

Promising results after percutaneous mitral valve repair

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ABSTRACT

INTRODUCTION: Mitral valve regurgitation (MR) is the second-most frequent valve disease in Europe. Untreated MR causes considerable morbidity and mortality. In the elderly, as many as half of these patients are denied surgery because of an estimated high surgical risk. Percutaneous mitral valve repair with the MitraClip system resembles the Alfieri-stitch where a clip is used to connect the tip of the mitral valve leaflets.

MATERIAL AND METHODS: Sixteen patients with MR of various origins (functional/degenerative) were treated with the MitraClip system. All patients were highly symptomatic with dyspnoea (New York Heart Association (NYHA) grade three) and MR grade three or more, and had been turned down for surgery due to an excessively high risk.

RESULTS: MR was reduced in all but one patient, generally from grade 3.5 ± 0.5 to grade 1.4 ± 0.9 . A total of four patients (25%) received two clips. Thirty-day complications were as follows: one patient died, one had a stroke (speech sequelae), one patient had a new chord rupture that was treated surgically. During 90 days of follow-up, symptoms of dyspnoea diminished (reduction of 1 NYHA grade) and the 6-minute walk test results improved from 171 ± 99 to 339 ± 134 metres ($p < 0.001$).

CONCLUSION: Percutaneous mitral valve repair with the MitraClip system is now available in Denmark. The treatment is a reasonable alternative in patients with MR and a high estimated surgery risk.

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Mitral valve regurgitation (MR) is the second-most frequent heart valve disease in Europe, only topped by aortic valve stenosis [1]. Untreated MR causes increased mortality in patients with primary MR and preserved left ventricular function [2] as well as in patients with ischaemic MR [3] and functional MR secondary to reduced left ventricular function [4]. The incidence of MR increases with age. In the community, moderate to severe MR is present in 10% of all persons above 75 years [5]. In the decades to come, the proportion of elderly will rise and it therefore raises concern that about half of the patients in this group are denied mitral valve surgery because of an estimated high risk [1]. For these reasons,

new percutaneous methods for the treatment of MR have been developed, among which the MitraClip system is currently the method with which we have most experience [6].

The MitraClip technique was introduced in 2003 and resembles the technique developed by the Italian cardiac surgeon Otavio Alfieri [7]. During "Alfieri-plasty" the tips of the mitral valve leaflets are stitched together to create a double orifice and thereby reduce the MR. The MitraClip system is a percutaneous device system that delivers a clip to stitch the anterior and posterior leaflet together and thereby reduce the degree of MR, also by creating a double orifice (**Figure 1**). The MitraClip system delivers the clip by a steerable sheath that is introduced into the femoral vein and advanced to the left atrium after puncture of the atrium septum. The positioning and the delivery of the clip are guided mainly by transoesophageal echocardiography.

At present, more than 2,000 patients have been treated with the MitraClip worldwide and more than half of these patients have been treated in Europe. Results from the USA [8], Germany [9] and Italy [10] look promising. We report the results of the first treatments with MitraClip in Denmark.

MATERIAL AND METHODS

Patients

Individual patient data are shown in **Table 1**. The type of MR was mixed, 31% were degenerative (mitral valve prolapse) and 69% functional due to ischaemic- or non-ischaemic cardiomyopathy. Patients were screened either in the outpatient clinic or during admittance. Patients received an echocardiography and had a 6-minute walk test (6MWT) and a clinical evaluation. The valve morphology and the coronary anatomy of all patients were discussed at our institutional conference with participation of invasive and non-invasive cardiologist as well as cardiac surgeons. The conference agreed for all patients that percutaneous treatment should be performed because the risk of surgery was unreasonably high. All patients were highly symptomatic with dyspnoea (New York Heart Association (NYHA) function class III) and MR \geq grade three. Patients gave written and informed consent.

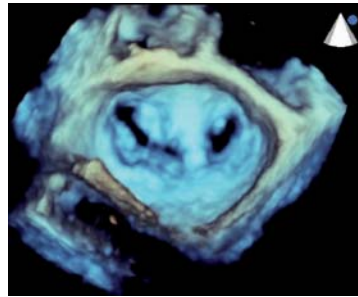
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FIGURE 1

Three-dimensional transoesophageal echocardiography. The mitral valve is viewed from the atrium side. Leaflets are clipped together creating a double orifice.



Methods

The MitraClip system (Abbott Vascular, Menlo Park, CA, USA) has previously been tested and described [11]. The system consists of a 24-French (8 mm) steerable guiding catheter through which the clips delivery system can be applied (**Figure 2**). The MitraClip is mounted on the tip of the clips delivery system and so the clip is steerable. The clip is a metal device made of cobalt and chrome and surfaced with polyester to improve endothelial growth. The device is 4 mm broad with two moveable arms that reach 2 cm when fully opened. Furthermore, the device has two 8-mm grippers to catch and lock the mitral leaflets. The MitraClip system is advanced through the femoral vein and reaches the left atrium after transeptal puncture. The clip is steered towards

the mitral leaflets aiming at the place in the commissure with the largest regurgitant jet. After initial orientation, the clip can be advanced into the left ventricle and opened. After adjusting for perpendicularity, the clip is withdrawn, and after ensuring appropriate amounts of leaflet tissue, the clip is closed. Before releasing the clip, leaflet insertion is tested as well as the effect on the mitral regurgitation. Opening and re-positioning of the clip is possible before final clip release. In approximately 30% of the cases, it is necessary to place two clips to achieve a satisfactory result [9, 10, 12].

The procedure is guided by transoesophageal echocardiography and fluoroscopy. During the procedure, close collaboration between the interventionalist and the echocardiographer is necessary. Three-dimensional echocardiography is of great help in this procedure (**Figure 1**). The patient is in general anaesthesia and arterial and venous pressure is monitored invasively. Anticoagulation during the procedure is achieved with unfractionated heparin. In most cases, the patient is extubated in the catheterisation laboratory and transferred to the intensive care unit for the first 24 hours of care and then the next day transferred to the stationary ward.

The anticoagulation strategy after the procedure was individually tailored to the patient's previous anti-coagulant regime: If the patient was on warfarin before the procedure, this was continued unchanged. Otherwise, clopidogrel 75 mg was prescribed for four


TABLE 1

Individual data on the patients treated with MitraClip.

	Age, years	MR type	Previous CABG	LVEF, %	MR grade	NYHA class	Euro-SCORE logistic, %	Reason for percutaneous treatment
Case 1	80	ICM	+	30	3	3	26.3	EuroSCORE
Case 2	65	ICM	+	20	3	3	35.4	EuroSCORE/low LVEF
Case 3	75	ICM	+	25	3	3	28.8	EuroSCORE
Case 4	67	DCM	-	20	4	4	21.5	Low LVEF
Case 5	73	ICM	-	20	3	3	33.8	EuroSCORE/low LVEF
Case 6	73	ICM	+	30	3	3	37.8	EuroSCORE
Case 7	84	MVP	-	60	4	3	15.5	Age, frailty
Case 8	90	MVP	-	60	3	3	15.2	Age, frailty
Case 9	62	ICM	-	20	4	3	5.3	Low LVEF
Case 10	77	ICM	+	45	3	3	24.2	EuroSCORE
Case 11	88	MVP	-	60	4	3	24	Age, frailty
Case 12	77	DCM	-	15	4	3	18.4	Low LVEF
Case 13	74	ICM	+	60	3	3	18.9	Previous CABG
Case 14	86	MVP	-	60	4	3	9	Age, frailty
Case 15	88	MVP	-	60	4	3	10	Age, kyphotic thorax
Case 16	74	ICM	+	45	4	3	34.4	EuroSCORE
Mean ± SD	77 ± 9	-		40 ± 18	3.5 ± 0.5	3.1 ± 0.3	22 ± 10	
n/N			7/16					

CABG = coronary artery bypass grafting; DCM = dilated cardiomyopathy; ICM = ischaemic cardiomyopathy; LVEF = left ventricular ejection fraction; MR = mitral valve regurgitation; MVP = mitral valve prolapse; NYHA = New York Heart Association; SD = standard deviation.

weeks and acetylsalicylic acid 75 mg was prescribed life-long. An experienced MitraClip interventionalist (Olaf Franzen, Department of Cardiology, Rigshospitalet) participated in all the procedures.

Echocardiography

Before the treatment, the patients were examined by transthoracic and transoesophageal examination. At discharge and during the first and third months of follow-up, a transthoracic examination was performed. All examinations were carried out using Philips IE 33 equipped with an S5-1 transthoracic probe and an X7-2 transoesophageal probe. Before the procedure, grading of the MR was done using the proximal isovelocity surface area (PISA) method and thus categorised into one of four grades [13].

After the procedure, MR was graded using colour Doppler flow area according to guidelines [13, 14] since the PISA method has not been evaluated for the double orifice and usually is not feasible because the PISA "shell" is covered by the clip. Left ventricle systolic function (LVEF) was evaluated using biplane planimetry (Simpson's method) or semiquantitatively using the wall motion index in cases of regional wall motion abnormalities. The stroke volume was estimated as the area of left ventricle outflow tract (LVOT) times the time velocity integral of a pulsed Doppler in LVOT. The transmitral flow gradient was measured with continuous wave (CW) Doppler through the mitral ostium parallel to the flow direction. The return gradient through the tricuspid ostium was measured with CW Doppler in systole parallel to the tricuspid return flow.

Statistics

Data are presented as mean values \pm standard deviation. Values before and after treatment were compared using a paired T test. $p < 0.05$ was considered significant.

Trial registration: not relevant.

RESULTS

Data are available on the immediate procedure effect in 16 patients and 90-day follow-up results are available in 11 patients. Patients were evaluated with NYHA function class, 6MWT and echocardiography measures. Immediate procedural success was noted in all 16 patients as defined by a reduction in MR to less than grade 2 (Figure 3). However, in two cases partial clip detachment was observed before discharge (cases one and eleven). Case one was re-treated by placing a new clip which produced a satisfactory result. Case number eleven could not be re-treated because of fragile leaflets and was discharged on medical therapy with an unchanged MR grade of 4. Surgery was not an option in this patient. In

FIGURE 2

The MitraClip system. Close-up of the clip is inserted.

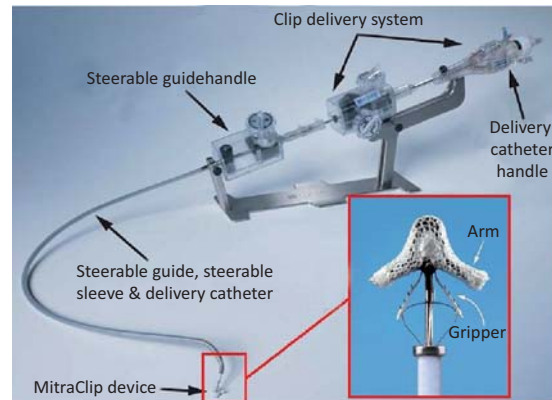
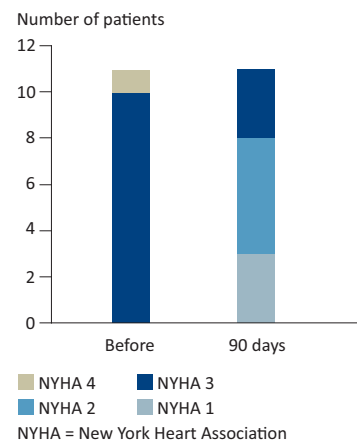


FIGURE 3

Grade of mitral valve regurgitation before and after the MitraClip procedure, as evaluated at discharge.



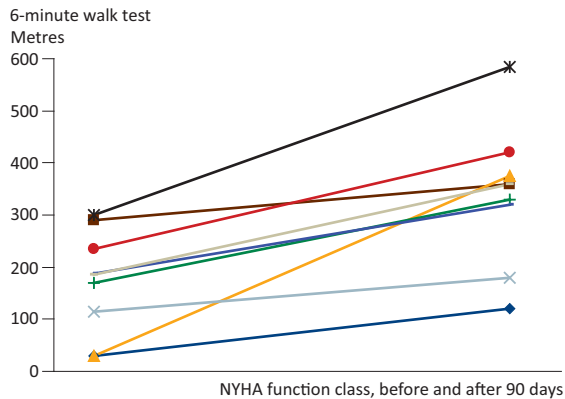
the remaining patients, MR was generally reduced from grade three to grade one. Four patients (25%) were treated with two clips. One patient had a pseudoaneurysm of the femoral artery after placement of a left ventricle catheter for pressure measurements. There were no bleeding complications from the venous puncture except small haematomas. Case number five was treated with a percutaneous coronary intervention (left main stem rotablation) because of angina after the clip procedure. The coronary stenosis was not related to the clip procedure.

The mean duration of admittance was 6.3 ± 3 days.

After 30 days, the following complications were noted: One death, case 9. The patient had a low LVEF and ischaemic heart disease and was offered an implantable cardioverter defibrillator before discharge according to guidelines, but wanted to evaluate the offer. The patient had cardiac arrest (ventricular fibrillation) during physical training. Another patient, case 12, developed

FIGURE 4

Grade of New York Heart Association (NYHA) function class and 6-minute walk test at 90 days follow-up.



symptoms of stroke with expressive aphasia, but symptoms were in regression. Furthermore, one new chord rupture developed in case 14. The patient was admitted with severe dyspnoea and severe MR and a transthoracic examination revealed a new ruptured chord beside the clip. Since the patient was relieved of symptoms with the MitraClip treatment, the cardiac surgeons chose to offer surgery despite the high surgical risk. A biological prosthetic valve was inserted without further complications.

In the group of patients with 90-day follow-up, improvement in 6MWT distance rose by a mean 171 ± 99 metres to 339 ± 134 metres ($p < 0.001$) (Figure 4). Symptoms of dyspnoea were also reduced by the treatment. Before treatment, all patients were in NYHA function class III-IV, but at the 90-day follow-up, eight of the 11 patients were in NYHA function class I or II, three patients remained unchanged in NYHA class three (Figure 4). Most patients could be reduced in diuretic treatment.

Echocardiography

LVEF was unchanged before treatment and 90 days after ($35 \pm 18\%$ versus $35 \pm 18\%$, $p = 0.17$) as was the left ventricle diastolic diameter (61 ± 0.7 mm versus 60 ± 0.9 mm, $p = 0.33$). Cardiac index evaluated before and after the procedure increased from 2.2 ± 0.8 to 2.7 ± 1.0 l/min/m² ($p = 0.03$) as a sign of increased forward flow owing to a decreased MR. The tricuspid regurgitant gradient, reflecting pulmonary pressure, was reduced from 37 ± 13 mmHg before to 31 ± 9 mmHg after the procedure ($p = 0.07$). The antegrade gradient through the mitral ostium increased from 2.7 ± 1.3 mmHg before to 4.6 ± 1.7 mmHg after the procedure ($p = 0.003$), but no patients developed mitral stenosis.

DISCUSSION

We present the first Danish experience with percutaneous mitral valve repair using the MitraClip system. Our initial experience confirms that the procedure can be performed with a reasonably low risk (no peri-procedure mortality and a 30-day mortality of 6%) and a good clinical result, even in patients with a very high surgical risk. We generally observed a reduction in MR of two grades, which is in line with international experience [8-10]. Moreover, the admittance time was reasonably low (6.5 days), even in patients with considerable co-morbidity. To achieve a satisfactory result, two clips were placed in 25% of the procedures, which is also in agreement with previously published data [9, 12].

At present the results of approximately 450 of the currently 2,000 treated patients have been published. Three studies treated very different patient populations.

In the EVEREST II trial, 279 patients eligible for MR surgery were randomised 2:1 for MitraClip treatment or surgery. Patients were symptomatic with an MR grade of 3-4 and LVEF $> 25\%$. Certain criteria for mitral valve morphology (length and depth of coaptation and degree of prolapse) were established to ensure the technical feasibility of the MitraClip treatment [12]. The type of MR was 70% degenerative and 30% functional. The study showed that MitraClip treatment could be done with a lower risk than surgery (mortality and stroke risk of 2.5% in the surgical group versus zero in the MitraClip group), but at the expense of a slightly lower clinical benefit: 66.9% versus 74.2% (composite endpoint including death, MR surgery, re-surgery and MR $<$ grade two). Both treatments showed a similar reduction in left ventricular volume, NYHA function class and quality of life [8].

Franzen et al from Hamburg, Germany, published 30-day follow-up data for 51 patients who had considerably higher co-morbidity than patients studied in the EVEREST II study [9]. Patients had a reduced LVEF function (35%) and the majority had functional MR (70% functional and 30% degenerative). MR was reduced by one grade in 33%, two grades in 49% and three grades in 18% of the patients. Accordingly, NYHA function class improved by one grade in 61% and two grades in 29% of the patients. Similar results were reported from Italy in a patient population somewhere between those of the EVEREST and the Hamburg publication (LVEF 40% and 58% with functional MR) [10].

Both Franzen and Tamburino only report 30-day follow-up and only the EVEREST registry offers follow-up data for up to three years. Mitral valve stenosis was not reported as a complication as one could fear given the nature of the procedure [15]; however, re-intervention is seen in up to 25% of the cases because of an unsatisfactory degree of MR [12].

We observed partial clip detachment in two patients before discharge. One could be re-treated successfully, but one was technically impossible to re-treat due to fragile leaflets. Partial clip detachment was described in 9% in the EVEREST II “midterm follow-up” study [12] and in 4% from the centre in Hamburg [9]. The occurrence of partial clip detachment is very dependent on valve anatomy, and in our group of patients, most had difficult valve morphology “beyond” the initial criteria proposed in the EVEREST trial. Adverse valve morphology would make clip detachment more likely. However, our patients had no surgical option for reduction of MR and in such context, we believe that the complications are acceptable.

In conclusion, percutaneous mitral valve repair with the MitraClip system can now be performed in Denmark in patients with an estimated high surgical risk. The periprocedural risk as well as 30-day mortality is low as compared with the risk evaluated by EuroSCORE. In the short term, a clinically relevant reduction in MR as well as improvement in symptoms is noted. The treatment is currently seen as a possibility to improve symptoms for patients in whom surgery is not advisable since the long-term results are unknown.

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