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MitraClip and repair surgery: comparable results?

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Mitral regurgitation (MR) is the most common valvular disease in industrialized countries, with a significant impact on patient quality of life and survival, especially in an increasingly elderly and comorbid population. Repair surgery is considered the treatment of choice for primary MR, offering excellent long-term outcomes. However, the MitraClip system, a less invasive percutaneous option based on the edge-to-edge principle, has proved to be a valid alternative for patients at high surgical risk, showing initial benefits in terms of fewer post-operative complications. Surgery remains superior in terms of durability and prevention of residual regurgitation, but the MitraClip system offers advantages in selected patients, with improvements in quality of life and reductions in hospitalizations for heart failure. A multidisciplinary approach and careful patient selection are essential to optimize outcomes.

Introduction

Mitral regurgitation (MR) is the most common valvular disease in industrialized countries, affecting an increasingly elderly population and often affected by significant comorbidities.[1] MR can be primary (organic) or secondary (functional), each with a distinct pathophysiology and different implications for treatment. Primary MR is caused by structural alterations of the valvular apparatus, including prolapse, rupture of the chordae tendineae, and fibroelastic degeneration. The most common form of primary MR in Western countries is related to degenerative processes, while in developing countries it is more frequently of rheumatic origin.[2] In contrast, secondary MR results from cardiac pathologies of the left atrium or ventricle that cause remodelling and dilation of the heart compromising the coaptation of the valve leaflets in the absence of intrinsic alterations of the valve itself. Myocardial infarction is a frequent cause of MR, and the occurrence of MR is a poor prognostic indicator in the acute and early phases following the ischaemic event. In the chronic post-infarction phase, the presence of MR is associated with increased mortality regardless of baseline characteristics and degree of ventricular dysfunction. In these patients, the prognosis seems to be mainly related to the degree of MR.[3] Moreover, the degree of MR has been shown to worsen the prognosis in patients with heart failure with reduced ejection fraction.[4] Over the past decades, surgical repair has consolidated its role as the standard treatment for primary MR, offering excellent results in terms of long-term survival and quality of life. However, surgical treatment of mitral valve disease may not be feasible in patients with high surgical risk, such as elderly patients or those with significant comorbidities (a population expected to grow in the future). Furthermore, in secondary MR, where mitral valve dysfunction is a consequence of an underlying cardiomyopathy, surgical treatment is often not feasible, making alternative treatments necessary. In this context, the introduction of percutaneous treatment with the MitraClip system (Abbott Vascular, Santa Clara, CA, USA) has represented

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a significant advance, offering a less invasive alternative to surgery for patients at high surgical risk. The MitraClip device was first implanted in humans in 2003. It has been available in Europe since September 2008, following the CE mark. Based on the edge-to-edge principle, the MitraClip procedure is designed to reduce MR by placing clips that improve the coaptation of the valve leaflets. Although initially proposed as a compassionate alternative in patients who are not candidates for surgical therapy, over the years it has evolved to become a safe alternative to surgery. This review aims to provide an updated overview of the comparison between reconstructive surgery and MitraClip in the treatment of MR, examining in particular the available evidence, clinical indications, and future perspectives.

Primary MR

Currently, there are data regarding a head-to-head comparison of repair surgery with the MitraClip system for the treatment of primary MR. The prospective, multicentre, randomized EVEREST II[5] (Endovascular Valve Edge-to-Edge Repair Study) compared percutaneous repair using the MitraClip system with conventional surgery (with a 2:1 randomization ratio in favour of MitraClip) in patients with significant MR (3–4+) and favourable anatomic criteria. At 5 years, the survival rate without death, surgery, or grade 3+/4+ MR was 44.2% for percutaneous repair vs. 64.3% for surgery ($P = 0.01$). This result was driven by higher rates of grade 3+/4+ residual MR (12.3 vs. 1.8%, $P = 0.02$) and the need for surgery (27.9 vs. 8.9%, $P = 0.003$) in the percutaneously treated group, with most surgeries occurring within the first 6 months. Beyond 6 months, rates of surgery and moderate-to-severe MR were comparable between groups. The 5-year mortality rates were 20.8% for percutaneous repair and 26.8% for surgery ($P = 0.4$).

Multivariate analysis showed no significant associations between treatment strategy and survival. Furthermore, in the subgroup analysis of patients with degenerative MR, surgery was superior in terms of freedom from death, surgical repair/re-operation, and 3+/4+ MR compared with MitraClip at 5 years (difference −30.7%, 95% CI −46.5–14.8%, $P < 0.001$). A retrospective study compared patient outcomes in elderly patients at low–intermediate risk (STS-PROM <8%) with degenerative MR. Between January 2005 and May 2017, 100 patients underwent MitraClip and 206 surgical repair at two centres. After propensity score adjustment, the MitraClip group showed a lower rate of post-operative complications ($P < 0.05$) but a higher prevalence of residual MR ≥2+ (27.0 vs. 2.8%, $P < 0.001$). One-year survival was superior with MitraClip (97.6 vs. 95.3%, $P = 0.001$), but inferior at 5 years (34.5 vs. 82.2%, $P < 0.001$). Recurrence of MR ≥3+ was more frequent in MitraClip patients (36.9 vs. 3.9%, $P < 0.001$). According to the most recent European guidelines[1] (*Figure 1*), surgery is recommended as the first-line option in patients with primary MR (Class of Recommendation I, Level of Evidence B); TEER may be considered in symptomatic patients who meet echocardiographic criteria for eligibility for surgery, or who are judged by the Heart Team to be inoperable or at high surgical risk and in whom the procedure is not considered futile (Class of Recommendation IIb, Level of Evidence B). It is also essential to take into account some aspects, which in the future could lead to a better selection of patients and therefore to a redefinition of the role of MitraClip in the management of degenerative MR. The indication (with appropriate patient selection) and timing of the intervention play a crucial role in the diagnostic and therapeutic process of patients with MR. Identifying the optimal time to intervene means considering not only the severity of MR, but also the involvement of other cardiac structures, as highlighted by the study by van Wijngaarden *et al.*[6] in patients with organic MR undergoing mitral valve repair surgery. As shown in this study, patients with significant left atrial dilatation or right ventricular dysfunction, for example, have a higher mortality risk and benefit from careful stratification and timely intervention. On the contrary, too late intervention, in the presence of secondary left ventricular damage or complications such as pulmonary hypertension, may compromise clinical outcomes even after technically successful treatment. On the contrary, a timely approach that takes into account advanced prognostic criteria, such as left atrial volume or right ventricular function, can significantly improve survival and quality of life. In addition, some procedural aspects must be considered. The MitraClip leads to a reduction in the valve orifice area and a consequent increase in transvalvular gradients. This haemodynamic feature becomes particularly relevant in cases of small valve areas or when multiple implants are needed to minimize residual mitral regurgitation (rMR).

The relationship between the resulting mean pressure gradient and clinical outcomes is of particular interest to guide operative decisions during percutaneous procedures, balancing the reduction in rMR and the risk of iatrogenic mitral stenosis. Although the prognostic impact of rMR has been well documented and its grade is a well-established predictor of prognosis, data on the clinical importance of mean MPG (you must define acronym) after MitraClip remain conflicting, especially in patients with severe primary MR. Furthermore, available studies differ significantly regarding the timing and modalities of echocardiographic assessments, limiting their applicability in daily clinical practice for intraoperative decision-making. The PRIME-MR (Outcomes of Patients Treated with Mitral Transcatheter Edge-to-Edge Repair for Primary MR) study analysed the prognostic impact of rMR and mean transvalvular gradient in patients with primary MR undergoing edge-to-edge transcatheter repair. Analysing an international registry with 1509 patients, an intraoperative rMR ≥ 2+ was associated with worse clinical outcomes, including increased mortality and heart failure hospitalizations at 2 years. In contrast, a mean transvalvular gradient >5 mmHg did not show an independent prognostic impact. The best outcomes were seen in patients with optimal rMR reduction (<2+) and low gradients. The study highlights the importance of minimizing rMR during the procedure to improve clinical outcomes, offering valuable guidance to optimize intraoperative decisions.

Secondary MR

Current European guidelines[1] consider surgical repair for secondary or functional MR in symptomatic patients

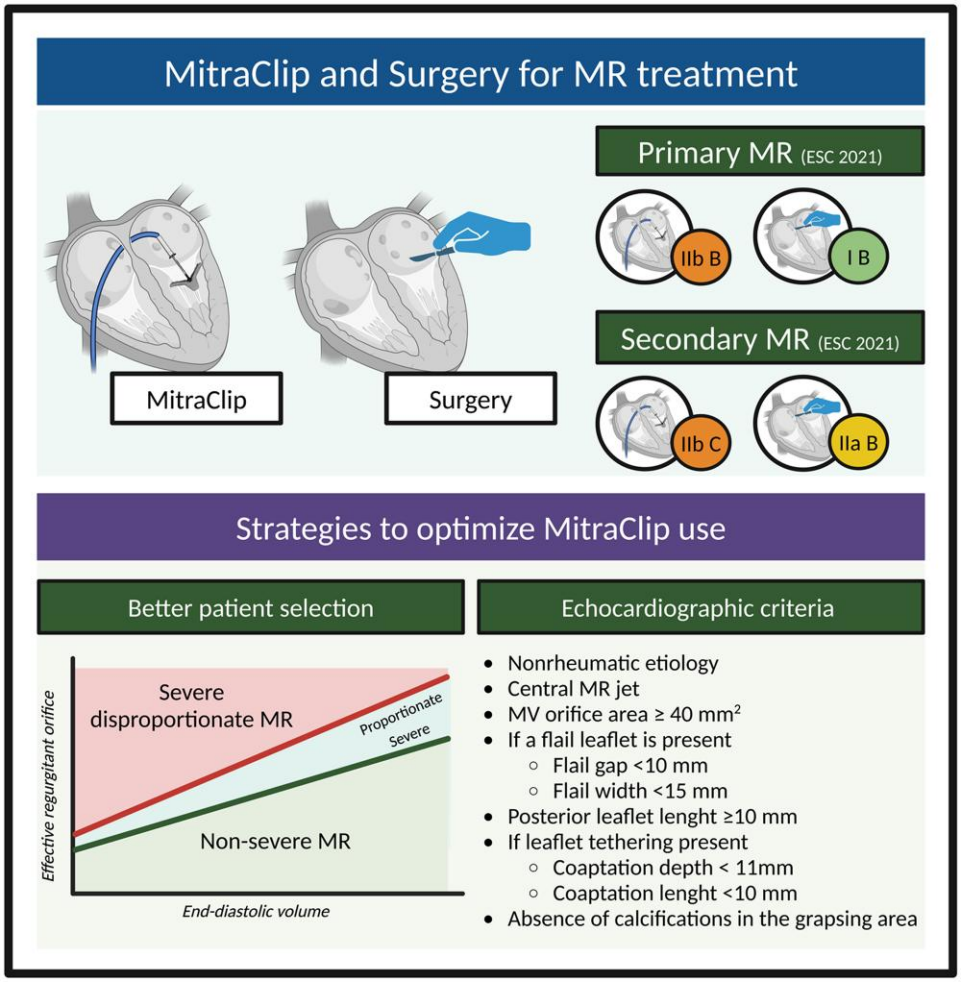

Figure 1 European Guidelines indications for the treatment of primary and secondary mitral regurgitation, with the indication for surgical repair and MitraClip based on echocardiographic criteria and risk of surgery.

deemed suitable by the Heart Team (Class of Recommendation IIb, Level of Evidence C). In contrast, edge-to-edge transcatheter repair is considered for symptomatic patients who are inoperable or at high surgical risk, following specific echocardiographic criteria (Class of Recommendation IIa, Level of Evidence B). The MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) studies evaluated the efficacy and safety of the MitraClip system in patients with severe secondary MR and systolic heart failure. Although targeting similar populations with the same disease and device, the results have been diametrically opposed. The MITRA-FR[7] trial randomized 304 patients with severe MR (regurgitant orifice area >20 mm^2 and/or regurgitant volume >30 mL) and ejection fraction between 15 and 40%, showing that the MitraClip did not significantly improve prognosis compared with optimized medical therapy. In contrast, the COAPT trial, with 614 patients characterized by more severe MR (regurgitant orifice area >30 mm^2, regurgitant volume >45 mL) and ejection fraction ≥20%, showed a significant reduction in mortality and heart failure hospitalizations at 2 years[8] and 5 years[9] in the MitraClip group compared with medical therapy alone. Over the years, several hypotheses have been formulated to explain the conflicting results of these two clinical trials.

Recently, Grayburn *et al.*[10] hypothesized that MITRA-FR and COAPT produced conflicting results because patients in the MITRA-FR study had regurgitation proportionate to significant ventricular dilation, whereas COAPT included patients with disproportionate regurgitation, in whom transcatheter repair therefore resulted in clinical benefit. Some recent evidence has added further elements. In the multicentre RESHAPE-HF2[11] (Randomized Investigation of the MitraClip Device in Heart Failure: Second Trial in Patients with Clinically Significant Functional MR) study, 505 patients with moderate-to-severe functional MR and heart failure were randomized to transcatheter repair and optimized medical therapy. At 2 years, the rate of hospitalizations for heart failure or cardiovascular death was 37 events per 100 patient-years in the MitraClip group vs. 58.9 events per 100 patient-years in the medical group ($P = 0.002$). The mean change in KCCQ-OS at 1 year was

21 points in the MitraClip group vs. 8 points in the medical group ($P < 0.001$). Regarding secondary endpoints, at 1 year, 74.5% of subjects in the MitraClip cohort vs. 58.5% of subjects in the medical cohort had NYHA Class I or II ($P < 0.001$), while the mean change in the 6-min test was 34 m in the MitraClip group vs. 5 m in the medical group ($P = 0.047$). 90.4% of subjects in the MitraClip group vs. 36.1% in the medical treatment group had 2+ or less MR at 1 year. These three studies play a crucial role in understanding patient selection strategies for functional MR for percutaneous treatment. They provide fundamental information to define the indications for MitraClip use in this patient population, helping to more precisely identify the clinical profiles that may benefit from this transcatheter therapy. Although patients with severe MR were primarily included, the effective regurgitant area was 0.40 cm^2 in COAPT, 0.31 cm^2 in MITRA-FR, and 0.25 cm^2 in RESHAPE-HF2. In COAPT, all-cause mortality was reduced with transcatheter therapy. However, in RESHAPE-HF2 and MITRA-FR, this reduction was not significant.

These studies therefore allow us to understand when it is too late to intervene (MITRA-FR) and when something can still be done (COAPT and RESHAPE-HF2). Recently, the multicentre randomized study MATTERHORN[12] (Multicenter Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin) directly compared MitraClip repair with surgery for the first time in the treatment of functional MR in patients at high surgical risk with symptomatic heart failure despite optimized medical therapy. At 1 year, MitraClip was shown to be non-inferior to surgery about the primary endpoint, i.e. a composite of death, hospitalization for heart failure, mitral valve reintervention, implantation of an assist device, or stroke (16.7 vs. 22.5%, $P < 0.001$). The results of this study therefore highlight how transcatheter repair may represent a valid alternative to surgery.

Conclusions

The choice between repair surgery and MitraClip depends on multiple factors, including the aetiology of the MR, the clinical condition of the patient, and the experience of the operating team. A multidisciplinary approach is essential to ensure optimal patient selection and improve long-term outcomes. Future studies and technological innovations will be essential to further refine treatment strategies.

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Data availability

No new data were generated or analysed in support of this research.

Disclaimer

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