Surgical or percutaneous mitral valve repair for secondary mitral regurgitation: comparison of patient characteristics and clinical outcomes†

Lenard Conradi*, Hendrik Treede‡, Volker Rudolph, Paul Graumüller, Edith Lubos, Stephan Baldus, Stefan Blankenberg and Hermann Reichenspurner

University Heart Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

* Corresponding author. University Heart Center Hamburg, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany. Tel: +49-40-741053440; fax: +49-40-741054931; E-mail: lconradi@uke.de (L. Conradi).

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Abstract

OBJECTIVES: Corrective surgery for secondary mitral regurgitation (MR) by restrictive annuloplasty has proven beneficial in that it improves New York Heart Association (NYHA) functional class and induces reverse left ventricular remodelling. However, proof of a survival benefit for these patients is still pending. Percutaneous techniques of mitral valve repair (MVR) have become a viable treatment alternative for selected high-risk patients with severe secondary MR.

METHODS: We retrospectively analysed our prospective hospital database of patients with severe secondary MR undergoing either surgical MVR or percutaneous treatment using the MitraClip device. Patient characteristics and 6-month clinical and effectiveness outcomes are reported.

RESULTS: From March 2002 through June 2010, 76 patients with secondary MR underwent isolated surgical MVR, while 95 were treated using the MitraClip device at our centre. Patients undergoing MitraClip treatment were significantly older (mean 72.8 ± 8.2 vs 64.5 ± 11.4 years, P < 0.001), had a lower left ventricular ejection fraction (mean 36.2 ± 12.5 vs 42.1 ± 16.2%, P = 0.014) and were generally more high risk, with a significantly higher mean logistic EuroSCORE I compared with surgical candidates (33.7 ± 18.7 vs 10.1 ± 8.7%, P < 0.001). Procedural success was 98.7% (75 of 76) for MVR and 95.8% (91 of 95) for MitraClip treatment (P = 0.383). Thirty-day mortality was 4.2% (4 of 95) and 2.6% (2 of 76; P = 0.557), and the mean grade of residual MR was 1.4 ± 0.8 and 0.2 ± 0.4 (P < 0.001) after MitraClip treatment and surgical MVR, respectively. Six-month survival rates after adjustment for baseline differences were not significantly different in the respective groups (P = 0.642).

CONCLUSIONS: In our experience, characteristics and risk factors of patients with severe secondary MR undergoing surgery differ significantly from those considered for percutaneous therapy. Surgery was more effective compared with MitraClip in reducing MR. However, a large proportion of patients benefits from percutaneous intervention with sustained MR Grade <2+ and improvement in NYHA functional class at 6 months. MitraClip therapy seems to be an adequate alternative to surgery, especially for elderly patients with reduced left ventricular function and relevant comorbidities. Assessment, treatment and postprocedural care of patients by an interdisciplinary team are of paramount importance for clinical success.

Keywords: Functional mitral regurgitation · Mitral valve repair · MitraClip · Percutaneous

INTRODUCTION

Surgical mitral valve repair (MVR) is currently the reference treatment for symptomatic severe mitral regurgitation (MR) with superior acute and long-term outcomes compared with prosthetic valve replacement [1, 2]. Due to low perioperative morbidity and mortality, MVR may even be considered in asymptomatic patients [3]. Implementation of minimally invasive surgical techniques has decreased surgical trauma and further enhanced postoperative recovery [4]. In patients with ventricular dysfunction and secondary MR, however, the merits of corrective mitral valve surgery may be more ambiguous, and a survival benefit has not been demonstrated to date [5]. In addition, a substantial share of patients with severe MR is not being referred for surgery due to perceived high surgical risk [6]. Frequently, these are elderly patients with relevant comorbidities, reduced left ventricular function and secondary MR [7]. It is for these patients that percutaneous treatment options may be an adequate alternative [8]. The MitraClip device is a transcatheter-based extension of the surgical edge-to-edge repair technique first described by Alfieri et al. [9].

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It allows for beating-heart approximation of the free edges of the anterior and posterior mitral leaflets at the origin of the regurgitant jet by use of a polyester fabric-covered cobalt-chromium clip [10].

We report our experience from an integrated mitral valve programme with percutaneous treatment using the MitraClip system and mitral valve surgery for the treatment of secondary MR.

PATIENTS AND METHODS

Patients

This analysis includes data from all consecutive patients with pure secondary MR treated at our centre by means of isolated surgical MVR or receiving MitraClip treatment from March 2002 through June 2010. Data were prospectively entered into a dedicated hospital database and retrospectively analysed. Indication for treatment was determined according to criteria defined by the European Society of Cardiology guidelines for patients with valvular heart disease [1]. All patients were reviewed by an inter-disciplinary dedicated heart valve team consisting of cardiac surgeons and interventional cardiologists and allocated to surgical or percutaneous treatment by mutual agreement.

Study endpoints

Primary safety endpoints of the study were mortality at 30 days and survival during further follow-up up to 180 days after the index procedure. Primary efficacy endpoint was defined as procedural success by placement of an annuloplasty ring or one or more MitraClips with acute reduction of MR to ≤Grade 2 graded according to current recommendations [11]. Clinical and haemodynamic outcomes are reported up to a follow-up of 6 months after the respective procedures. Patients requiring secondary MVR after failed MitraClip treatment were followed as interventional patients according to an intention-to-treat principle.

Study procedures

Mitral valve surgery was performed via median sternotomy in 69 patients and using minimally invasive techniques in the remaining 9 patients. In all cases, cardiopulmonary bypass was implemented and valve repair was performed on the arrested heart under mild hypothermia (32°C). Access to the mitral valve was gained either via a direct left atrial or via a trans-septal access according to the surgeons’ preference. Complete, rigid or semi-rigid annuloplasty rings were used in all cases. All procedures were quality controlled using intraoperative transoesophageal echocardiography (TEE).

MitraClip treatment was performed in a cardiac catheterization laboratory or hybrid operating suite as previously described [12]. In brief, the MitraClip device was inserted via the femoral vein and advanced into the left atrium after trans-septal puncture. The clip was positioned above the regurgitant jet, opened and oriented perpendicularly to the line of leaflet coaptation. Finally, the clip was advanced into the left ventricle and retracted, grasping the free edges of both anterior and posterior mitral leaflets. Before final deployment of the clip, reduction of the grade of MR was assessed by TEE under physiological haemodynamic conditions. Multiple imaging modalities, including two- and three-dimensional TEE and fluoroscopy, were used to guide the implantation procedure, to control for treatment success, to rule out iatrogenic mitral valve stenosis or relevant atrial septal defect formation.

Statistical analysis

Data are presented as absolute numbers and percentages for categorical variables, and mean values and standard deviations for continuous variables written as mean ± SD. Dichotomous variables were compared using Fisher’s exact test, and continuous variables by unpaired t-tests with different variance assumption. Kaplan–Meier analysis and log-rank test were used for time-to-event analyses. P-values are reported without correction for multiple testing, and P-values <0.05 were considered statistically significant. Baseline variables were entered into a univariate Cox regression model. Variables associated with a univariate P-value <0.05 were subsequently entered into a multivariate model using backward selection. Patients were allocated to either treatment group following an intention-to-treat analysis. All statistical analysis was performed using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA) or the statistical package R version 2.12.2 [13].

RESULTS

Patient demographics and risk profile

From March 2002 through June 2010, 171 consecutive patients were treated by isolated surgical MVR (n = 76) or received MitraClip treatment (n = 95) for secondary MR. Patient baseline demographics and risk factors are detailed in Table 1. Between the surgical and the percutaneous cohort, there were several important differences regarding patient characteristics. Patients receiving MitraClip treatment were significantly older (P < 0.001), had a significantly lower left ventricular function (P = 0.014) and were generally more high risk due to a higher incidence of important risk factors, resulting in a significantly higher mean logistic EuroSCORE I (P < 0.001) compared with surgical candidates. In particular, patients receiving MitraClip treatment had undergone previous cardiac surgery (mostly coronary revascularization) by far more often compared with surgical patients (P < 0.001) and accordingly, aetiology of MR was significantly different between the two cohorts with a predominance of ischaemic MR in MitraClip patients (Table 1). In both cohorts, the vast majority of patients was highly symptomatic with 88.2 and 97.8% of patients in New York Heart Association (NYHA) functional Classes III or IV for MVR and MitraClip, respectively (P < 0.001).

Periprocedural data

Procedural success was 98.7 (75 of 76) for MVR and 95.8% (91 of 95) for MitraClip treatment (P = 0.383). In one surgical patient, residual MR was >Grade 2 at discharge. In 4 patients, MitraClip treatment was unsuccessful with conversion to elective surgery in 3 cases on Days 0, 2 and 4, respectively, after the index procedure. Surgical MVR was performed in 2, biological mitral valve replacement in 1 of these cases. One patient with persistent severe MR died 9 days later due to exacerbation of chronic heart failure refractory to medical therapy.
In the surgical cohort, time on cardiopulmonary bypass was 122.5 ± 38.2 min, and aortic cross-clamp time was 72.9 ± 18.1 min. All surgical patients received an annuloplasty using a complete rigid or semi-rigid ring: 44 Physio I or II, 18 IMR ETlogix, 13 Memo 3D (Sorin Biomedica Cardio, Saluggia, Italy). The mean ring size was 28.7 ± 1.8 mm. In the MitraClip cohort, the majority of patients, multivariate analysis was performed using baseline parameters with P-values <0.05 from prior univariate analysis (Table 3). Independent significant predictors of mortality up to 180 days of follow-up were age (6.4% increase with each year, 95% confidence interval [95% CI] 1.004–1.0, P = 0.049) for the overall group of patients.

**Mortality**

Mortality rates at 30 days were not significantly different between surgical and interventional cohorts with 2.6% (2 of 76) and 4.2% (4 of 95), respectively (P = 0.557, Table 2). The cause of death was cardiac in 2 patients in the surgical cohort, and it was cardiac in 3 and non-cardiac in 1 patient in the MitraClip cohort. During further follow-up, Kaplan–Meier survival estimates demonstrated unadjusted cumulative survival rates of 96 and 87% at 6 months for MVR and MitraClip, respectively (mean follow-up MVR 168 ± 39 and MitraClip 155 ± 55 days). To adjust for baseline differences in surgical compared with percutaneous patients, multivariate analysis was performed using baseline parameters with P-values <0.05 from prior univariate analysis (Table 3). Independent significant predictors of mortality up to 180 days of follow-up were age (6.4% increase with each year, 95% confidence interval [95% CI] 1.004–1.0, P = 0.049) for the overall group of patients. Accordingly, survival curves adjusted for age and LVEF no longer showed statistically significant survival differences between the two cohorts (P = 0.642) underscoring the impact of baseline differences (Fig. 1).

**Echocardiographic and clinical outcomes**

Surgery was more effective in reducing the grade of MR acutely compared with MitraClip treatment with a mean grade of residual MR of 0.2 ± 0.4 and 1.4 ± 0.8 (P < 0.001) after surgical MVR and MitraClip treatment, respectively. Postoperatively, residual MR was ≥Grade 2 in 98.7% (75 of 76) after MVR and 95.8% (91 of 95) after MitraClip treatment (P = 0.383). During further follow-up up to 180 days after the index procedure, freedom from recurrent MR >Grade 2 was significantly higher in patients after MVR compared with MitraClip therapy (P (log rank) < 0.001, Fig. 2).
At latest follow-up, 82.8 and 69.9% of patients were in NYHA functional Classes I or II for MVR (mean follow-up 212 ± 85 days) and MitraClip (mean follow-up 198 ± 59 days), respectively (P = 0.104). Compared with baseline, 79.3 and 79.5% of patients improved by at least one NYHA functional class, 22.4 and 20.5% of patients improved by two or more NYHA functional classes for MVR and MitraClip, respectively. Rates of rehospitalization for heart failure up to 180 days after the index procedure were significantly higher in patients receiving MitraClip therapy (22.1%, 21 of 95) compared with surgery (5.5%, 5 of 76; P = 0.005).

**DISCUSSION**

Even though surgical MVR has become a routine procedure for the treatment of secondary MR, good short-term functional outcomes are impaired by increased perioperative mortality compared with degenerative disease [14, 15] and relevant rates of recurrent MR [16, 17]. Percutaneous MitraClip therapy may be an adequate and less invasive alternative for selected high-risk patients. Furthermore, clinical experience in Europe and North America indicates that secondary MR may be the primary entity for this new non-surgical treatment option [8, 10, 18, 19]. However, patient selection for either treatment modality remains controversial.

**Main findings**

This study demonstrates that patients considered for surgical or percutaneous MVR for secondary MR are fundamentally different regarding baseline demographics and many risk factors. A higher overall risk profile in percutaneous patients culminates in significantly higher mean logistic EuroSCORE I. It is therefore very likely that differences between the two groups in clinical
outcomes stem from these fundamental differences at baseline. This circumstance has to be considered whenever looking at clinical endpoints, especially mortality. However, comparison of the two groups is still justified to investigate whether the two treatment modalities are competitive or complementary and to discriminate and characterize the two respective populations. These findings suggest that MitraClip is rather a complementary treatment option, and patients considered for percutaneous MVR likely stem from an on-top recruitment process instead of being drawn from the surgical patient population.

Periprocedural data

Procedural success defined as a placement of one or more clips or an annuloplasty device, respectively, with acute reduction of MR to Grade ≤2 was high in both cohorts. Rates of periprocedural complications were acceptable for both types of procedures. Naturally, the comparison of rates and the type of periprocedural complications between the two cohorts make little sense due to the completely different technical nature of the two respective procedures.

Mortality

Acute mortality to 30 days was low in both cohorts with 2.6% after surgery and 4.2% after MitraClip therapy ($P = 0.557$), demonstrating that both procedures are safe for the respective patient population. Results after MitraClip treatment compare favourably with other published reports on use in high-risk patients with severe secondary MR. In a multicentre series by Franzen et al. [18], 30-day mortality was 6% in a population of patients with ischaemic and non-ischaemic secondary MR and comparable operative risk with the present report with a logistic EuroSCORE I of $34 \pm 21\%$. The high-risk registry from the EVEREST Trial [20] reports acute mortality at 7.7% in a population of patients with predominantly degenerative MR. Even though logistic EuroSCORE I is not specified in this analysis, a mean Society of Thoracic Surgeons (STS) score of $14.2 \pm 8.2\%$ suggests a comparable risk profile. Recently, the German transcatheter mitral valve interventions (TRAMI) registry reported the results in a mixed patient population with secondary MR in 67% of cases, a mean logistic EuroSCORE I of 23% and in-hospital mortality of 2.5% [21].

Survival during further follow-up was 87% for MitraClip patients in the present report and ranges around slightly lower rates in comparable series [18, 20, 22], reflecting the high-risk character of the investigated patient populations with advanced age, impaired ventricular function and high prevalence of further important comorbidities. Direct comparison of these results with data from surgical studies is difficult, since patient characteristics differ substantially. For example, results from the mitral valve surgery stratum of the Acorn Trial showed 30-day mortality of only 1.6% [23]. However, patients were younger and had a markedly lower LVEF compared with the present study or other cited MitraClip studies. In our experience, after multivariate analysis and adjustment for significant baseline differences regarding age and LVEF, survival differences were not significant ($P = 0.642$). This finding underscores once again the obvious impact of fundamentally different patient demographics on clinical outcome among the two cohorts.

Effectiveness of treatment and clinical outcome

Judged by the commonly applied primary efficacy endpoint of reducing MR to Grade ≤2, both MVR and MitraClip treatment were similarly effective ($P = 0.383$). However, both mean grade of residual MR and distribution of residual grades of MR were significantly more favourable after surgery compared with MitraClip ($P < 0.001$). Furthermore, freedom from MR >Grade 2 steadily declined during further follow-up in the MitraClip cohort reaching a rate of 88% at 180 days, but was largely stable.
in patients after MVR. This is a finding well supported by previous reports in the literature [8, 18]. This may at least, in part, be explained with the fact that performing a surgical edge-to-edge repair without concomitant annuloplasty is known to result in higher rates of reoperation for recurrent MR [1], and the same may be true for percutaneous edge-to-edge repair. Taramasso et al. showed similar results to ours in a cohort of 25 secondary MR patients treated with MitraClip with a mean logistic EuroSCORE I of 21.9±4.8% [24]. Here too, the grade of MR was significantly higher in interventional compared with surgical patients during follow-up. However, important baseline characteristics were different between their experience and the present report, and it is likely that these differences have contributed to differences in clinical outcome. This is even more so, since Taramasso et al. included patients undergoing concomitant procedures in the surgical group, whereas only isolated MVR was analysed in the present study. Since it is well known that residual MR adversely impacts patient survival, it is probably not justified at present to extend MitraClip therapy to operable patients.

Despite suboptimal functional results after MitraClip therapy, the majority of patients (69.9%) improved substantially regarding NYHA functional class, and this improvement was sustained in many patients up to the latest follow-up of 198±59 days. Further studies are needed to assess the durability of MitraClip therapy at longer follow-up and to identify patient characteristics predictive of long-term benefit from MitraClip therapy.

CONCLUSIONS

MitraClip should probably not be offered to patients eligible for surgery at present. However, in patients without surgical options due to contraindications or exceedingly high surgical risk, MitraClip therapy appears to be a viable alternative with marked clinical improvement in the majority of patients treated. This judgment has been included in the recent update of the guidelines on valvular heart disease by the European Society of Cardiology where MitraClip treatment for secondary MR in patients deemed inoperable or at high surgical risk received a Class IIb, level of evidence C recommendation [1] with interdisciplinary assessment recommended. From our perspective, patients considered for percutaneous mitral valve therapy should be evaluated by a dedicated heart team consisting of cardiologists and cardiac surgeons to ensure optimal clinical outcome.

LIMITATIONS

This is a retrospective, observational single-centre experience with limited patient numbers, and unknown confounding factors cannot be excluded to have had an effect on results and conclusions. Follow-up data were in part obtained by telephone interview or from external reports and accuracy of the grading of MR or NYHA functional class may have been compromised by interobserver bias. Furthermore, patient selection for the respective procedures did not follow standard operating procedures, but was determined following interdisciplinary discussion of cases within the heart team. The completely different technical nature of the two respective procedures with subsequent impact on clinical outcomes is another important limitation.

Conflict of interest: Stephan Baldus has received lecturing fees and research grant from Abbott Vascular Inc.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr A. Hensens (Enschede, Netherlands): As you conclude in your talk, we should be carefully comparing both treatment strategies in different patient groups, apples and pears indeed, as you mentioned already. And I agree with you that the MitraClip is a complementary solution for treating functional MR in high-risk patients. I have three questions for you. The first is, how were the patients selected? Were they selected by the heart team to go in either the MitraClip group or in the conventional surgery group, and was age the patient factors? We know that all the risk stratiﬁcation of the patients was done, but you only presented six-month follow-up. So I don’t understand that. If you could clarify why you have not presented ﬁve-year survival or recurrence of MR or need for reoperation, for which I am sure you have the data.

The second point is that although there was already a difference in the mortality in the group comparison at six months, your multivariate regression analysis kind of eliminated that by also including LV ejection fraction in the evaluation, but we do know that ejection fraction measured in patients with mitral regurgitation is nonsense because it is not reliable and realistic. So at the end, I am not sure which method you were testing. I would be very happy if you could explain a little bit more about that.

Dr Conradi: The first question is a very easy one to answer. Of course, the overall time frame of the study began in 2002, but MitraClip only became available much later, so the first procedure that we performed was in mid-2008. So that is probably the main reason for that. Of course, we have the data for the surgical patients, but for the sake of comparability of those two populations, we truncated follow-up at 180 days, or six months.

Dr R. Ascione (Bristol, UK): I have a couple of questions. If I remember well, your time of observation was almost 10 years during which these operations were done, but you only presented six-month follow-up. So I don’t understand that. If you could clarify why you have not presented five-year survival or recurrence of MR or need for reoperation, for which I am sure you have the data.

Dr A. Hensens (Enschede, Netherlands): That is a very good question, very important I think in terms of clinical outcome. For this particular study, this type of analysis was not part of the protocol. However, for the overall MitraClip cohort treated at our centre, there is a manuscript out now with two years’ data which has been just been accepted for publication, and here we are looking exactly at those predictors of outcome regarding haemodynamic parameters.

Dr Hensens: And finally, did you have the patient show your in-patient stay and requirement for inotropes in your experience post-MitraClip in this group of patients?

Dr Conradi: I showed you that the length of the procedure is a lot shorter. So the procedure itself is not only less invasive but somehow lighter on the patient. We see much shorter intubation times and the procedure time is shorter, and we have a strategy of keeping those patients intubated and in ICU for as short as a time as possible, in a sort of a fast-track fashion. So what we saw was that ICU stay and ventilation times were significantly shorter compared to surgery, but this does not translate into overall reduced length of stay, probably and most likely due to the fact that those patients were a lot sicker compared to the surgical population.

Dr E. Ferrari (Lausanne, Switzerland): I have just one question regarding the residual mitral valve regurgitation. You have 15% in grade 3 mitral valve regurgitation after six months in the MitraClip group and more than 50% in grade 2. What is your attitude with these patients? Do you still consider them inoperable, at high risk, or will you go for surgical repair treatment, in this group of high-risk patients?

Dr Conradi: I would say, again, it has to be an individual decision. Of course, in this experience there are probably examples for each and every scenario. So, of course, there is the MitraClip patient with recurrent MR who comes back and gets a second clipping; of course, there is the occasional patient who comes back with recurrent severe MR and has to be operated on because there is no more benefit expected from renewed clipping; and, of course, there is the very frail, very sick heart failure patient who will not receive any further intervention apart from medical therapy. So again you have to make that decision, or find the correct decision in the heart team, on an individual basis.

Regarding LVEF, we analysed the one-year outcome in our overall MitraClip cohort and then again for two-year outcomes, and we found that a multivariate predictor in the overall cohort was forward stroke volume. These were just the things that popped up in the multivariate analysis, age and LVEF. We analysed a great number of parameters in a univariate manner. But of course, I don’t have to explain this, these are very limited patient numbers, and it is impossible to include more than just a few parameters in that multivariate analysis. So these were the things that came up, age and LVEF.

If you consider, again, maybe EVEREST II and the post hoc analysis that Francesco alluded to earlier, those were two main factors indicating possible benefit from MitraClip, advanced age and reduced LVEF. So we think we are in line pretty much with what has been reported in the literature so far.