful assessment of other relevant comorbidities. Although the TEE EVEREST criteria for FMR were initially used as main reference (pathology in A2–P2 zone, coaptation length of >2 mm, coaptation depth of <11 mm, mitral valve orifice area of >4 cm) [12], with increasing experience, many patients were treated with criteria beyond EVEREST recommendations (for instance, patients with a coaptation depth of >11 mm and/or commissural rather than central regurgitant jet).

Procedural data

All patients undergoing surgical EE repair received a concomitant annuloplasty with a complete undersized ring, rigid or semirigid in most of the cases. This approach was preferred to the restrictive annuloplasty alone due to the presence of significant leaflet tethering (coaptation depth of ≥1 cm) with the aim to decrease the rate of recurrent MR [13]. The EE suture was positioned following an echo-guided approach: centrally (in case of central jet at TEE) or postero-medially (when the regurgitant jet at TEE was in correspondence with the posterior commissure).

MitraClip implantation was performed under general anaesthesia. Fluoroscopy, TEE and live real-time 3D echocardiography were used. Through a trans-septal puncture, a steerable guide catheter was advanced into the left atrium followed by the insertion of the delivery system. The MitraClip was implanted in correspondence with the origin of the regurgitation jet and when necessary, more than 1 clip was delivered in order to achieve the best possible immediate result.

Follow-up

A dedicated outpatient clinic for patients undergoing surgical treatment of secondary MR has been present in our institution since the year 2000 and is used to follow regularly those patients. A similar dedicated outpatient clinic for patients undergoing MitraClip therapy was started in 2008. Physical examination, electrocardiogram, TTE and arrhythmology consultation are routinely performed. All data are prospectively entered in a dedicated database and were reviewed and compared for the purpose of this study.

Statistical analysis

All data were prospectively entered in a dedicated database and analysed. Calculations were performed using SPSS version 22.0 (SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corp.) software package. The distribution of variables was evaluated using the Shapiro–Wilk test. Continuous data were expressed as mean + standard deviation or as median and interquartile range (IQR). Categorical data were reported as number and percentage. If continuous data were normally distributed, comparison between two groups was performed with the Student's *t*-test for (un)paired samples, as indicated. If they were not normally distributed, the Mann–Whitney *U*-test or the Wilcoxon signed-rank test was employed for independent or related samples, respectively. χ^2 test was used for categorical data and Fisher's exact test was used when the minimum cell size requirements for the χ^2 were not satisfied. New York Heart Association (NYHA) functional class and grade of MR were treated as ordinal variables and compared with the Wilcoxon signed-rank test (related samples) or with the Mann–Whitney *U*-test (independent samples). Time-to-event data (survival and freedom from events) were analysed by Kaplan–Meier method and differences among groups were evaluated with

the log-rank test. Cox proportional-hazard regression was used to estimate the HRs of potential predictors of cardiac death and recurrence of MR ≥ 3+ and MR ≥ 2+ at follow-up. Variables with a *P*-value <0.1 in univariate analysis were entered in a multivariable model.

RESULTS

Patient characteristics

The preoperative clinical and echocardiographic data of the patients are reported and compared in Table 1. Unlike our previous study [9], only patients with no or mild residual MR were included in this series. Most of the patients had severe LV dysfunction and were in NYHA functional class III or IV. The two groups were comparable for the vast majority of the variables. LV dimensions and function, systolic pulmonary artery pressure (SPAP), MV coaptation depth and tented area were not significantly different. Only age (*P* = 0.0001) and logistic EuroSCORE (*P* = 0.04) were significantly higher in the MitraClip group.

Procedural data

In the surgical group, the EE repair was performed centrally in 52 cases (52/58, 90%) and postero-medially in the remaining 6 patients (6/58, 10%). All patients received an undersized annuloplasty with complete semirigid (Seguin, St. Jude Medical) or rigid (Carpentier–Edwards, Classic) rings in 91% of the cases (53/58). Flexible rings (Duran, Medtronic, Inc. or Tailor St. Jude Medical) were used only at the beginning of our experience in 9% of cases (5/58). The mean ring size was 28.8 ± 2.32. Concomitant coronary artery bypass graft surgery (CABG) was performed in 27 patients (46%) with ischaemic DCM. Other associated procedures were tricuspid valve repair in 11 patients (19%), bipolar radiofrequency ablation of permanent atrial fibrillation in 8 (14%) and cardiac support device (CorCap™, ACORN Cardiovascular) implant in 1 (2%).

In the MitraClip patients, one clip was implanted in 30 patients (30/85, 35%), two clips were implanted in 53 (53/85, 62%) and three clips were implanted in 2 (2/85, 2%).

Table 1: Clinical and echocardiographic preoperative data in the 'MitraClip' and 'Surgical edge-to-edge' groups

	MitraClip group *n* = 85	Surgical EE group *n* = 58	*P*-value
Male gender (*n*, %)	70 (82)	40 (69)	0.06
Age (years)	69 ± 9.4	62 ± 10.1	0.0001
Ischaemic DCM (*n*, %)	62 (73)	36 (62)	0.1
NYHA class (*n*, %)			0.9
II	13 (15)	9 (15)	
III	57 (67)	36 (62)	
IV	15 (17)	13 (22)	
Atrial fibrillation (*n*, %)	24 (28)	12 (20)	0.3
Log EuroSCORE	19 ± 15.9	11.4 ± 3.2	0.04
LVEF (%)	28 ± 9.7	28 ± 6.5	0.4
LVEDD (mm)	67 ± 7.8	69 ± 5.8	0.1
LVESD (mm)	54 ± 9.1	52 ± 7.9	0.3
LVEDV (ml)	188 ± 66.2	203 ± 58.02	0.1
SPAP (mmHg)	47 ± 14.2	48 ± 13.2	0.5
SPAP > 40 mmHg (*n*, %)	46 (54)	33 (56)	0.1
TR 3+ or 4+ (*n*, %)	17 (20)	11 (19)	0.8
Coaptation depth (cm)	1.2 ± 0.34	1.2 ± 0.46	0.5
Tented area (cm^2)	2.8 ± 0.99	2.8 ± 0.88	0.6

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEDV: left ventricular end-diastolic volume; SPAP: systolic pulmonary artery pressure; TR: tricuspid regurgitation; EE: edge-to-edge; NYHA: New York Heart Association; DCM: dilated cardiomyopathy.

Clinical hospital outcomes

Prophylactic support with intra aortic balloon pump (IABP) was used in 39 patients (39/58, 67%) in the surgical group and in 1 patient (1/85, 1.1%) in the MitraClip group (*P* < 0.0001), IABP support was required during the postoperative period in 2 more surgical patients and in 8 MitraClip ones (*P* = 0.1). Postoperatively, no significant differences were observed in terms of acute renal failure requiring continuous veno-venous haemofiltration (3.4 vs 3.5%, *P* = 1.0), low output syndrome (3.4 vs 3.5%, *P* = 1.0), cerebrovascular accident (1.7 vs 0%, *P* = 0.4), respiratory failure requiring tracheostomy (3.4 vs 0%, *P* = 0.1) and sepsis (3.4 vs 3.5%, *P* = 1.0), between surgery and MitraClip. Mediastinitis occurred in 1 surgical patient (1/58, 1.7%). One MitraClip patient (1/85, 1.1%) had a retroperitoneal haematoma and one patient (1/85, 1.1%) underwent sternotomy to repair a tear in the right ventricle. Postoperative median length-of-stay was 10 days (IQR: 8–13 days) for surgery and 4.8 days (IQR: 3.8–7 days) for MitraClip (*P* < 0.0001).

Follow-up

Clinical outcomes. Follow-up was 100% complete and was significantly longer in the surgical patients (median 7.2 years, IQR 3.4;9.9 vs 2.5 years, IQR 1.5;3.6) (*P* = 0.0001).

Overall survival (77 ± 5.6 vs 74 ± 5.1%, *P* = 0.2) and freedom from cardiac death at 4 years (82 ± 5.2 vs 84 ± 4.6%, *P* = 0.5) were not significantly different between surgery and MitraClip (Fig. 1). During follow-up, 31 patients died in the surgical group and the cause was cardiac related in 19 of them: congestive heart failure

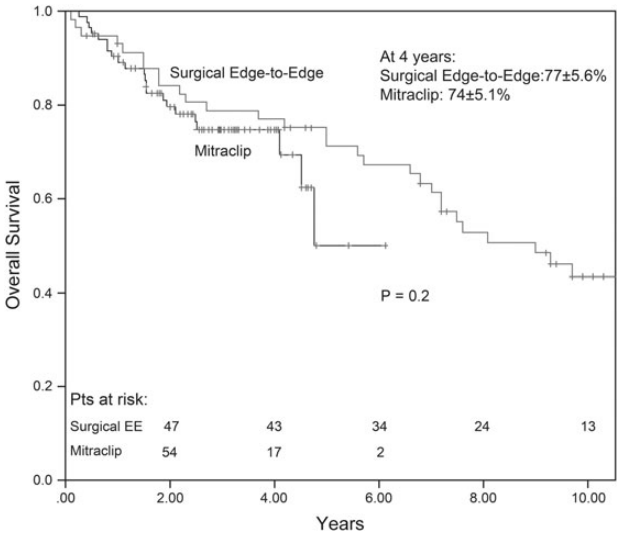

Figure 1: Overall survival. EE: edge-to-edge.

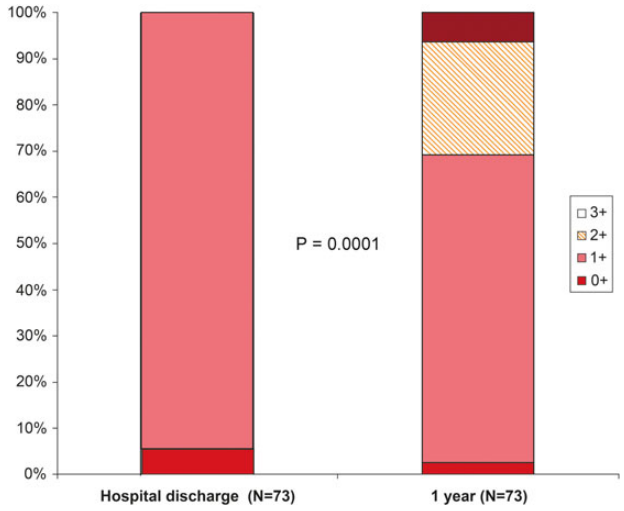

Figure 2: MR severity at hospital discharge and 1 year after MitraClip procedure. Results are matched and paired comparisons are presented for patients who had an echocardiographic follow-up at both time points. MR: mitral regurgitation.

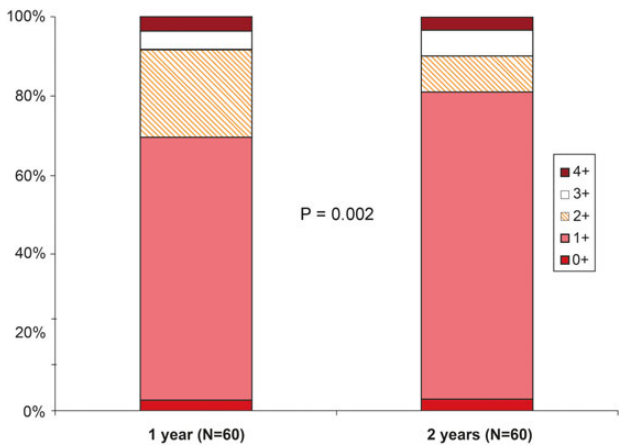

Figure 3: MR severity at 1 and 2 years after MitraClip procedure. Results are matched and paired comparisons are presented for patients who had an echocardiographic follow-up at both time points. MR: mitral regurgitation.

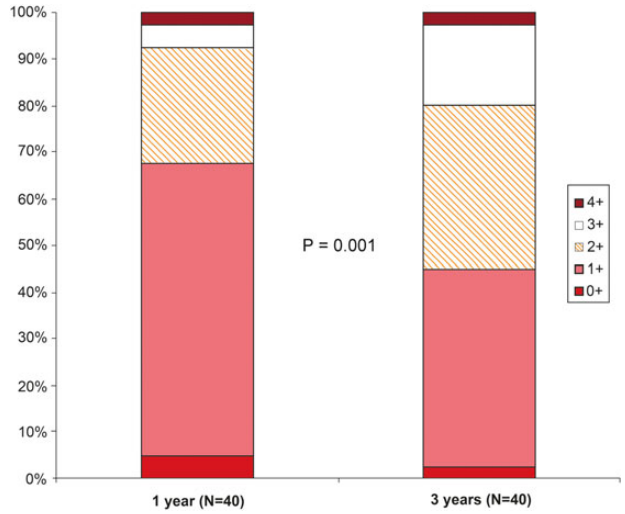

Figure 4: MR severity at 1 and 3 years after MitraClip procedure. Results are matched and paired comparisons are presented for patients who had an echocardiographic follow-up at both time points. MR: mitral regurgitation.

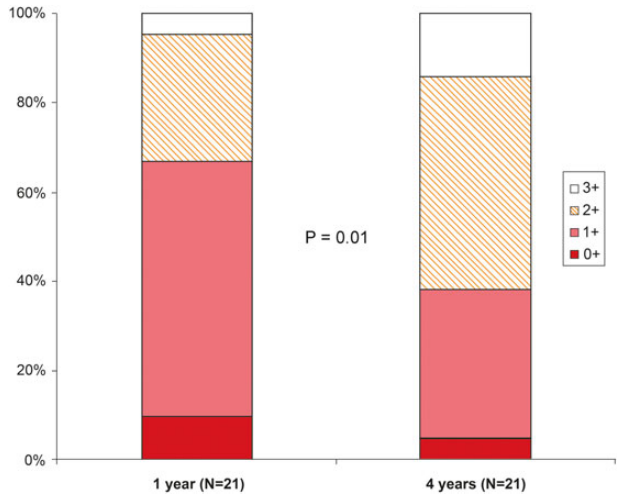

Figure 5: MR severity at 1 and 4 years after MitraClip procedure. Results are matched and paired comparisons are presented for patients who had an echocardiographic follow-up at both time points. MR: mitral regurgitation.

(10 patients), sudden death (5 patients), myocardial infarction (2 patients), RV failure following heart transplantation (1 patient) and RV failure after left ventricular assist device (LVAD) implantation (1 patient). Three surgical patients were reoperated (3/58, 5%): 1 patient underwent heart transplantation, 1 patient was submitted to LVAD implantation and 1 to MV replacement.

In the MitraClip group, 22 patients died and 10 deaths were cardiac related: congestive heart failure (5 patients), sudden death (1 patient), refractory ventricular arrhythmia (1 patient), pulmonary oedema with superimposed pulmonary infection (1 patient), acute myocardial infarction (1 patient), RV failure following heart transplantation (1 patient). Among the MitraClip population, 1 patient underwent heart transplantation, 2 patients with recurrent severe MR underwent repeat MitraClip implantation, 1 patient was submitted to CABG surgery (left internal mammary artery to left anterior descending), 1 patient with severe aortic stenosis underwent transcatheter aortic valve implantation and 2 patients were submitted to surgical MV replacement for severe MR (one of them needed subsequent LVAD implantation). The reoperation rate for recurrent severe MR was not significantly different between the two groups ($P = 0.7$).

In the surgical group, no risk factors for cardiac mortality were identified. On the other hand, in the MitraClip patients, the preoperative LV end-diastolic diameter (EDD) was the only independent predictor of cardiac death at multivariate analysis (HR 1.2, 95% CI 1–1.4, $P = 0.03$).

Echocardiographic and clinical data. According to the inclusion criteria of the study, at hospital discharge 96% of the MitraClip patients had mild (1+) residual MR and 6% had no MR at all. At 1 year, the echocardiographic prevalence of MR ≥ 2+ was 32.5% (25.5% of the patients had MR 2+ and 7% had MR 3+) ($P = 0.0001$ compared with hospital discharge) (Fig. 2). Furthermore, to assess whether the degree of MR at 12 months remained stable or changed over the years, we used paired comparisons of the MR grade between 1 and 2 years (60 patients), 1 and 3 years (40 patients) and 1 and 4 years (21 patients). All comparisons

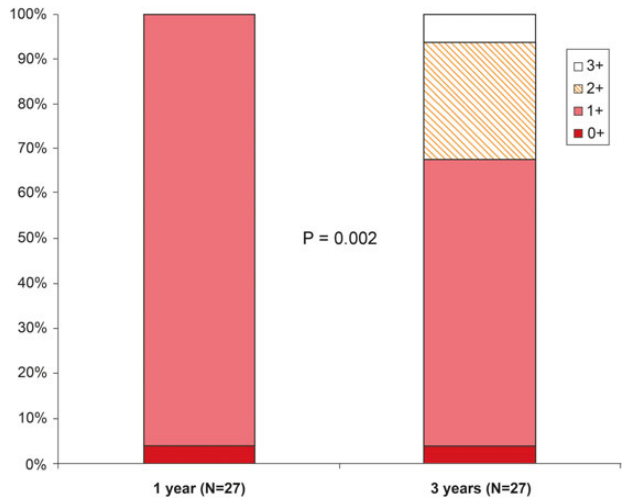

Figure 6: MR severity at 1 and 3 years after MitraClip procedure in patients who had been discharged with no or mild MR and still showed the same grade of MR after 12 months. Results are matched and paired comparisons are presented for patients who had an echocardiographic follow-up at both time points. MR: mitral regurgitation.

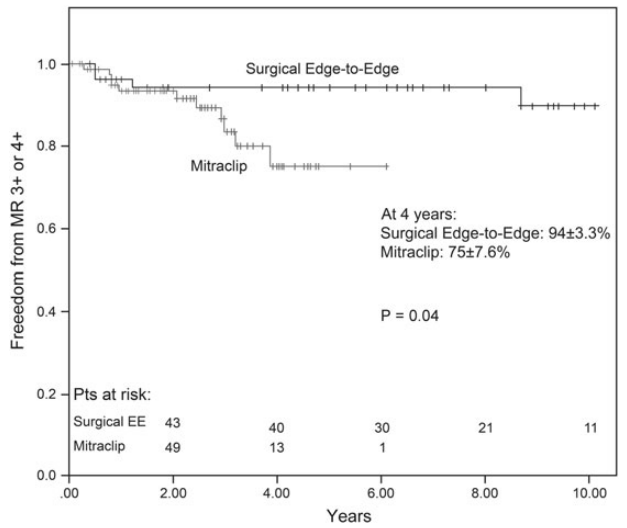

Figure 7: Freedom from recurrent MR ≥ 3+. MR: mitral regurgitation; EE: edge-to-edge.

showed a statistically significant increase in the prevalence of MR ≥ 2+ compared with 1 year (all $P < 0.01$) (Figs 3–5). In addition, we decided to evaluate whether the patients who maintained at 1 year their initial optimal result had sustained MV competence even 3 or 4 years after the procedure. For that purpose, we carefully assessed the behaviour of 53 patients who had been discharged with no or mild MR and still showed the same grade of MR after 12 months. The degree of MR could be compared between 1 and 2 years in 42 of those patients and between 1 and 3 years in 27 of them. Again, we found a progression of MR of at least one grade in 19% of these selected patients (8/42) at 2 years and in 33% of them (9/27) at 3 years (Fig. 6). Therefore, in our series, the initial optimal competence of the mitral valve after MitraClip implantation did not prevent the progression of MR at longer follow-up and the results at discharge did not remain stable over time up to 4 years.

When MitraClip patients were compared with those undergoing surgical EE repair, the overall efficacy of surgery was significantly higher than that of MitraClip. Among 44 surgical patients with a TTE control at 4 years, the prevalence of MR2+ was 14% (6/44 patients) and of MR 3+ or 4+ was 4.5% (2/44 patients) ($P < 0.001$ compared with the MitraClip group). The 4-year freedom from MR ≥ 3 and freedom from MR ≥ 2+ were both significantly higher in patients who underwent surgical EE repair compared with those treated with Mitraclip (94 ± 3.3 vs 75 ± 7.6%, $P = 0.04$ and 82 ± 5.2 vs 37 ± 7.2%, $P = 0.0001$) (Fig. 7). Cox regression analysis identified the MitraClip as a predictor of recurrent MR ≥ 3 (HR 3.7, 95% CI 1.0–13.8, $P = 0.04$) as well as of MR ≥ 2+ (HR 5.2, 95% CI 2.5–10.8, $P = 0.0001$). Other variables which were tested and which were not identified as predictors of MR recurrence were age (HR 1, $P = 0.7$), atrial fibrillation (HR 1.1, $P = 0.8$), logistic EuroSCORE (HR 1, $P = 0.5$), left ventricular ejection fraction (LVEF) (HR 0.9, $P = 0.5$), LV EDD (HR 0.9, $P = 0.4$), SPAP (HR 1, $P = 0.4$), idiopathic DCM (HR 2.1, $P = 0.1$).

In both the groups, an improvement in LVEF and SPAP was observed from baseline to the last follow-up. In particular, LVEF increased from 29 ± 6.6 to 35 ± 12.4% in the surgical group ($P = 0.0001$) and from 28 ± 10.06 to 33 ± 11.5% in the MitraClip group ($P = 0.004$). The SPAP decreased from 48 ± 12.3 to 38 ± 8.9 mmHg in patients who underwent surgery ($P = 0.0001$) and from 46 ± 14.07 to 39 ± 11.7 mmHg in patients who underwent MitraClip implantation ($P = 0.0001$). Finally, a decrease in the LVEDD was documented for surgery (from 69 ± 5.5 to 62 ± 9.5 mm, $P = 0.0001$) but not for MitraClip (from 67 ± 7.8 to 66 ± 10.3 mm, $P = 0.1$).

At last follow-up, a significant clinical improvement was also noted in both the groups. NYHA class III or IV was present preoperatively in 85% of the MitraClip patients (72/85) and in 11% (9/85) at last follow-up ($P < 0.0001$). In the surgical group, NYHA III or IV was reported in 84% of the patients (49/58) at baseline and in 22% (13/58) at follow-up ($P < 0.0001$).

DISCUSSION

This study was performed with the purpose of verifying the observations reported in the Everest II trial indicating that, if the MitraClip therapy for FMR was initially successful, the results were sustained at 4 years and were most comparable with that of surgery [8]. Both those findings are of critical importance but, as acknowledged by the Everest investigators, they should be viewed as exploratory for several reasons. The overall number of FMR patients in the Everest II trial is very small: 75 patients were randomized and 66 of them had follow-up data at 4 years (only 22 belonging to the surgical group). In addition, the efficacy endpoint used in the Everest II (freedom from death, reoperation for MV dysfunction and freedom from MR ≥ 3+) might not be able to detect less severe degree of MR progression, which can have anyway prognostic implications [14, 15]. Those preliminary findings, therefore, need to be further confirmed and, for that reason, we thought it would have been important to address this issue.

Since the Everest II showed that an initial success represents the key point to achieve late MitraClip durability, we decided to select only MitraClip patients with optimal initial results (residual MR ≤ 1+ at hospital discharge) to assess whether they remained really stable at 4 years. A strength of our study is that regular echocardiographic follow-ups were performed in a dedicated outpatient clinic. Prospectively collected data demonstrated that about one-third of the MitraClip patients with no or mild MR at hospital discharge developed at least moderate MR at 1 year. This observation, by itself, proves that an initial optimal MV competence after MitraClip implantation is not sufficient to prevent MR

progression in a number of patients. Further deterioration of the severity of MR occurred at longer follow-up and up to 4 years. Interestingly, even the MitraClip patients with stable optimal results 1 year after the procedure showed MR progression of at least one grade in more than 20% of the cases. Overall, those data indicate that the initial optimal results of the percutaneous EE repair do not remain stable throughout the follow-up period and up to 4 years, as suggested by the Everest II trial.

When MitraClip patients were compared with those undergoing surgical EE repair, the efficacy of surgery was significantly higher than that of MitraClip. Although this was not a randomized study, the baseline characteristics of patients in both the groups were generally well balanced in terms of LV size and function, SPAP, atrial fibrillation, MV tethering. Only age and logistic EuroSCORE were significantly higher in the MitraClip group. Such a similarity can be explained by the fact that the surgical patients enrolled in this analysis were treated at a time when the Mitraclip was not yet available and, therefore, surgery was the only treatment option even for cases at high surgical risk due to severe LV remodelling and dysfunction.

While there was no difference between the two groups in late mortality and operation for MV dysfunction, the rate of recurrent MR at least moderate (2+) was significantly higher in the MitraClip patients. The higher efficacy of surgery was further demonstrated by a 4-year freedom from MR $\geq$ 3+, which was 20% higher in the surgical group, and a freedom from MR $\geq$ 2+, which was 45% better. Not surprisingly, the MitraClip was identified as an independent predictor of both recurrent MR $\geq$ 3 and MR $\geq$ 2+. The absence of a concomitant annuloplasty is one of the most likely explanation of the higher recurrence rate of MR in the percutaneous approach despite the initial restoration of valve competence [16, 17]. We already reported that, in secondary MR, MitraClip is less effective than surgical EE repair [9] but in that series, as in other similar [18], the presence of residual MR > 1+ in a significant proportion of MitraClip patients led to later deterioration of the initial suboptimal results, compromising since the beginning the overall outcomes of those patients. In the present study, for the first time, this bias has been eliminated by selecting only patients with optimal initial results. Despite this optimal initial MV competence, MitraClip results did not remain stable and were inferior to those achieved by the surgical EE repair in terms of recurrent MR. Surprisingly, overall survival and freedom from cardiac death at 4 years were similar between surgery and transcatheter treatment. This is most likely due to the small sample size precluding sufficient power to fully understand the impact of the degree of recurrent MR on long-term survival.

From a clinical point of view, MitraClip patients had a shorter hospital stay and most of them were discharged home, confirming that the overall impact on the patients of the MitraClip procedure was substantially lower than surgery. In both the groups, an improvement in LVEF and SPAP was observed while a significant decrease in the LVEDD was documented only for surgery but not for MitraClip. This observation is in agreement with the Everest II data, which also showed smaller LVEDD in the surgical group at 4 years [8]. The higher rate of recurrent MR could justify this finding. Finally, at last follow-up, a significant clinical improvement was noted in both the groups.

In summary, our study showed that, in patients with secondary MR and optimal mitral competence after MitraClip implantation, the initial results did not remain stable up to 4 years after the procedure and were inferior to those achieved by the surgical EE repair in terms of recurrence of MR.

Limitations

This study does have several limitations. The number of FMR patients selected for this analysis is relatively small although it remains higher than that assessed in the Everest II trial. Outcomes like survival and freedom from cardiac death might have been significantly influenced by the numerical limitations of the selected population. According to the selection criteria of the study population, hospital deaths were not included and this should be considered when assessing late overall survival and freedom from cardiac deaths. The two groups were not randomized and selection bias cannot therefore be excluded. Data were prospectively collected but the limitations of the retrospective analysis should not be overlooked. Finally, only variables that were consistently measured at baseline and at follow-up could be compared. Conversely, several clinical and echocardiographic parameters were not available in all patients and could not be analysed including MV tethering angles, LV sphericity index, LV volumes, interpapillary distance. The surgical patients used as control group underwent EE repair combined with annuloplasty. The reported comparative outcomes with MitraClip are therefore limited to this specific surgical approach.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

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Dr V. Delgado *(Leiden, Belgium):* Treatment of patients with functional mitral regurgitation and poor left ventricular ejections fraction is currently a very hot topic. My question to you is, since these two populations were not contemporary, which of the patients that you treated surgically, would have been eventually better candidates for Mitraclip and which of the patients who were treated with Mitraclip would you select now for surgical repair?

Dr De Bonis: I will answer the second one. None of the patients treated with MitraClip would have been nowadays treated in our institution with surgery, because they were really very high risk patients. So probably a significant proportion of the patients treated surgically would have nowadays been considered for MitraClip, because they were very sick. At that time we did not have MitraClip but many of those patients did have pulmonary oedema, two or three episodes in the previous six months, despite optimal medical therapy. So we felt we had to do something and we did operate on them. Currently we would have considered many of them for Mitraclip and probably those who were likely to have significant concomitant revascularization, would have still been considered for surgery.

Dr Delgado: My second question is that based on the Kaplan-Meier results on all-cause mortality and cardiovascular mortality that you showed, do you think that having significant recurrent mitral regurgitation has any impact on outcome and if we need to check the presence of mitral regurgitation anyway at follow-up?

Dr De Bonis: The surprising finding is that it seems that it does not make any difference. Now, the possibilities are basically two. So the first one is that the patients are too few and if you add 2,000 patients you don't know what is going to happen. That's the first point. The second point is, that if you wait for those patients to be so sick, then to have 2+ or 3+ recurrent mitral regurgitation doesn't seem to make any difference. If we want to do something which is more than palliation and more effective, we have to intervene much earlier.

Dr Delgado: Then the next question would be, do we need maybe also to check other end points, like, for example, in terms of left ventricular reverse remodelling to define response to Mitraclip?

Dr De Bonis: We did that actually, not in this study but before. We had in our population 52% of the patients who had reverse remodelling despite starting with an end-diastolic diameter of approximately 70 mm. But, of course, they also had in two-thirds of the cases myocardial revascularization. So what we have been learning in those 15 years is that, again, reverse remodelling is not a dichotomous event. You have reverse remodelling after two years, and then in some patients the left ventricle starts to remodel again. So where do you put the bar, where do you stop your assessment? At two years we had 52% of the patients having reverse remodelling but then several of them went on progressing in their disease. So, yes, we should look at reverse left ventricle remodelling but it does not solve the question I guess.

Dr V.A. Subramanian *(New York, NY, USA):* What you have shown is that the early inexperience in MitraClip in your institution has produced more recurrent mitral regurgitation. Longstanding surgically you do have recurrent mitral regurgitation. It is not as severe but it is still progressive. So something else is going on, as I said. We need to understand the mechanism of recurrence in any of these procedures. We absolutely have no idea. If we understand the mechanism, it will be better.