

Considerations on the use of MitraClip in the treatment of mitral regurgitation

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Mitral regurgitation (MR) is, by occurrence, the second most common valvular heart disease in the Western world, with a significant impact on prognosis and mortality. A significant number of patients with significant mitral incompetence cannot be submitted to conventional surgery due to high surgical risk. The need for an adequate therapeutical strategy prompted the development of innovative endovascular techniques. Among them, the MitraClip percutaneous system, mimicking the ‘edge-to-edge’ surgical technique introduced by Alfieri in 2003 has emerged as the treatment of choice in patients not suitable for conventional surgery. Since its introduction, this procedure has been effectively carried out in more than 35 000 patients. The evidences from the first randomized clinical trial, EVEREST II, suggested that the MitraClip system is effective in improving survival and quality of life in patients with severe MR. Further randomized trials, MITRA-FR and COAPT, added some more information, showing that an appropriate patient selection, close attention to the specific anatomical characteristics of the mitral valve, and adequate experience of the centre providing the treatment, are important determinants of the outcome of the procedure.

Introduction

By frequency, mitral valve disease represents the second form of valve disease in the western world after aortic disease. Mitral regurgitation (MR), which is one of the most frequently acquired valvular diseases, affects about 10% of the population over 75 and is continuously increasing with the increase in average age. Without proper therapy, patients with significant MR have an unfavourable outcome, resulting in left ventricular remodelling and systolic dysfunction, atrial dilatation, and pulmonary hypertension. All these conditions are associated with an increase in the frequency of hospitalizations for heart failure and death.¹

Timing and treatment strategy still represent an important challenge for cardiologists, both for the clinical prevalence of the disease and for the anatomical complexity of the mitral valve. A significant number of patients with a

significant MR are not suitable candidates for surgical treatment, in relation to high rate comorbidities and an excess of surgical risk. Notably, until the recent introduction of the transcatheter mitral valve repair technique, surgical mitral replacement, and/or repair was the only therapeutic option available, and still represents the ‘standard of care’ in patients with low or intermediate surgical risk.

In 1991 Maisano, Alfieri *et al.*² described for the first time the mitral repair technique that become the most used repair technique to date. It consists in positioning a surgical suture between the medial portions of the anterior and posterior mitral leaflets, anatomically generating a double valve orifice that allows to reduce the degree of regurgitation without causing significant stenosis. This ‘edge-to-edge’ suture technique has been implemented over the years with the addition of annuloplasty, resulting in significantly better results on the reduction of valve regurgitation.³

The success of the Alfieri’s technique inspired the development of a transcatheter technology capable of

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replicating the same type of treatment with a percutaneous procedure. The first transcatheter system introduced for the 'edge-to-edge' repair of MR was the MitraClip system (Abbott) and has recently been joined by the Pascal system (Boston).

The first percutaneous repair procedure for MR with MitraClip system (Abbott Vascular, Abbott Park, IL, USA) was carried out in 2003, the system obtained the CE mark of European conformity in 2008, and the FDA approval in 2014.

The first clinical data of transcatheter technique derive from the randomized trial Endovascular Valve Edge-to-Edge Repair Study (EVEREST II), which assessed safety and efficacy of Mitraclip implantation in patients with treatment of moderately severe or severe MR both degenerative and functional.⁴ Compared to conventional surgery, percutaneous repair although less effective at reducing MR, was associated with superior safety and similar improvements in clinical outcomes, with a reduction in mortality and hospitalizations, and an improvement in the quality of life, as well. The benefit of mortality is likely related to the interruption of the pathophysiological mechanism whereby the degree of valve regurgitation, causing a worsening of the degree of left ventricular dilation and consequently a further worsening of the degree of MR, ultimately determines the increase in mortality.

The randomized trial was part of a larger project called the 'EVEREST Investigational Device Exemption (IDE) clinical program', which included two registries, one for high-risk patients treated with MitraClip and another registry (REALISM) which enrolled intermediate-risk patients. These registries provided important insights on the clinical results of MitraClip in 'real-world' patients. On the basis of the favourable data deriving from the Everest II study, together with those of the European multicentric registers, the percutaneous repair procedure is now suggested as a therapeutic option in the European guidelines, with an indication Class IIb level of evidence C, thus representing a valid alternative to surgery in those patients where surgical risk is prohibitive.

The Everest II study results raised some concerns in the scientific community, mostly due to biased patients' selection. In particular, the population initially identified by the study was affected by degenerative MR and only later the study included patients with functional MR, to whom today the procedure is mainly addressed. Despite criticism, the Everest trial with its results represents the watershed that allowed MitraClip to become part of therapeutic strategies in patients who are not suitable for conventional surgery due to top prohibitive risk.

In 2017, two randomized trials (the MITRA-FR and the COAPT studies) compared percutaneous treatment vs. conservative medical therapy.

The MITRA-FR study represents a multicentre randomized trial conducted entirely in French hospitals that has received support from the Ministry of Health and Research. The inclusion criteria in patient enrolment included specific echocardiographic markers, such as the presence of severe secondary MR, defined by a regurgitation volume >30 mL/beat or an EROA >20 mm² (in accordance with the

European guidelines on valvular heart disease drawn up in 2012) in symptomatic patients for heart failure with New York Heart Association (NYHA) functional class equal to II-IV and ejection fraction (EF) values between 15% and 40%. The cohort of enrolled patients was initially treated with optimal medical therapy and subsequently underwent randomization 1:1 for percutaneous treatment of MR or medical therapy alone. The analysis of the data highlighted the absence of a statistically significant difference for the primary endpoint (mortality and re-hospitalization) in the two arms. Similar results have been shown for clinical secondary endpoints, such as death from cardiovascular causes, survival free from major cardiovascular adverse events (which included death, stroke, myocardial infarction, and unscheduled hospitalization for recurrence of heart failure) and bleeding events.⁵

The disappointment in the scientific community aroused by the results of the MITRA-FR study was reversed by the data deriving from the COAPT trial. The COAPT study is a randomized multicentre study which included patients with moderate to severe secondary MR (3+ to 4+) and severe ventricular dysfunction (EF between 20% and 50%) with NYHA class from II to IV, despite maximal medical therapy and/or cardiac re-synchronization therapy. The results of the intention-to-treat analysis showed a statistically significant trend in favour of the percutaneous repair treatment both for the primary efficacy endpoint (incidence of all hospitalizations for recurrence of heart failure), and for the primary safety endpoint (device-free complications survival at 12 months). The trend in favour of MitraClip treatment was also confirmed for secondary endpoints, mainly represented by echocardiographic data, such as left ventricular function and volumes or by clinical criteria, such as the NYHA class or 6 min walking test results.⁶

The discordant results deriving from the two randomized multicentre trials, might be in part explained by the following considerations:

- the MITRA-FR trial likely enrolled patients with a milder degree of MR compared with the COAPT study, where the mean regurgitation fraction (EROA) was greater, thus reflecting a more severe degree valvular disease. Of note, a sub-analysis of patients stratified by the degree of MR in the MITRA-FR study revealed results comparable to those found in the COAPT trial.
- the MITRA-FR study highlighted a lower number of implanted clips, on average, compared to the COAPT cohort and a greater degree of post-procedural residual MR. A 12-month higher incidence of device failure, stroke, and cardiac tamponade was reported at follow-up compared to patients in the COAPT study.
- patients in the COAPT study had been selected for the persistence of symptoms in spite of the optimization of medical therapy, which was more discretionary in the MITRA-FR study.
- the COAPT trial provided a better patient selection with different procedural expertise among the operators compared to the MITRA-FR study, which might explain a greater rate of procedural failures in the MITRA-FR study (Table 1).

Table 1 Ultrasound criteria for selecting the most suitable patient for Mitraclip treatment

Optimal valve morphology	Possible valve morphology	Difficult or impossible valve morphology
Central pathology in scallop 2 Absence of valve calcification	Pathology in scallops 1 or 3 Mild calcification outside the grasping zone, annulus calcification, postannuloplasty	Mitral valve perforation or cleft Significant calcification in the grasping zone
Mitral valve area >4 cm ²	Mitral valve area >3 cm ² with good residual motion	Haemodynamically significant mitral stenosis (MVA <3 cm ² and mean gradient ≥5 mmHg)
Mobile length of posterior leaflet ≥10 mm	Mobile length of posterior leaflet 7-10 mm	Mobile length of posterior leaflet <7 mm
Coaptation depth <11 mm	Coaptation depth ≥11 mm	
Normal leaflet thickness and motion	Restricted motion during systole (Carpentier type IIIb)	Restricted motion during systole and diastole (Carpentier type IIIa)
Flail width <15 mm and gap <10 mm	Flail width >15 mm in case of dilated annulus and possibility of multiple clip implantation	Barlow syndrome with flail in multiple scallops

From Li *et al.*⁷

After the publication of these studies, a meta-analysis was published⁸ which reported the results of 21 international studies with more than 3000 high-risk patients undergoing MitraClip implantation. The meta-analysis showed a high procedural success, with a reduction in the degree of valve regurgitation, low procedure-related mortality, a good mid-term procedural efficacy on the reduction of MR, and improvement of the NYHA class. A further comparison study between conservative treatment and mitral clip implantation in patients with severe functional MI and left ventricular dysfunction showed a lower rate of re-hospitalization and cardiovascular mortality,⁹ also in elderly patients and with a longer follow-up.^{10,11}

These data suggest that percutaneous treatment with MitraClip of symptomatic secondary MR on top of optimal medical therapy, may lead to an improvement in symptoms, functional capacity and quality of life up, with an improvement in terms of survival.¹²

Conclusions

Mitral regurgitation is associated with an unfavourable outcome in patients with ventricular dysfunction and heart failure. The pathophysiological nexus of interrelation between ventricular dysfunction and worsening of the degree of MR is not yet fully clarified but the impact on the quality of life and survival of patients is particularly relevant.

European Guidelines still limit percutaneous treatment to patients at high surgical risk. Data from the COAPT study demonstrated efficacy in the treatment of high-risk patients and this could lead to an extension of the indications in the guidelines. A multidisciplinary approach (Heart Team) involving clinical cardiologists, imaging experts, cardiac surgeons, and interventional cardiologists is a key element in ensuring the best therapeutic success strategy in these patients.

Conflict of interest: none declared.

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