

# Mortality after percutaneous edge-to-edge mitral valve repair: a contemporary review

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**Abstract:** Percutaneous edge-to-edge mitral valve (MV) repair is a relatively new treatment option for mitral regurgitation (MR). After the feasibility and safety having been proved in low-surgical-risk patients, the use of this procedure has shifted more to the treatment of high-risk patients. With the absence of randomized controlled trials (RCT) for this particular subgroup, observational studies try to add evidence to the safety aspect of this procedure. These also provide short- and mid-term mortality figures. Several mortality predictors have been identified, which may help the optimal selection of patients who will benefit most from this technique. In this article we provide an overview of the literature about mortality and its predictors in patients treated with the percutaneous edge-to-edge device.

**Keywords:** Mitral valve (MV); percutaneous edge-to-edge; mortality

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## Introduction

Mitral regurgitation (MR) is the second most common valvular disease after aortic stenosis. Without intervention, patients with symptomatic MR have reduced survivability despite optimal medical therapy (1-3). In patients with either symptomatic-, or asymptomatic (provided diagnostics show signs of developing left-sided heart failure) degenerative mitral regurgitation (DMR) the gold standard treatment is mitral valve (MV) repair. For functional mitral regurgitation (FMR) the indication for surgical treatment is less well-established due to the etiologic nature of this disease. In the latter, surgery is mainly limited to patients who will also benefit from coronary artery bypass grafting (4-6). Nevertheless, reports show that approximately half of the population with an indication for surgery, are being denied this treatment because of high-surgical-risk factors like advanced age, co-morbidities or reduced left ventricular

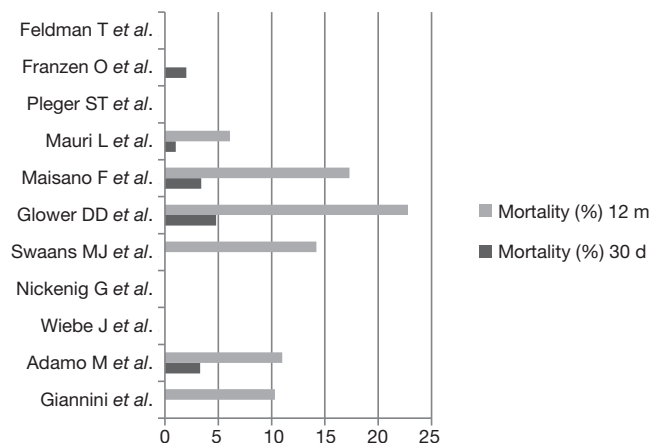
(LV) function (7,8).

For these patients, percutaneous techniques may be an alternative therapy. Currently, the device with the widest clinical use is the MitraClip® (MC) (Abbot Vascular, Santa Clara, California, USA). The MC is a percutaneous transcatheter device for MV repair. The technique used mimics the surgical edge-to-edge Alfieri technique (9) through mechanical coaptation of the MV leaflets. Short-term effectiveness and safety of this percutaneous device have already been proved in both high- and low-risk patient groups (10-16). Considering short-term mortality, we know that patients treated with the MC are not at a disadvantage (13,17,18). However, since the MC is still a relative novelty, long-term survival results remain largely unknown. The goal of this review is to present an overview of the current literature about mortality and predictors for mortality in regard to the MC procedure.

**Table 1** Available baseline characteristics and mortality data from the reviewed literature

Study	N	Mean age (yrs)	Male (%)	Mean LES <sup>†</sup> (%)	Mean STS <sup>‡</sup> (%)	Mean LVEF <sup>§</sup> (%)	FMR <sup>¶</sup> (%)	NYHA* III–IV (%)	Observed mortality (%)	
									30 d	12 m
Feldman <i>et al.</i> [2005] (19)	27	69±12	59	–	–	–	7	44	0	–
Franzen <i>et al.</i> [2010] (21)	51	73±10	67	28±22	16±11	36±17	69	98	2	–
Pleger <i>et al.</i> [2011] (22)	33	76±13	61	41±7	24±4	39±8	63	100	0	–
Mauri <i>et al.</i> [2013] (20)	184	67.3±12.8	62	–	5.0	60.0	27	51	1	6.1
Maisano <i>et al.</i> [2013] (12)	567	73.7±9.6	64	23.0±18.3	–	–	77	82	3.4	17.3
Glower <i>et al.</i> [2014] (23)	351	75.7	61	–	11.3	47.5	70	85	4.8	22.8
Swaans <i>et al.</i> [2014] (17)	139	74.6±9.4	67.6	23.9±16.0	–	36.8±15.3	77	88.5	–	14.2
Nickenig <i>et al.</i> [2014] (24)	628	74.2±9.7	63.1	20.4±16.7	–	–	72	85.5	–	–
Wiebe <i>et al.</i> [2014] (10)	1002	75.2	62	23.2	9.6	–	63	86	–	–
Adamo <i>et al.</i> [2015] (25)	304	72.0	64	17.0	8.0	37.0	79	–	3.3	11
Giannini <i>et al.</i> [2015] (26)	60	74±8	70	16	–	33	100	73	0	10.3

<sup>†</sup>, Logistic European System for Cardiac Operative Risk Evaluation score (LES); <sup>‡</sup>, Society of Thoracic Surgeons (STS) score; <sup>§</sup>, left ventricular ejection fraction (LVEF); <sup>¶</sup>, functional mitral regurgitation (FMR); \*, New York Heart Association (NYHA) Functional Classification for heart failure.

**Figure 1** Available mortality data at follow up.

## Review

The Endovascular Valve Edge-to-Edge Repair Study I (EVEREST), which was conducted in 2004 (19), demonstrated the safety, feasibility and significant hemodynamic improvement of the MC. The EVEREST II (20), a multicenter and to date the only randomized controlled trial (RCT) on this topic, compared the safety and efficacy of MC to conventional MV surgery (either replacement or repair) among patients with severe MR (grade ≥3+). All included patients were potential candidates

(selected by the guideline criteria) for MV surgery and were relatively low-risk patients [mean left ventricular ejection fraction (LVEF)] of 60%±10% and mean Society of Thoracic Surgeons (STS) score of 5%±4% (Table 1). In total, 279 patients with a mean age of 67 years were randomized in a 2:1 ratio (MC: surgery) with FMR being present in only 27%. Mortality rate was 6.1% at 1 year and 17.4% at 4 years (Figure 1), which was not significantly different from the surgical group. The safety was superior in the MC group compared to the surgery group, with a significant higher need for blood transfusion in the latter.

Franzen *et al.* studied a group of 51 patients differed much from the EVEREST II by the cohort being older (mean age 73±10 years), having a worse LV function (mean LVEF of 36%±17%), and by having more comorbidities (mean STS score of 16%±11%). FMR was present in 69% of the cohort. They showed feasibility with a high implantation success of 96% (n=49) and a low 30-day mortality of 2% (n=1), the deceased concerning an 84-year-old male with a LVEF of 14% and a Logistic EuroSCORE (LES) of 86% (21).

Based on those data the guidelines on valvular heart disease of the European Society of Cardiology (ESC, 2012) added catheter-based interventions to correct MR. Mitraclipping may be considered in patients with symptomatic severe MR who fulfil the transesophageal

echocardiographic criteria of eligibility, who are judged to be inoperable or at high-surgical-risk by a team of cardiologists and cardiac surgeons, and who have a life expectancy greater than 1 year (recommendation class IIb, level of evidence C) (4).

Several medium- and large-sized European registries have added to the evidence of safety and efficacy of the MC. Although being non-randomized, these were conducted in a real-world setting, presenting mortality figures of the MC in today's practice.

The ACCESS-EU registry, in which 567 patients (mean age  $73.4 \pm 10$  years) were prospectively enrolled at 14 European sites, FMR was present in 77%. A LVEF  $\leq 40\%$  was present in 53% and the mean LES score was  $23 \pm 18$ . They reported a 30-day mortality and an estimated 12-month mortality of 3.4% and 18.2%, respectively (12). A large European sentinel registry enrolled 628 patients between 2011 and 2012 at 25 centers (mean age  $74 \pm 10$  years). The cohort consisted predominantly of FMR (72%), there was a mean LVEF of  $43\% \pm 16\%$  and a high mean LES score of  $20\% \pm 17\%$ . They presented a 2.9% mortality at 30 days and 15.3% at 12 months. There was no significant difference in mortality between DMR and FMR (24). More recent publications of German and Italian registries, with 1,002 and 304 patients respectively, show similar short-term results, with in-hospital and 30-day mortality rates of 2.9% and 3.3% respectively (10,25).

The EVEREST II high-risk registry (HRR), which enrolled 78 patients between 2007 and 2008, and the ongoing EVEREST II REALISM (Real World Expanded Multicenter Study of the MC System) high-risk arm included 351 symptomatic elderly patients (mean age  $76 \pm 11$  years), with significant MR (70% FMR), of whom 60% had a history of cardiac surgery (23). This represents a population with more severe comorbidities (mean STS score of  $11\% \pm 8\%$ ) and worse LV function (mean LVEF of  $48\% \pm 14\%$ ). One-year mortality was 22.8%.

Pleger *et al.* described 51 very high-risk patients (mean LES score  $41\% \pm 7\%$ ) and analyzed the cohort for effectiveness and safety. They observed one death of a patient (LES score of 63%) who died 31 days post-procedural (22). More recently and being comprised of a larger pool, patients from the TRAMI registry were reviewed for age and mortality. In total, 525 patients with an age of  $\geq 76$  years (mean  $81 \pm 3$  years) showed an in-hospital and 30-day mortality of 2.9% and 6.7%, respectively. There was no significant difference compared to the 539 patients of the cohort with an age  $< 76$  years. Also, the multivariate

analysis did not point out advanced age as a predictor for in-hospital major adverse cardiac events (27).

To address this need to compare the MC to alternative treatment options, especially for high-risk patients, Swaans *et al.* retrospectively formed conservatively and surgically treated matched control groups. To try correct for confounding factors, propensity scoring was used to correct for cardiac resynchronization and LES score among others. MC patients mainly had FMR (77%), mean age was  $75 \pm 9$  years, there was a mean LES score of  $24\% \pm 16\%$  and a mean LVEF of  $37\% \pm 15\%$ . The median follow up for the MC group was  $1.7 \pm 1.1$  years, and mortality after 1, 2 and 3 years was 14.2%, 24.5% and 37.7% respectively. The conservatively treated cohort (age  $72 \pm 10$  years, mean LES  $19\% \pm 13\%$  and mean LVEF of  $19\% \pm 13\%$ ) had a median follow up of  $2.7 \pm 2.2$  years and a mortality ratio of 32.3%, 47.5% and 54.2% after 1, 2 and 3 years follow up, respectively.

When comparing MC treatment with conservative treatment, the hazard ratio (HR) for mortality was 0.41 [95% confidence interval (CI): 0.22–0.78,  $P=0.006$ ]. After propensity matching, the outcome remained comparable with a HR of 0.47 (95% CI: 0.24–0.93). In a sub-analysis of patients with FMR the HR for mortality also remained significant (HR 0.46, 95% CI: 0.23–0.93,  $P=0.03$ ). The HR for mortality for percutaneously treated patients compared with surgically treated patients, showed no significant difference. The limitation of this study lies in its non-randomized retrospective character, which could potentially give rise to patient selection bias and to the inclusion of unknown confounding factors (17).

More recently, a study by Velazquez *et al.* used similar methodology and data from the HRR and REALISM and the Duke Echocardiography Laboratory Database (28) to perform a propensity matched comparison between MR patients treated with the MC (mean age  $74 \pm 11$  years, mean LVEF  $42\% \pm 12\%$ ) and medically treated patients. Also recently, an online publication by Giannini *et al.* compared conservative to percutaneous edge-to-edge (mean age  $74 \pm 8$  years, mean LVEF 33 years) treatment for patients with FMR. Both, in line with Swaans *et al.*, showed significant lower mortality rates at follow up for MC treatment compared to conservative treatment, with adjusted HR's for mortality being 0.60 (95% CI: 0.42–0.85) and 0.43 (95% CI: 0.24–0.77) for Velazquez *et al.* and Giannini *et al.*, respectively (26,29).

In order to obtain a higher level of evidence, a RCT is required. Several RCT's have been set up over the past

few years. In 2013 the study protocol of A Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF) was registered. In this European RCT, percutaneous intervention and conservative treatment will be compared by investigating mortality and re-hospitalization differences. Unfortunately, due to low recruitment rate, this study has been terminated prematurely (ClinicalTrials.gov number, NCT01772108). Currently, the Cardiovascular Outcomes Assessment of the MC Percutaneous Therapy (COAPT) for Heart Failure Patients With Functional Mitral Regurgitation trial is recruiting patients in the USA and Canada to either undergo MC (n=215) or conservative treatment (n=215). The target date for analysis of primary outcome, of which the safety outcome is a combined endpoint of several major complications and the effectiveness outcome being recurrent heart failure hospitalizations, is scheduled for early 2018 (ClinicalTrials.gov number, NCT01626079). Other similar RCT's have been introduced, but until now there have been no published results (ClinicalTrials.gov numbers, NCT01431222 and NCT01920698). Recently, A Multicenter Randomized Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigin (MATTERHORN) was started. It is the first study which compares MV surgery and MC treatment in patients with depressed LV function and investigators intend to include 210 patients to be divided over the two study arms (ClinicalTrials.gov number, NCT02371512).

To further help treating physicians in deciding which high-risk patients will benefit most from MC treatment, the relation between pre- or peri-procedural characteristics and post-procedural mortality should be studied. Several performed analyses have shown acute procedural success, defined as MR reduction to  $\leq 2$  ( $\leq$  mild), to have a positive impact on survival (18,30-34). An univariate analysis of an early conducted [2009-2012] observational study in Switzerland, with 77 patients who had reached a follow-up of 2 years (mean age  $72 \pm 12$  years, mean LES score  $21\% \pm 17\%$ ), also resulted in NT-proBNP, chronic obstructive pulmonary disease and kidney failure to be predictors for mortality (31). In a more recent study of 84 patients, the multivariate analysis showed NT-proBNP, previous valve surgery and tricuspid insufficiency to be independent mortality predictors during a follow up of 2 years (33). Advanced age, New York Heart Association (NYHA) III-IV, STS score  $\geq 12$ , pulmonary hypertension,

MR of ischemic heart disease and pre-procedural MR-grade have also all been proved to be predictors for mortality (18,27,32,34,35).

## Synopsis

Percutaneous edge-to-edge MV repair with the MC<sup>®</sup> has proved to have a relatively low peri-procedural mortality rate in both patients with a low- or high-surgical-risk. In contrast to surgery, it seems to be a safe alternative for the frail patient. Though three non-randomized studies suggested a survival benefit of MV repair using the MC compared to conservative management, this finding awaits confirmation in a RCT with adequate length follow-up.

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## Footnote

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