

# Treatment of mitral regurgitation

Roberto Violini, Alberta Cifarelli, Francesco De Felice, Diana Chin

UO Cardiologia Interventistica, Azienda Ospedaliera S. Camillo Forlanini, Rome, Italy

## Abstract

In the elderly mitral regurgitation is very frequent and surgical correction of mitral regurgitation (MR) has often a high operative risk, consequently, over the years, different percutaneous transcatheter techniques have been developed as a valid alternative to surgery. The edge-to-edge repair with the MitraClip device has gained a wide clinical application, supported by several studies, both randomized trials and registries. It is indicated in functional MR as in degenerative MR. The outcome is usually positive, resulting in a reduction of the regurgitation to grade 1+ or 2+ and an improvement in the NYHA functional class to I or II, even reducing the hospitalizations. Its cost-effectiveness too is supported by some studies.

## Introduction

Mitral regurgitation (MR) is a relatively frequent cardiac disease in the elderly and often results in significant morbidity and mortality. Its pathogenesis can be primary (degenerative), due to leaflet malformations (prolapse), chordal rupture or tissue degeneration of the mitral valve (MV), or secondary (functional) when there is no valvular disease but the regurgitation is due to ventricular remodeling (regional or global) with modifications of the papillary muscles, dilatation of the annulus and reduction of leaflet coaptation. The etiology is usually ischemic or dilatative cardiomyopathy [1]. In the former, surgical correction is effective, usually done with MV repair, rather than replacement, and has been associated with first-time operative mortality rates near 2%, and re-operative mortality rates near 8% [2]. The surgical intervention in the functional forms has a worse outcome and is often not indicated.

Corresponding author: Roberto Violini, UO Cardiologia Interventistica, Azienda Ospedaliera S. Camillo Forlanini, Piazza Carlo Forlanini 1, 00151 Roma, Italy. E-mail: r.violini@scf.gov.it

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Obviously, the surgical risk is significantly higher in older patients, so different percutaneous techniques are being clinically evaluated in order to treat surgical high risk patients. The transcatheter approaches are different: some of them aim to reduce annulus enlargement, whilst the MitraClip® system reproduces the Alfieri surgical operation, with the edge-to-edge repair to reduce valvular regurgitation. Actually, only this technique has emerged as a widespread transcatheter method for treating MR (implanted in over 40.000 patients worldwide) whilst the direct and indirect anuloplasty methods are also moving their first steps in the clinical world.

## Technique

The MitraClip® device is inserted via the femoral vein and utilizes a 24Fr guiding catheter to gain transeptal access to the left atrium. The tip of this catheter has a bidirectional steering mechanism so it can be positioned centrally above the mitral valve annulus and a V-shaped clip is introduced while closed. This clip, made of cobalt-chromium and polyester-covered, is opened and advanced into the left ventricle; then it is slowly retracted to snare the anterior and posterior leaflets during systole; the clip can be opened and closed repeatedly to ensure optimal positioning. When the grasping appears optimal, the clip is released, so creating a double valvular orifice (Figure 1). Sometimes more than one clip, up to three or four, are used to gain the best result.

After the implant a regimen of aspirin at a dose of 325 mg daily for 6 months with clopidogrel at a dose of 75 mg daily for 1 month is suggested [2], although this therapy has not been validated.

## Studies

In the first randomized trial comparing the MitraClip® device *versus* standard MV surgery [3], two hundred and seventy-nine patients with grade 3+ MR were randomized in a 2:1 ratio to undergo MitraClip® implantation or conventional surgical MV correction (either repair or replacement). The composite endpoint of freedom from death, surgery, or grade 2+ MR at 12 months was achieved in 55% of MitraClip® patients *vs* 73% of surgical patients ( $p=0.007$ ); Both groups demonstrated similar symptom reduction up to 24 months, while surgical patients experienced superior decreases in MR grade, (76% demonstrating MR grade 1+ *vs* 43% of MitraClip® patients). The authors concluded that, though surgery appeared more effective in treating MR, percutaneous treatment was also effective and safer in a large number of patients and was associated with lower rates of major adverse events (15% of MitraClip® patients *vs* 48% of surgical patients).

Several studies of “real-world” experience with the MitraClip® system have been published with satisfactory results. A large European study, the Amsterdam Center for Contemporary European Studies – A Two-Phase Observational Study of the MitraClip® System in Europe (ACCESS-EU) prospective nonrandomized trial, found 81.8% survival at 1 year and 78.9%

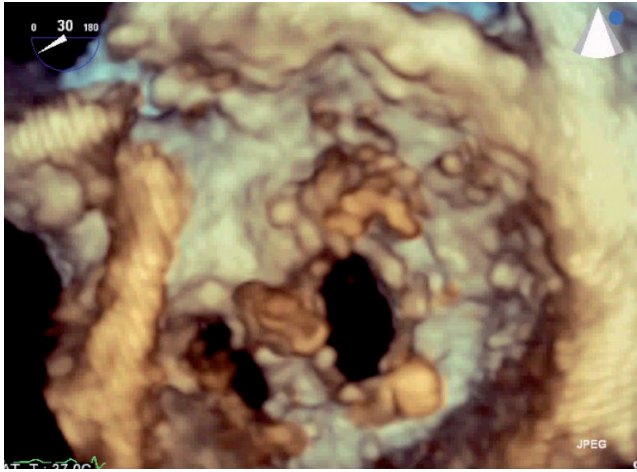


Figure 1. Transesophageal three-dimensional echocardiogram showing the double orifice after MitraClip implantation.

freedom from MR grade 3+ [4]. The Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation (GRASP) registry showed freedom from the composite endpoint of death, surgery, or MR grade 3+ in 75.8% of 117 treated patients at 1 year [5]. These data also did not show any differences in safety or outcomes when comparing patients with degenerative *vs* functional MR. A recent meta-analysis reviewing 16 studies confirmed a low adverse event rate and only 14.7% of patients demonstrating MR grade 3+ at 1 year [6]. The largest series of treated patients (749 patients with 1-year follow-up from the German transcatheter mitral valve interventions registry) demonstrated 79.7% 1-year survival among all patients, as well as a decreased rate of hospital readmission for heart failure [7].

The MitraClip® has been beneficial in several other experiences: survival of 98.3% in the percutaneous therapy group compared to 89.7% in the conservative group at 1 year and 61.4% *vs* 34.9% ( $p=0.007$ ) at 3 years were demonstrated in a recent study of 60 patients treated with MitraClip compared to 60 patients managed medically [8].

Other studies were conducted in patients with renal impairment [9], in patients with grade 3+ MR nonresponsive to cardiac resynchronization therapy [10] and in end-stage systolic heart failure patients [11].

## Indications

At present, the MitraClip® implant is indicated in patients with severe MR despite optimal medical therapy, who are not surgical candidates, for high risk (degenerative MR) or lack of indication (functional MR in cardiomyopathies), when life expectancy is longer than one year and when a Heart Team confirms the indication. In the ESC guidelines MitraClip® has a recommendation in class IIb, evidence level C [12]. The predictors of 1-year mortality [6] are summarized in Table 1. Anatomical criteria are evolving and are actually larger than in the Everest trial. In the elderly, the frequent fibroelastic degeneration of MV seems an indication with a favorable outcome.

## Final considerations

The indications of MitraClip® therapy in patients with functional MR have gained an important role, because these patients have worse

Table 1. Predictors of 1-year mortality after MitraClip® intervention [6] (modified).

NYHA IV
Anemia
Previous aortic valve intervention
Creatinine $\geq 1.5$ mg/dl
Peripheral artery disease
Left ventricular ejection fraction $<30\%$
Severe tricuspid regurgitation
Procedural failure

outcomes following valve repair compared to degenerative MR [13]. Recently mitral valve replacement too has been demonstrated to have equivalent outcomes for functional MR patients in a randomized trial, even though earlier data has suggested a superior outcomes for MV repair [14]. However, an excess incidence of recurrent MR was noted at 1-year among patients undergoing MV repair [15].

In the US, the MitraClip system is currently approved by the Food and Drug Administration for patients with degenerative MR grade 3+ and symptoms (New York Heart Association functional class III or IV) who meet prohibitive risk criteria (30-day Society of Thoracic Surgeons predicted mortality risks of 8% for planned mitral valve replacement, or 6% for planned MVR).

The MitraClip® device does not solve all aspects of mitral valve dysfunction which result in MR: it improves leaflet coaptation, but does not modify the mitral annulus (as it can be done surgically by suturing a ring) nor does it correct problems related to the mitral chordal apparatus. Consequently, different technologies designed to improve annular geometry or chordal function are under development, where a number are already being introduced for clinical use.

At present, in order to evaluate MitraClip® cost effectiveness in patients with MR and severe heart failure, a comparison must be done *vs* medical treatment, and not *vs* surgical intervention as most patients receiving the clip are not suitable for surgery. This comparison should be done calculating how many hospitalizations are saved after the MitraClip® implantation. Several papers demonstrate that MitraClip® is cost effective [1,16]. Finally, some randomized controlled trials (Reshape, Mitral FR, COAPT) are currently enrolling patients to compare efficacy of MitraClip® *vs* best medical therapy in the treatment of heart failure and severe MR.

The future of severe MR treatment is projected towards percutaneous mitral valve implantation: the first in man experiences have already been done with at least five different prosthesis.

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