Novel devices

Percutaneous edge-to-edge MitraClip therapy in the management of mitral regurgitation

Jason H. Rogers¹ and Olaf Franzen²

¹Division of Cardiovascular Medicine, Davis Medical Center, University of California, Sacramento CA, USA; and ²University Heart Center, Righospitalet, Copenhagen, Denmark

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MitraClip therapy consists of percutaneous edge-to-edge coaptation of the mitral leaflets that is analogous to the surgical Alfieri technique. The safety profile of the MitraClip device is favourable, and survival outcomes in high-surgical-risk patients are superior to historical controls. However, questions remain regarding long-term efficacy and durability. In the USA, the MitraClip device has been studied in a safety and feasibility trial, a randomized pivotal trial against surgical mitral valve repair, and a non-randomized high-risk registry. In addition, the MitraClip now has over 2 years of CE-mark approval and a rapidly expanding clinical experience in Europe, primarily in patients at high risk for surgery. A dedicated multidisciplinary team is necessary, as well as thoughtful patient selection, familiarity with the technical aspects of the procedure including transesophageal ultrasound imaging and post-procedure monitoring. Currently available clinical data are herein reviewed, with emphasis on the current role of MitraClip therapy in relation to existing surgical techniques. Since the MitraClip procedure is still relatively new, continued investigation is required to further define patient populations that will benefit most.

Keywords Mitral regurgitation • Percutaneous valve therapies • MitraClip

Introduction

MitraClip therapy is a new percutaneous approach for treating mitral regurgitation (MR) which involves mechanical edge-to-edge coaptation of the mitral leaflets that is analogous to the surgical Alfieri technique.¹ In the USA, the MitraClip device has been studied in a safety and feasibility trial, a randomized pivotal trial against surgical mitral valve repair, and a non-randomized high-risk registry (HRR). In addition, the MitraClip now has over 2 years of CE-mark approval and a rapidly expanding clinical experience in Europe. Our understanding of patient selection, technical approaches, and integration with existing therapies for MR has advanced considerably since the first human use of this device.²

We herein review clinical results of MitraClip therapy, and discuss the evolving role of MitraClip in the management of patients with clinically significant MR. It has been shown that MitraClip therapy can be delivered safely with low morbidity, and can reduce MR in a broad spectrum of pathologies.

Mitral regurgitation prevalence, aetiology, and clinical background

Mitral regurgitation is one of the most commonly encountered valvular lesions, with at least moderate regurgitation present in 6.4% of the general population ≥65 years.³ Moderate–severe MR is present in 15–30% of patients with congestive heart failure and up to 12% of patients within 1 month after myocardial infarction. Mitral regurgitation severity has been positively correlated with the subsequent development of heart failure and death.⁴–⁶ It is estimated that as many as 500,000 people in North America alone have clinically significant congestive heart failure-associated or functional mitral regurgitation (FMR), many of whom are currently not offered mitral valve intervention. In Europe, it is estimated that in individuals aged 55, almost one in three will develop heart failure during their remaining lifespan.⁷ Since even asymptomatic patients with severe MR have higher 5-year rates of death, heart, failure and atrial fibrillation, consideration of valve repair is clinically warranted in these patients. Until
the advent of the percutaneous MitraClip procedure, surgical mitral valve repair or replacement had been the sole option for treating MR, and while this is efficacious, many patients with co-morbidities and high-surgical risk do not undergo surgery because of a failure to refer and perceived excessive morbidity and mortality.\textsuperscript{8,9}

The anatomic aetiologies of MR are multiple and have been previously described by Carpentier, Barlow, and others.\textsuperscript{10–12} These include degenerative pathologies in which the leaflets or chordae are structurally ‘degenerated’, such as in fibroelastic deficiency with leaflet prolapse, myxomatous leaflet degeneration, or Barlow’s disease with diffuse excess tissue and chordal elongation. In degenerative MR, the 10-year natural history of severe MR due to a flail posterior leaflet has been documented, with 90% of patients either expiring or requiring an MV operation.\textsuperscript{15} Surgical MV repair has been the preferred treatment for clinically significant degenerative MR, and generally affords improved post-operative outcomes and survival when compared with MV replacement.\textsuperscript{14}

Surgical intervention for degenerative MR consists of multiple techniques including leaflet repair with resection, chordal transfer, use of polytetrafluoroethylene neochordae, and prosthetic ring or band annuloplasty.\textsuperscript{15} These approaches are efficacious and result in excellent freedom from reoperation.\textsuperscript{16} Edge-to-edge surgical repair of the mitral valve with annuloplasty (or without annuloplasty in selected patients) has also been shown to afford favourable outcomes in patients with degenerative or FMR.\textsuperscript{17,18}

Functional mitral regurgitation is a direct consequence of underlying left ventricular dysfunction and anular dilation which secondarily impairs the coaptation of otherwise structurally normal leaflets. Surgical correction of FMR has been shown to improve functional class and left ventricular remodelling,\textsuperscript{19} but a survival benefit has yet to be shown.\textsuperscript{20} Additionally, even with current surgical annuloplasty techniques, up to 35% of treated patients have moderate or greater MR recur within 1 year of surgery.\textsuperscript{21–23} Pre-operative predictors of recurrent MR and poor outcomes after restrictive annuloplasty for FMR include LV end-diastolic diameter >65 mm,\textsuperscript{24} posterior leaflet angle ≥45°,\textsuperscript{25} and MV coaptation depth ≥11 mm.\textsuperscript{26} Since surgical FMR repair in patients with low ejection fraction is associated with significant recurrence rates, morbidity, and mortality outside of select centres of excellence, surgery for isolated FMR is not routinely offered despite the demonstrated improvements in quality of life.

The MitraClip system

MitraClip therapy is based on the surgical edge-to-edge repair first described by Alfieri.\textsuperscript{7} The surgical technique involves the use of suture to convert a regurgitant mitral orifice into a competent double orifice valve with decreased or eliminated regurgitation. The MitraClip device, which was designed to mimic an edge-to-edge repair, consists of a percutaneously delivered MRI-compatible cobalt chromium implant with two arms and two grippers which are used to grasp the opposing free edges of the anterior and posterior leaflet in order to improve leaflet coaptation and generate a double-orifice valve. Each arm is 4 mm wide and 8 mm long, and the device is covered in a polyester fabric to promote tissue in-growth. Complete encapsulation of the device occurs by 12 weeks in a porcine model.\textsuperscript{30} The device is delivered by a transcatheter route using a steerable guide catheter (24 Fr proximally and 22 Fr at the interatrial septum), through which the steerable clip delivery system with the MitraClip attached at the distal end is delivered. The MitraClip is steered and advanced under echocardiographic and fluoroscopic guidance into the left ventricle at the point of regurgitation, and withdrawn with the arms opened to allow capture of both leaflets with the grippers and arms. Once adequate leaflet insertion is confirmed, the MitraClip can then be tightened to assess efficacy. If the desired result is achieved, the MitraClip is deployed and released from the catheter. If the grasp is felt to be suboptimal, the leaflets can be released and the grasping procedure can be repeated (Figure 1). Although no more than two MitraClips could be implanted per patient in the US feasibility and pivotal trials, up to four MitraClips have been implanted in a single patient in Europe. The only limitation to the number of MitraClips implanted from a safety standpoint appears to be the development of mitral stenosis.

The procedure is performed in the catherization laboratory under general anaesthesia for patient comfort (due to use of TEE during the procedure), but more importantly to eliminate patient movement and to perform controlled breath-holding during the MitraClip grasping step, thereby allowing accurate placement and controlled leaflet insertion. However, as the technique is refined, it may be possible that in selected patients the procedure could be performed using conscious sedation.\textsuperscript{31} The MitraClip

Current ACC/AHA and ESC guidelines for correction of mitral regurgitation

The current 2008 American College of Cardiology/American Heart Association (ACC/AHA) and 2007 European Society of Cardiology (ESC) Guidelines for the Management of Valvular Heart Disease make no specific statements related to appropriate patient selection and timing for application of MitraClip therapy.\textsuperscript{27,28} The 2008 ACC/AHA guidelines describe three types of MV operations: (i) MV repair; (ii) MV replacement with chordal preservation; and (iii) MV replacement with removal of the mitral apparatus. The ACC/AHA guidelines support MV surgery for patients with severe (3–4+) MR who are symptomatic with preserved LV size and function, asymptomatic with LV dysfunction or increased LV size, who have recent onset atrial fibrillation or evidence of pulmonary hypertension, or in symptomatic patients with severe LV dysfunction (LVEF <30%) despite optimal medical therapy. The guidelines address the fact that overall mortality from MV surgery for patients older than 75 can be significant, especially when combined with CABG, with operative mortality exceeding 14%.\textsuperscript{29} This constitutes an unmet clinical need and potential target for MitraClip therapy. The 2007 ESC guidelines mention percutaneous edge-to-edge repair but state that ‘further evaluation is needed’ before the specific role of this technique can be established. This likely refers to the importance of having robust safety, efficacy, and durability data for new percutaneous approaches.
The MitraClip System and Procedure. (A) The MitraClip delivery system consists of a guiding catheter and nested delivery catheter which can be steered in multiple planes with control knobs. (B) The MitraClip attached to the clip delivery system. The leaflets are grasped between the two clip arms (covered with Dacron) and two gripper elements. (C) 3D TEE view showing the MitraClip delivery system across the interatrial septum with the clip in the left atrium. (D) The MitraClip is oriented perpendicular to the coaptation plane of the mitral valve. (E) Final appearance of the MitraClip in place at the A2/P2 interface with generation of a double orifice valve.

### Table 1  Resource utilization, MitraClip procedure vs. surgical mitral valve repair

<table>
<thead>
<tr>
<th></th>
<th>MitraClip procedure</th>
<th>Surgical mitral valve repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition treated</td>
<td>Mitral regurgitation</td>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>Implant</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>General anaesthesia</td>
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<tr>
<td>TEE guidance</td>
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<td>Yes</td>
</tr>
<tr>
<td>Overall procedure time</td>
<td>2–4 h</td>
<td>2–4 h</td>
</tr>
<tr>
<td>ICU</td>
<td>24 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Post-procedure LOS</td>
<td>3</td>
<td>4–7</td>
</tr>
<tr>
<td>MD’s required (including Anaesthesiologists)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Operating room staff</td>
<td>3–4</td>
<td>3–4</td>
</tr>
<tr>
<td>Procedure location</td>
<td>Cath lab/hybrid</td>
<td>OR/hybrid</td>
</tr>
</tbody>
</table>

LOS, length of stay.

The MitraClip has been applied to a wide spectrum of degenerative (anterior, posterior, and bileaflet prolapse) and functional regurgitant pathologies. The presence of active endocarditis, rheumatic valve disease, and mitral stenosis are contraindications to MitraClip therapy. Regardless of regurgitation aetiology, the final common pathway of MitraClip implantation is the generation of a double-orifice valve. The MitraClip is analogous to surgical suture, and can be used to approximate leaflets at different locations along the leaflet coaptation surface (Figure 2). For wide regurgitant orifices, more than one clip might be needed. Treating MR at the medial and lateral commissures requires care as the ability to manoeuvre the MitraClip in the left ventricle is limited. Given the complex structure of the subcommissural chordae a higher risk of clip entanglement can be expected. Treatment of para-commissural jets is nonetheless feasible.

MitraClip therapy is highly compatible with other minimally invasive procedures that are often applied to patients with MR. For example, access to the left atrium is not restricted for atrial fibrillation ablation procedures, and access to the coronary sinus is preserved for biventricular lead ICD placement or for future coronary sinus mitral annuloplasty devices. Biventricular pacing and cardiac resynchronization therapy is an important treatment for patients with ischaemic cardiomyopathy and can reduce FMR acutely and chronically in selected patients. Greater than one-half of responders to CRT have sustained reductions in MR by at least one grade for 6 months or longer.32
Current registry and randomized trial data

EVEREST trials

The key results of currently published North American and European clinical experience with the MitraClip are shown in Table 2. Feldman et al.33 published results from 55 patients treated in the EVEREST (Endovascular Valve Edge-to-Edge Repair STudy) Phase I feasibility trial, and 52 patients treated in the pre-randomization start-up experience (roll-in phase) of the EVEREST II pivotal trial. These data represent the early North American experience with the MitraClip device, with 70% of these procedures being the first, second, or third procedures at each respective site. Patients were selected if they were candidates for MV surgery, met major ACC/AHA indications for MV surgery, and had specific anatomic criteria including a primary central regurgitant jet associated with the A2/P2 segments, a coaptation length \( \geq 2 \text{ mm} \), a coaptation depth \( \leq 11 \text{ mm} \), a flail gap \( < 10 \text{ mm} \), and a flail width \( < 15 \text{ mm} \). Key exclusion criteria included LVEF \( \leq 25\% \), LV end-systolic dimension \( > 55 \text{ mm} \), mitral valve orifice area \( < 4 \text{ cm}^2 \), or recent myocardial infarction. These EVEREST-specific clinical and anatomic criteria were used for all North American trial and registry data, but have not been consistently applied in the European experience. Of the 107 patients who underwent the MitraClip procedure in this early US experience, 70 (74%) achieved acute procedural success (APS), defined as a post-procedure reduction in MR to \( \leq 2+ \). Of subjects who did not achieve APS, 17 (16%) had MitraClip implantation with acute MR grade \( > 2+ \), and 11 (10%) had no MitraClip implanted with post-procedure MR \( > 2+ \). At 12 months, not including crossover to surgery, 50 of 76 APS patients (66%) had echocardiographic follow-up and continued with MR \( \leq 2+ \). A total of 32 patients underwent MV surgery after a clip procedure, and when repair was planned, 84% were successfully repaired, demonstrating that MV repair is feasible after prior MitraClip attempt or implantation. Freedom from death at up to 3-year follow-up was 90.1%, and freedom from surgery was 76.3%. The majority of patients included had degenerative MR (79%), but patients with FMR (21%) had similar acute results and durability.

An important feature of the EVEREST data is that an independent echocardiographic core laboratory assessed all echocardiograms. Mitral regurgitation was graded strictly according to American Society of Echocardiography guidelines using a composite of colour flow Doppler of the regurgitant jet area, pulmonary vein flow, regurgitant volume, and regurgitant fraction. Interobserver variability was low using this methodology, with 84% concordance in regard to MR severity. This analysis of echocardiograms pre- and post-percutaneous or surgical MV therapy differs from the majority of prior surgical repair studies which have not used quantitative echocardiographic methods or core laboratories. Analyses of echocardiograms from enrolling EVEREST sites demonstrated that without the use of quantitative methodology baseline MR grade is often overestimated by using qualitative methods.34
The landmark prospective, randomized EVEREST II trial is the first randomized trial of a percutaneous mitral repair device measured against conventional surgical therapy; it also represents the first echocardiographic core-laboratory adjudicated follow-up after surgical mitral valve repair. This trial randomized 279 patients with 3–4+ MR prospectively to receive either device therapy with the MitraClip device (n = 184) or conventional surgical repair or replacement (n = 95) in a 2:1 ratio. The primary safety endpoint was the major adverse event rate (MAE) at 30 days, and the primary efficacy endpoint was defined as 12 month freedom from the combined outcome of death, new surgery for mitral valve dysfunction, or the occurrence of >2 + MR. Prespecified MAEs were death, major stroke, reoperation of mitral valve, urgent/emergent CV surgery, myocardial infarction, renal failure, deep wound infection, ventilation >48 h, new onset permanent atrial fibrillation, sepsisemia, GI complication requiring surgery, or transfusion ≥2 units. The intention-to-treat 30-day MAE rate was lower in the MitraClip group when compared with the surgery group (15 vs. 48%, superiority P < 0.001). The MAE difference was driven largely by transfusion requirements in the surgical arm; however, in response to this critique, a modified MAE analysis which defined major bleeding as transfusion ≥4 units or requiring surgical intervention still demonstrated a lower MAE rate in the MitraClip group (5.0 vs. 30.9%, P < 0.0001). Primary clinical efficacy at 12 months by intention-to-treat was achieved in 55% of the MitraClip device patients and 73% of the surgery group (non-inferiority P = 0.007). At 2 years of follow-up, primary clinical efficacy was preserved in 52% of the percutaneous-repair group and 66% in the surgery group (P = 0.04). It is important to emphasize that the EVEREST II trial examined the safety and efficacy of MitraClip therapy as an initial approach to the treatment of patients with MR. Not every procedure was successful in reducing MR, but of these failures at APS, the majority went on to have successful subsequent mitral valve surgery. A non-prespecified analysis reported in the EVEREST II publication showed that in subgroups with age ≥70 years, FMR, and LVEF <60%, surgery was not superior to percutaneous treatment with regard to efficacy. Concomitant with the EVEREST II trial, a single-arm ‘HRR’ enrolled 78 patients with MR and an STS or surgeon-estimated surgical procedural mortality risk of ≥12%. The HRR enrolled a higher percentage of patients with FMR, and demonstrated superior safety compared with the estimated surgical risk, as well as improved symptoms in most patients. Formal results of the HRR have not yet been published. Until FDA-approval is granted, in the USA the MitraClip is available only through the REALISM continued-access registry.

### European registry data

In March 2008, the MitraClip received CE-mark approval. Since then, the majority of MitraClip implants has been performed in Europe. In addition, the clinical characteristics of European patients are different than those enrolled in the EVEREST trials, as the relatively limiting mitral leaflet anatomic inclusion and exclusion criteria were not required. The two largest reports to date on the European MitraClip experience emanate from a single centre in Germany and two centres in Italy for a total of 82 patients.
enrolment criteria for the EVEREST trials. Ing patients were defined as 'EVEREST autoimmune disease, severe renal failure requiring haemodialysis, ≤ prior chest radiation therapy, frailty, prior stroke, and prior ster-

The exclusion criteria were relatively few and consisted of a mitral valve area (MVA) ≤ 2.0 cm², active endocarditis, or extensively prolapsed or flail leaflets (prolapse width > 25 mm, flail gap > 20 mm).

Patients in this series had significantly worse left ventricular dys-

function and more adverse valve morphology than those patients enrolled in the EVEREST trials. Specifically, there was no lower limit on LVEF or upper limit on LV size, and there was a broader spectrum of allowable leaflet anatomy and regurgitant jet location (non-central jet allowed). Of the patients undergoing MitraClip therapy, there were 35 patients (69%) with LV or leaflet characteristics that would have excluded them from enrolment in the EVEREST trials. These were termed the 'EVEREST –' cohort, and had a significantly higher logistic EuroSCOREs (33 vs. 18) and larger LV end-systolic volumes (124 vs. 101 mm³). The remaining patients were defined as 'EVEREST +', and would have met enrolment criteria for the EVEREST trials.

MitraClip therapy was performed in 51 consecutive patients with a mean logistic EuroSCORE of 29 ± 22 and a Society of Thoracic Surgeons score of 15 ± 11. MitraClip implantation was successful in 49 patients (96%), with the majority of patients (34/49, 69%) treated with a single clip, 14 patients (29%) receiving two clips, and one patient receiving three clips. All 16 EVEREST + patients had successful MitraClip implantation, where as 2 of the 35 EVEREST – patients did not have clips implanted. This was due to a 17-cm left atrium in one case, and substantial subvalvular calcification in the other case. Procedure-related reduction in MR severity was one grade in 16 patients (31%), two grades in 24 patients (47%), and three grades in 9 patients (18%). There was no clinically significant mitral stenosis observed after therapy, and there were no procedure-related major adverse events and no in-hospital mortality. In summary, the authors demonstrated the feasibility and short-term efficacy of the MitraClip in high-surgical-risk patients, with a substantial proportion of patients treated that would have been excluded from the EVEREST trials. Longer term outcomes from this cohort have not been reported, and therefore effects on prognosis, left ventricular remodelling, and durability of MR reduction cannot yet be assessed.

**German experience**

Franzen et al. have reported their initial experience with the MitraClip system in patients who met current guideline criteria for treatment of MR. Their interdisciplinary team of interventional cardiologists and cardiac surgeons treated 51 patients with &ge; 3 + MR who were at high risk for mitral valve surgery based on a logistic EuroSCORE &gt; 20, an STS score &gt; 12, or by other clinical factors which the team felt conferred a high-surgical risk (i.e. prior chest radiation therapy, frailty, prior stroke, and prior sterno-

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**Italian experience**

Tamburino et al. have reported results from the initial Italian clinical experience with the MitraClip at two centres. Their multidisci-

plinary teams selected patients who met criteria for mitral intervention based on established guidelines, and who were high-risk for surgery based on the consensus between cardiologist and cardiac surgeon, logistic EuroSCORE &gt; 20, hepatic cirrhosis, autoimmune disease, severe renal failure requiring haemodialysis, or any contraindication to extracorporeal circulation. Anatomic leaflet criteria were similar to EVEREST criteria, with a require-

ment for primarily central regurgitation (at the A2/P2 interface) and sufficient leaflet tissue for mechanical coaptation. Key exclusion criteria were very similar to the EVEREST trials, including mitral valve orifice area &lt; 4 cm², flail width ≤ 15 mm, flail gap ≥ 10 mm, coaptation depth ≥ 11 mm, and coaptation length &lt; 2 mm. Importantly, unlike EVEREST, there was no exclusion for very low LV ejection fraction, nor was there an upper limit on LV size. The primary efficacy endpoint was acute device success defined as clip placement with reduction in MR to ≤ 2+. The primary acute safety endpoint was 30-day freedom from major adverse events, defined as the composite of death, myocardial infarction, non-elective cardiac surgery for adverse events, renal failure, transfusion of ≥ 2 units of blood, ventilation for &gt; 48 h, deep wound infection, sepsicaemia, and new onset atrial fibrillation.

Thirty-one patients were successfully treated using standard techniques, with 19 patients undergoing single MitraClip implantation, and 12 patients having 2 clips placed. There were no unsuccessful attempts at MitraClip placement, and no procedural mortality. At 30 days, there was an intra-procedural cardiac tamponade (treated successfully with pericardiocentesis and subsequent MitraClip implantation), and one non-cardiac death, resulting in a primary safety endpoint of 93.6%. Acute device success was observed in 96.8% of patients. At 30 days, there was favourable LV remodelling seen, with reduction in the diastolic mitral annular septal-lateral dimension. Mitral valve area significantly diminished at 30 days, but this did not result in any clinically significant mitral stenosis. In summary, the Italian registry demonstrated the excellent acute safety and efficacy of MitraClip therapy in a population of patients similar to EVEREST patients but at higher surgical risk. Longer term efficacy and durability in this initial cohort has not yet been reported.

**MitraClip safety and patient selection**

Based on the available data from expert high-volume centres, it has been demonstrated that the MitraClip can be safely and success-

fully applied to a diverse patient population in terms of age, surgical risk, and mitral valve pathologies. These findings will need to be confirmed in centres with more limited experience. The rate of major adverse events after MitraClip placement is very low. The anatomic leaflet criteria for MitraClip patient selection were rigor-

ously defined in the EVEREST trials, but the European experience has shown us proof of principle that the MitraClip can be delivered to more complex (non-EVEREST) leaflet anatomy. Although further investigation will undoubtedly refine our understanding of ‘acceptable’ leaflet anatomy, the main limitations appear to be the ability to grasp both leaflets, and the undesired development of mitral stenosis.

Herrmann et al. 39 examined the effect of implanting one or two MitraClips on MVA and mean transmitral gradient (MVG) in 96 patients enrolled in the EVEREST studies followed for up to 24 months. By planimetry the authors found that the mean MVA decreased from 6.0 ± 1.3 to 3.6 ± 1.2 cm² after clip placement, and remained unchanged after 24 months of follow-up. There was also a small increase in the mean MVG after clip placement
from 1.7 ± 0.9 to 4.1 ± 2.2 mmHg, which did not increase further after 24 months. Although patients with FMR had a slightly smaller baseline and follow-up MVA, there were no differences in MVA or MVG between patients who received one clip (69%) and those receiving two clips (31%). These data confirm that MitraClip repair with the EVEREST inclusion criteria of a baseline MVA ≥4.0 cm² does not result in significant mitral stenosis.

**MitraClip efficacy and surgery after MitraClip therapy**

A concern with any new therapy is how it will compare in efficacy with existing therapies. A key issue at this point is that the longer term durability (5–10 year) of the MitraClip procedure is not yet known. In high-surgical-risk populations, the safety advantage of the MitraClip may partially outweigh durability concerns, although the point at which this balance becomes equivalent or favours surgery is yet to be defined. For instance, a younger patient at low surgical risk with degenerative MR and a high likelihood of successful surgical repair may be more appropriately treated with surgical mitral valve repair.

In the surgical literature (mostly dealing with degenerative repair with leaflet resection techniques), post-operative MR > mild has been shown to be a risk factor for reoperation. Suri et al. examined the durability of mitral repair for leaflet prolapse in 1411 patients. At up to 15 years of follow-up, greater than mild residual post-operative MR prior to discharge was shown to be a multivariate predictor for reoperation, but not for mortality. Fix et al. reported that those patients with 1–2+ MR by post-pump intraoperative echocardiography had a trend towards more reoperations than ‘echo-perfect’ patients with zero or trivial post-operative MR, but there was no difference in morbidity or mortality at up to 5-year follow-up. While less post-procedure MR is certainly desirable, these data cannot be directly extrapolated to the MitraClip experience, as the predictors of recurrent MR in degenerative and functional subgroups are not known. The primary endpoint of MitraClip therapy in the EVEREST trials was post-procedure MR ≤2+. Previously published surgical literature cannot answer the question of whether a patient undergoing MitraClip therapy with post-procedure 1+ MR has a inferior long-term outcome than a patient with 2+ post-procedure MR. Abstract data have shown that patients with residual MR of 1+ or 2+ at 12 months following MitraClip therapy both experience meaningful clinical benefits in terms of LV size reduction, LV volume reduction, and functional class improvement.

Although the initial clinical results with the MitraClip are encouraging, there has been discussion as to the potential importance of concomitant annuloplasty in edge-to-edge leaflet repair. Annuloplasty has become routine during surgical degenerative mitral valve repair, and it is also an essential component of surgery for FMR. Failure to perform annuloplasty at the time of degenerative leaflet repair (mostly with partial leaflet resection techniques) has been shown to adversely affect the repair durability. The MitraClip procedure specifically mimics the Alfieri procedure in which the free edges of the A2 and P2 segments are sutured together, generating a double orifice mitral valve. In ischaemic MR, the application of edge-to-edge repair without annuloplasty has resulted in significant rates of recurrent MR. In a series with mostly degenerative MR, Alfieri et al. demonstrated that freedom from reoperation was less in patients that did not have concomitant annuloplasty. In defence of the edge-to-edge approach without annuloplasty, Maisano et al. have published outcomes on a retrospective series of 29 patients with degenerative or FMR, reporting the 5-year freedom from recurrent MR > 2+ or reoperation as 90 ± 5%. Whether or not emerging percutaneous annuloplasty procedures will be complementary to the MitraClip procedure, and whether either will have robust stand-alone or long-term efficacy remains to be shown.

A desirable feature of any percutaneous therapy for MR is that subsequent surgical options for MV repair are preserved if needed. Argenziano et al. have previously reported on the 32 patients who underwent MV surgery after a MitraClip procedure from the EVEREST and EVEREST II roll-in cohort. Twenty-seven patients underwent the surgical procedure planned before surgery (21 repairs, 6 replacements), one patient without a known pre-procedure strategy had MV replacement, and four planned repairs subsequently underwent MV replacement. The overall repair rate after the MitraClip procedure was 66%. Glower et al. have presented data from EVEREST II regarding repairability of the mitral valve after MitraClip placement and found that the surgical repair rate ≤90 days after MitraClip attempt or placement was 52% (14 of 27 patients), and the repair rate >90 days after MitraClip was 60% (6 of 10). The presence of anterior/biblaflet flail or prolapse was a significant predictor of the need for MV replacement. However, surgeon experience, defined as the number of surgeries performed annually, duration of implant, or an operative note of valve injury or difficulty removing the device did not have an impact on whether a repair or replacement was performed. Geidel et al. have reported that mitral valve pathology can be aggravated by MitraClip implantation, but complex successful mitral valve repair was still achieved. Rogers et al. reported a series of four patients who underwent successful surgical MV repair up to 5 years and 2 months after MitraClip device implantation, demonstrating that very late MV repair remains possible, including after implantation of two clips. Other than for degenerative MR, it is debatable whether mitral valve repair after a failed MitraClip procedure in ischaemic MR should be attempted. Mage et al. did not find a mortality difference between repair vs. replacement in patients with ischaemic MR 6 years after surgery.

**Conclusion and future directions**

The MitraClip procedure is rapidly evolving as an important option among the current therapies for MR. The safety profile of this device appears to be excellent. Acute outcomes are favourable, and for those patients with APS, mid-term durability (up to 2 years) is reasonable. Although surgical risk calculators may overestimate morbidity and mortality in high-risk patients with MR undergoing surgery, early survival outcomes with MitraClip therapy in these high-surgical-risk patients have been superior to historical controls. There is no question that surgical mitral valve repair for degenerative MR has been shown to be highly effective.
in multiple large series, resulting in a 10-year freedom from reopera-
tion of up to 97%. Minimally invasive degenerative surgical mitral valve repair has also been shown in expert hands to have
excellent efficacy and durability, with a 5-year freedom from the
cardiac repair rate of 95.6%. Surgical repair options have matured over time and are numerous, including leaflet repair
with resection, chordal transfer, use of polytetrafluoroethylene
neochordae, and prosthetic ring or band annuloplasty. However,
we are still early in the MitraClip experience, and unanswered
questions remain regarding long-term efficacy, adoption, and
approval indications. Based on adoption patterns in Europe, and
subgroup analyses from the EVEREST II trial, it would appear
that patients who are older, at higher risk for surgical therapy,
or with FMR and depressed ejection fractions will constitute the
initial target population for MitraClip therapy. Since FMR is primar-
ily a ventricular problem, it remains to be seen whether a leaflet
intervention will have durable efficacy. Numerous predictors of
recurrent MR after restrictive annuloplasty for FMR have been
identified and their relevance to determining patient selection
for MitraClip therapy is yet to be determined. Whether or
not the MitraClip should be translated for use in lower risk patients
with degenerative valve disease is a matter of debate, but clearly
the surgical bar has been set quite high in these patients.
While some MitraClip cases are straightforward, many cases can be
technically challenging, comparable with complex percutaneous
aortic valve replacement, multivessel stenting or chronic total
occlusion interventions. Future MitraClip and delivery system
designs may allow a wider range of valve anatomies to be
treated, and may simplify leaflet insertion and grasping. In addition,
innovations in echocardiographic and intracardiac imaging will
increasingly revolutionize this and other structural heart pro-
cedures. For instance, 3D TEE was not widely available at the
outset of the MitraClip experience but has now become standard
during the procedure, markedly improving the ease and visualiza-
tion of the procedure.
The MitraClip procedure is a promising new therapy, but new
ways must continue to be found to refine its application and estab-
lish ever more meaningful clinical indications for its use. Like all first
generation techniques, the MitraClip will evolve and change in the
future.

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References
1. Alfieri O, Maisano F, De Bonis M, Stefano PL, Torracca L, Oppizzi M, La Canna G. The
double-orifice technique in mitral valve repair: a simple solution for complex
2. Condado JA, Acquatella H, Rodríguez L, Whitlow P, Velez-Gimo M, St Goar FG.
Percutaneous edge-to-edge mitral valve repair: 2-year follow-up in the first
3. Nikomoto VT, Gardin JM, Skelton TN, Gottlieb JS, Scott CG, Enriquez-Sarano M. Burden
4. Bursi F, Enriquez-Sarano M, Nikomoto VT, Jacobsen SJ, Weston SA, Meverden RA,
Rogler VL. Heart failure and death after myocardial infarction in the community:
5. Robbins JD, Maniar PB, Cotts W, Parker MA, Bonow RO, Gheorghiade M. Preval-
ence and severity of mitral regurgitation in chronic systolic heart failure. Am J
Cardiol 2003;91:360–362.
6. Trichon BH, Feller GM, Shaw LK, Cabell CH, O’Connor CM. Relation of fre-
quency and severity of mitral regurgitation to survival among patients with left
7. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW,
Wittenberg JC, Strickler BH. Quantifying the heart failure epidemic: prevalence,
incidence rate, lifetime risk and prognosis of heart failure The Rotterdam
Butchart EG, Ravaud P, Vahanian A. What are the characteristics of patients with
severe, symptomatic mitral regurgitation who are denied surgery? Eur
Delong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP.
The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—iso-
10. Carpenterier A. Cardiac valve surgery—the “French correction”. J Thorac Cardio-
12. Barlow JB, Pocock WA. The significance of late systolic murmurs and mid-late sys-
335:1417–1423.
repair improves the outcome of surgery for mitral regurgitation. A multivariate
15. Seeberger J, Falk V, Borger MA, Passage J, Walthier T, Doll N, Mohr FW. Chordae
replacement versus resection for repair of isolated posterior mitral leaflet pro-
Smedira NG, Saba JF, McCarthy PM, Loop FD. Durability of mitral valve repair
17. Maisano F, Torracca L, Oppizzi M, Stefano PL, D’Addario G, La Canna G, Zagno M,
245–6.
18. Maisano F, Vigaio G, Blaso A, Colombo A, Calabrese C, Alfieri O. Surgical iso-
lated edge-to-edge mitral valve repair without annuloplasty clinical proof of the
19. Bax JJ, Braun J, Somer ST, Klauss R, Holman ER, Versteegh MI, Boersma E,
Schalij Mj, van der Wall EE, Dion RA. Restrictive annuloplasty and coronary revas-
cularization in ischemic mitral regurgitation results in reverse left ventricular
20. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of
mitral valve annuloplasty on mortality risk in patients with mitral regurgitation
Mechanism of recurrent ischemic mitral regurgitation after annuloplasty: contin-
22. Marwick TH. Restrictive annuloplasty for ischemic mitral regurgitation: too little
or too much? J Am Coll Cardiol 2008;51:1702–1703.
23. Maisano EC, Gillinov AM, Blackstone EH, Ramaswamy J, Cohen G, Najam F,
Shiota T, Sabik JF, Lytle BW, McCarthy PM, Cosgrove DM. Recurrent mitral
regurgitation after annuloplasty for functional ischemic mitral regurgitation.
24. Braun J, van de Veere NR, Klauss RJ, Versteegh MI, Holman ER, Westenberg JJ,
Boersma E, van der Wall EE, Bax JJ, Dion RA. Restrictive mitral annuloplasty
25. Magne J, Pibarat P, Dagares F, Hachiya Z, Dumesnil JG, Senechal M. Preopera-
tive posterior leaflet angle accurately predicts outcome after restrictive mitral
valve annuloplasty for ischemic mitral regurgitation. Circulation 2007;115:
782–791.
26. Calafiore AM, Gallina S, Di Mauro M, Gaeta F, Iaco AL, D’Alessandro S, Mazzzi V,
Di Giammarco G. Mitral valve procedure in dilated cardiomyopathy: repair or
27. Bonow RO, Carabello BA, Chang BH, Leon AC Jr, Faxon DP, Freed MD, Gaasch
WH, Lytle BW, Nishimura RA, O’Gara PT, O’Rourke RF, Otto CM, Shah PM,
Shanewise JS. 2008 Focused update incorporated into the ACC/AHA 2006
guidelines for the management of patients with valvular heart disease: a report
of the American College of Cardiology/American Heart Association Task
Force on Practice Guidelines (Writing Committee to Revise the 1998
Guidelines for the Management of Patients with Valvular Heart Disease):
endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardio-
vascular Angiography and Interventions, and Society of Thoracic Surgeons.


