Correction of Mitral Regurgitation in Nonresponders to Cardiac Resynchronization Therapy by MitraClip Improves Symptoms and Promotes Reverse Remodeling

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Objectives
This study evaluated the safety, efficacy, and effect of MitraClip treatment on symptoms and left ventricular (LV) remodeling in nonresponders to cardiac resynchronization therapy (CRT).

Background
Moderate to severe functional mitral regurgitation (FMR) frequently persists after CRT, contributing to reduced or no response to CRT. Percutaneous repair with the MitraClip has been proposed as an additional therapeutic option in select patients with significant FMR.

Methods
Fifty-one severely symptomatic CRT nonresponders with significant FMR (grade ≥2, 100%) underwent MitraClip treatment. Changes in New York Heart Association functional class, degree of FMR, LV ejection fraction (EF), and LV end-diastolic/end-systolic volumes (EDV/ESV) before and after (3, 6, and 12 months) MitraClip implantation were recorded. Mortality data, including cause of death, were collected.

Results
MC treatment was feasible in all patients (49% 1 clip, 46% 2 clips). There were 2 periprocedural deaths. Median follow-up was 14 months (25th to 75th percentile: 8 to 17 months). New York Heart Association functional class improved acutely at discharge (73%) and continued to improve progressively during follow-up (regression model, p < 0.001). The proportion of patients with significant residual FMR (grade ≥2) progressively decreased during follow-up (regression model, p < 0.001). Reverse LV remodeling and improved LVEF were detected at 6 months, with further improvement at 12 months (regression model, p = 0.001, p = 0.008, and p = 0.031 for ESV, EDV, and LVEF, respectively). Overall 30-day mortality was 4.2%. Overall mortality during follow-up was 19.9 per 100 person-years (95% confidence interval: 10.3 to 38.3). Nonsurvivors had more compromised clinical baseline conditions, longer QRS duration, and a more dilated heart.

Conclusions
FMR treatment with the MitraClip in CRT nonresponders was feasible, safe, and demonstrated improved functional class, increased LVEF, and reduced ventricular volumes in about 70% of these study patients. (J Am Coll Cardiol 2011;58:2183–9) © 2011 by the American College of Cardiology Foundation
MitraClip in CRT Nonresponders

Methods

Participants. PERMIT-CARE (Percutaneous Mitral Valve Repair in Cardiac Resynchronization Therapy) is a prospec-

The presence of functional mitral regurgitation (FMR) in the set-
ting of left ventricular (LV) dysfunction is associated with in-
creased morbidity and mortality (1,2). Moderate to severe FMR is
common in heart failure (HF) patients; it occurs in approxi-
mately one-third of those with indications for cardiac resynchro-
nization therapy (CRT) (3,4). FMR has been reported to per-
sist in about 20% to 25% of CRT patients and, in an additional
10% to 15%, it may actually worsen after CRT (5). In this
subset of CRT nonresponders, reduced reverse remodeling, increased morbidity, and increased mortality have been reported compared with CRT patients in whom FMR is significantly reduced or abolished (4).

Patients with significant FMR (i.e., grade ≥2) and advanced LV dysfunction pose a particularly difficult man-
agement dilemma because the benefits of surgical FMR reduction in this population have been variable, inconsis-
tent, and suboptimal (6). When surgery is performed in this
HF population, repair with undersized ring annuloplasty rather than replacement of the mitral valve is usually
preferred; however, its safety and effectiveness have not been
well established, and the potential occurrence of valve
stenosis has been reported (7). In addition, to the best of our
knowledge, there have been no reported morbidity and mortality data in CRT nonresponders undergoing mitral
valve surgery.

Catheter-based treatment with the MitraClip has been
proposed as an additional therapeutic option in select
patients with degenerative mitral regurgitation or FMR
(8,9); early trials demonstrated safety, mitral regurgitation
reduction, and clinical benefit. More recently, different
groups of patients have been successfully treated (10,11),
including elderly patients with significant comorbidities
such as severe LV dysfunction, renal failure, or chronic
obstructive pulmonary disease (11). These patient groups
were either underrepresented or excluded in EVEREST
(Endovascular Valve Edge-to-Edge Repair Study) I (8,9)
and II (12).

The present study reports the safety, efficacy, and the
effect of MitraClip therapy on symptoms and LV remodel-
ing in CRT patients who remained highly symptomatic
de spite optimal pharmacological and device therapy (i.e.,
CRT nonresponders).

Device and procedure. Both the device and procedure
have been extensively described previously (8–12). Briefly,
the MitraClip system is a catheter-based system designed to
perform a double orifice repair of the mitral valve while the
heart is beating. The system includes a clip, a steerable guide
catheter, and a clip delivery system that enables positioning
and placement of the clip on the mitral valve leaflets,
resulting in permanent leaflet approximation (12). Given
the nature of this feasibility study, there was no pre-
specified end point treatment. However, there was consen-
sus among operators that procedural success was defined as
the implantation of at least 1 clip and reduction of severity
of mitral regurgitation of at least 1 grade.

Follow-up. Clinical and echocardiographic evaluation and
CRT device follow-up were performed before and after
MitraClip treatment at each participating institution. Pa-
ients were evaluated every 3 to 4 months, or more fre-
quently, if required. CRT device programming was left to
the discretion of the local electrophysiologist or HF
physician.

Echocardiographic examination. All echocardiographic
examinations were conducted at each institution and were
subsequently independently reviewed by one of the investi-
gators (S. F.) not affiliated with the institutions. In addition,
institutional self-reporting data were compared with the
independently collected data, and in case of discrepancy,
an evaluation was made by consensus. The severity of FMR
was graded according to American Society of Echocardiog-
raphy guidelines by using quantitative and qualitative meth-
ods (16,17). Systolic pulmonary artery pressure was mea-
ured using the gradient derived from the maximal velocity
of tricuspid regurgitation, adding 5 mm Hg if the inferior
vena cava had a normal diameter, or 10 mm Hg if the vena
tics. Mortality was summarized with counts and percent-used to compare survival according to baseline characteris-

Meier method. The log-rank test and Cox regression were

Meier curve and median follow-up with the inverse Kaplan-

White robust SEs to account for intrapatient correlation

identity link, as appropriate) and calculation of Huber-

assessed by means of a general linear model (with logistic or

categorical. Changes

Clinical and echocardiographic parameters were

continuous, and counts and percent if categorical. Changes

over time of clinical and echocardiographic parameters were

assessed by means of a general linear model (with logistic or

identity link, as appropriate) and calculation of Huber-

identity link, as appropriate) and calculation of Huber-

Statistics. Mortality was summarized with counts and percent-

change over time according to baseline characteristics. Mortality was summarized with counts and percent-

ages. Stata version 11 (StataCorp, College Station, Texas) was

used for computation. All tests were 2-sided; \( p < 0.05 \)

was considered statistically significant.

Results

Study population. Demographic characteristics, pharma-

cological treatment, and baseline echocardiographic evalu-

ation (Table 1) were typical of a CRT nonresponder

population. Indeed, most patients were elderly males in an

advanced NYHA class despite pharmacological and device

optimization, had high N-terminal pro-B-type natriuretic

peptide (NT-proBNP), had ischemic heart disease and

renal disease, had been treated with a CRT system including

implantable cardioverter-defibrillator for a mean of nearly 3

years, and had a high logistic EuroSCORE and STS score, the

latter of which frequently excluded surgical options.

FMR was judged to be moderate to severe in 46% and

severe in 54% of patients. In 88% of patients, the FMR

originated in the A2/P2 region of the valve. The left

ventricle was particularly dilated (LV end-diastolic vol-

ume 238.7 ± 72.2 ml; LV end-systolic volume 174.5 ± 61.0

ml) and LV function was significantly depressed (LVEF

27.1 ± 8.7%) without a meaningful improvement com-

pared with pre-CRT values (LV end-diastolic volume

220.4 ± 70.5 ml; LV end-systolic volume 161.4 ± 59.6

ml; LVEF 25.5 ± 7.9%).

Procedural outcome. In most patients, FMR reduction

was achieved within 3 h of placement of either 1clip (49%)

or 2 clips (46%). There was some degree of residual FMR in

nearly all patients, but its severity was mild or moderate

(Fig. 1); residual FMR was frequently located at A2/P2. No

clinical or echocardiographic signs of mitral stenosis were

observed. Most patients required inotropic support either

before or during the procedure (Table 2).

There were 2 major adverse events at 2 different

centers. One patient died in the course of the procedure;

the patient had a low EF (33%), severe FMR, and could

not be weaned of intravenous inotropic support during

hospitalization pre- or post-MitraClip treatment. In the

other patient, chordal rupture occurred during the pro-

Table 1. Demographic Characteristics (N = 51)

| Age (yrs) | 70.26 ± 9.16 |
| Male | 44 (86) |
| Etiology (%) |  |
| Ischemic cardiomyopathy | 37 (73) |
| Nonischemic cardiomyopathy | 14 (27) |
| Previous interventions (%) |  |
| CABG or PCI | 24 (47) |
| Valve surgery | 4 (8) |
| New York Heart Association functional class |  |
| III | 32 (63) |
| IV | 17 (35) |
| Previous CRT-D (%) | 47 (92) |
| CRT-P | 4 (8) |
| Comorbidities |  |
| Previous stroke | 8 (16) |
| Diabetes | 11 (22) |
| COPD | 15 (29) |
| Renal insufficiency | 36 (70) |
| Logistic EuroSCORE | 29.7 ± 19.4 |
| STS score | 13.9 ± 14.6 |
| Laboratory findings |  |
| Creatinine (\( \mu \)mol/l) | 149.5 ± 63.2 |
| Sodium (mmEq/l) | 139.74 ± 4.2 |
| Potassium (mmEq/l) | 4.25 ± 0.41 |
| Hemoglobin (g/dl) | 12.34 ± 1.5 |
| NT-proBNP (ng/l) | 3,702 (1,794–8,148) |
| Month since CRT | 32.9 ± 25.7 |
| ECG |  |
| Sinus rhythm | 18 (35) |
| QRS width during CRT (ms) | 149.26 ± 26.84 |
| Echocardiography |  |
| LV end-diastolic diameter (mm) | 71.0 ± 8.7 |
| LV end-systolic diameter (mm) | 60.3 ± 9.8 |
| LV end-diastolic volume (ml) | 238.7 ± 72.2 |
| LV end-systolic volume (ml) | 174.5 ± 61.0 |
| LV ejection fraction (%) | 27.1 ± 8.7 |
| Mitral regurgitation grade ≥2 | 51 (100) |
| Systolic pulmonary artery pressure (mm Hg) | 44.6 ± 11.7 |
| Medication |  |
| ACE inhibitors or ARBs | 47 (92) |
| Beta-blockers | 45 (88) |
| Diuretics | 50 (98) |
| Aldosterone antagonists | 27 (53) |
| Statins | 26 (51) |
| Oral anticoagulation | 24 (47) |

Values are mean ± SD, n (%), or median (25th to 75th percentile).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchroni-

zation therapy; CRT-D = cardiac resynchronization therapy with a defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; ECG = electrocardiography; LV = left ventricular; NT-

proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.
procedure, which resulted in acute HF and death despite emergent surgery.

Clinical and echocardiographic outcomes. At discharge, many patients (73%) already had improved NYHA functional class. The proportion of patients classified as NYHA functional class I and II progressively increased over time (regression model, \( p < 0.001 \)) (Fig. 1). Similarly, the proportion of patients with significant residual FMR (grade \( \geq 2 \)) progressively reduced over time (regression model, \( p < 0.001 \)) (Fig. 1). No patient was reported to have a significant mitral gradient during the follow-up period.

Reverse LV remodeling was observed later in follow-up, and the first significant change in both LV end-diastolic and end-systolic volumes were detected 6 months after MitraClip treatment (Fig. 2) and further reduction was observed 12 months after treatment (regression model, \( p = 0.001 \) and \( p = 0.008 \) for end-systolic and end-diastolic volumes, respectively). In a similar manner, LVEF was nearly unchanged at 3 months but significantly increased at 6 and 12 months after MitraClip treatment (regression model, \( p = 0.031 \)).

Mortality and hospitalization rate. In addition to the periprocedural mortality, 2 additional patients died 14 and 18 days after MitraClip treatment. Overall 30-day mortality was 4.2%. Median follow-up was 14 months (25th to 75th percentile: 8 to 17); there were 7 additional deaths during the follow-up period. Thus, a total of 9 patients died (18%). The most common cause of death was cardiac, occurring in 6 of 7 patients, with 1 of these 6 deaths occurring suddenly; in this patient no autopsy and no device interrogation could be performed. One of the 7 deaths was due to noncardiac causes. Mortality primarily occurred within 6 months of treatment, as demonstrated in the Kaplan-Meier curve (Fig. 3).

None of the clinical and echocardiographic characteristics appeared to be significantly associated with survival except for previous valvular surgery, which increased the risk of dying by 5 (Online Table 1). However, nonsurvivors frequently seemed to be older, to have more previous valvular surgery, a much higher logistic EuroSCORE and STS, much higher mean value of NT-proBNP, longer QRS duration, and a more dilated heart (Online Table 1).

During follow-up, 5 patients were hospitalized: 2 patients for acute HF decompensation and 3 patients for noncardiac reasons.

Discussion

Main findings. The results of the PERMIT-CARE survey confirm that significant FMR is one of the causes of clinical nonresponse to CRT and that FMR reduction with MitraClip treatment is feasible, safe, and leads to substantial improvement in NYHA functional class and reverse ventricular remodeling. Although the MitraClip procedure in this population with advanced HF carries a certain peri- and post-procedural morbidity and mortality risk, it is important to note that nearly
all patients were considered ineligible for mitral valve surgery due to a very high estimated mortality risk.

**General considerations.** The results of the PERMIT-CARE survey should be interpreted in the context of the patient population that was treated. Patients had several demographic characteristics that distinguish them from typical CRT patient populations or from patients included in mitral valve surgery series or reported patients treated with the MitraClip device. All patients included in the PERMIT-CARE survey can be considered nonresponders to CRT because they had unchanged symptoms and ventricular volumes after at least 6 months of CRT. Moreover, the vast majority of patients had ischemic cardiomyopathy, a group of CRT patients who usually shows minor reduction in or unchanged ventricular volumes at follow-up (20,21).

It is well known that patients with advanced HF with ischemic cardiomyopathy and severe FMR have a particularly adverse outcome as shown by Mihaljevic et al. (6) and by Braun et al. (22). As reported, our patients have distinct clinical features compared with recently published series of MitraClip patients. The EVEREST I (8,9) and the EVEREST II (12) trials systematically excluded patients with severely depressed LVEF and large ventricles, whereas Franzen et al. (11) reported patients with a mean LVEF higher (0.36) than ours (0.27). It is fair to state that patients included in PERMIT-CARE may be considered patients with extremely limited, if any, other therapeutic options.

**Effect of therapy on symptoms and valvular regurgitation.** MitraClip treatment significantly improved functional NYHA class in the vast majority of CRT nonresponders. The change over time was similar to what has been reported in other recent MitraClip studies. In the high-risk study of the EVEREST II trial, about 75% of patients were in NYHA functional class I or II at discharge and at 12-month follow-up (9). Similarly, Franzen et al. (11) reported, in a single-center study which included 51 high-risk, significantly symptomatic patients, that about 70% of patients were already in NYHA functional class II or lower at discharge. The symptomatic improvement was closely related to significant reduction in FMR severity. Residual FMR grade ≥2 was present in <20% of PERMIT-CARE patients at discharge, and this proportion decreased over time, present in only about 10% at 1 year. This finding is consistent with all previously reported MitraClip studies independently of etiology of FMR (10,11), in both low- and high-risk patient populations (10,11), in single-center observational (11) or in prospectively controlled trials (8,9). Comparable results in FMR reduction have been reported in surgical FMR series (22–25), showing that 6% to 10% of surgically repaired mitral valve patients had residual FMR grade ≥2; however, it should be noted, that the most frequently treated FMR etiology in surgical series con-
ducted in patients with advanced HF was nonischemic cardiomyopathy. Reduction in FMR was achieved in patients in whom FMR was unaffected by CRT. There are limited data about the long-term evolution of FMR in CRT patients. A recent, observational multicenter study by Di Biase et al. (4) conducted in 794 patients with a mean follow-up of 26 months reported that, in about one-third of patients with moderate to severe FMR, FMR severity and LV volumes remained unchanged after CRT. Although our study does not provide insight into the mechanisms for unchanged FMR or worsening FMR in CRT nonresponders, it emphasizes the need to stratify early after CRT those patients who may either develop FMR or in whom FMR severity is unlikely to change as well as the need to consider additional therapeutic options such as surgery or MitraClip treatment.

**Effect of MitraClip on reverse remodeling.** Evidence suggests that the improved outcomes observed with CRT are associated with reverse remodeling, a process characterized by a reduction in LV volumes leading to improved systolic and diastolic function. The structural and functional changes associated with this process occur as early as 3 months and are even more pronounced by 6 months, at which time the magnitude of reverse remodeling has been shown to predict the long-term prognosis in both medically treated patients as well as CRT patients (21,26,27). In the PERMIT-CARE survey, changes in both end-diastolic and end-systolic volumes after MitraClip were clearly evident. The observation that reverse remodeling occurred even in the presence of a moderate mitral regurgitation is particularly interesting because about 60% to 70% of our patients retained FMR of grade >2 at 6 months. This finding may suggest that a limited change in ventricular loading condition could be sufficient to induce reverse remodeling in CRT nonresponders. Unfortunately, the sample size was too small to determine if a larger reduction in FMR after MitraClip implantation may have more dramatic effects on reverse remodeling.

**Major clinical events after MitraClip implantation.** The peri-procedural mortality rate was 5.8%, whereas the overall mortality was 20 per 100 person-years; the most frequent cause of death was HF. Although these rates may be considered high, one should carefully consider the results in the context of the demographic characteristics and expected outcome of surgical treatment as well as in the context of the “natural” history of CRT nonresponders. Although the logistic EuroSCORE accuracy at predicting surgical mortality risk in different surgical subgroups has been questioned (28), it is a commonly used score; it predicted a 29.7% perioperative mortality in the study cohort. A similar high perioperative mortality was predicted by the STS risk score, thus making surgical mitral valve repair or replacement unlikely. In addition, the age of our patients would prevent eligibility for a LV assist device or for cardiac transplantation. Compared with recent surgical series that reported perioperative mortality ranging from 3.3% to 4.8% (29,30), the event rate observed in our cohort was similar (5.8) but slightly higher, which may be explained by the fact that our patients were significantly older, had low EF, and multiple comorbidities, and primarily ischemic etiology. The “natural” history of CRT nonresponders has been primarily reported in single-center, observational studies. According to Ypenburg et al. (5), NYHA functional class III CRT nonresponders have a 3-year mortality ranging from 35% to 70%. Therefore, even a minor reduction in mortality combined with a significant gain in functional capacity may be considered a major therapeutic success in this patient cohort with advanced HF. Obviously, a properly designed, randomized controlled trial is needed to confirm our positive findings.

**Study limitations.** Although this study represents the largest multicenter experience with MitraClip therapy reported to date, the total number of 51 CRT nonresponders is small, and a larger number of patients with adequate long-term follow-up is needed. This was an observational study implying that changes in pharmacological therapies during follow-up may have influenced FMR severity, outcome, and remodeling. However, we believe that the observational nature of the study makes the results more representative of real-world clinical practice. Finally, the value of surgical repair compared with replacement is also debatable because FMR often recurs after repair as a consequence of continued ventricular remodeling, which results in recurrent valve tenting. However, our preliminary data do not substantiate this view for MitraClip repair, as continuous reduction in the severity of FMR and reverse remodeling was observed. Although an echocardiographic protocol was not predefined, all examinations were reviewed by an independent experienced echocardiographer, which partially mitigates the issue of institutional variability self-reporting.

**Conclusions**

MitraClip treatment in CRT nonresponders with clinically significant FMR was feasible and safe, and produced improved NYHA functional class, increased LVEF, and reverse LV remodeling in a significant proportion of these study patients. Prospective studies are warranted to confirm our findings and to evaluate appropriate timing of MitraClip treatment after CRT.

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Key Words: cardiac resynchronization therapy • heart failure • mitral regurgitation.

APPENDIX

For a supplementary table and a list of other investigators participating in the PERMIT-CARE registry, please see the online version of this article.