



Edge-to-Edge Percutaneous Repair of Severe Mitral Regurgitation — State-of-the-Art for Mitraclip® Implantation —

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MitraClip® therapy is a percutaneous edge-to-edge plication of the mitral leaflets, mimicking the Alfieri surgical technique. MitraClip® implantation is a safe procedure, and survival outcomes in high-surgical-risk patients are superior to historical controls. Despite these results, questions remain concerning long-term efficacy and durability. The MitraClip® device has been studied in a safety and feasibility trial in the USA, a randomized pivotal trial against surgical mitral valve repair. Moreover, 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 and procedural steps are herein reviewed. Because the MitraClip® procedure is still relatively new, continued investigation is required to further better define the patient populations that will benefit most. (*Circ J* 2012; **76**: 801–808)

Key Words: Echocardiography; Heart failure; MitraClip®; Mitral regurgitation; Mitral valve repair

Mitral regurgitation (MR) is the second most frequent valve disease after aortic stenosis.¹ Organic or primary MR includes all etiologies in which the primary cause of the disease is leaflet abnormality, in contrast with ischemic or functional MR, where the valve disorder is a consequence of left ventricular (LV) dilatation or contraction abnormalities. The reduced prevalence of rheumatic fever has changed the balance between the 2 etiologies of MR in Europe, with ischemic and functional MR playing an increasing role in the past years.^{1–3}

Mild regurgitation is well tolerated and rarely leads to symptomatic disease. However, severe regurgitation overloads the LV because blood is pumped both backward across the mitral valve (MV) and forward to the systemic circulation. Over time, volume overload results in ventricular dilatation and eventual contractile dysfunction. Moreover, increased left atrial (LA) pressure leads to atrial fibrillation (AF) and elevated pulmonary pressures.⁴ Patients experience shortness of breath, initially on exertion, as stroke volume increases and thus volume overload raises pulmonary pressures. If untreated, these physiological changes lead to increasing heart failure symptoms and reduced survival. Both can be prevented by an intervention

to reduce or eliminate MR in the early stages.

Medical treatment alone has shown an estimated 5-year overall mortality rate up to 22% in asymptomatic MR.⁵ Predictors of poor outcome are the presence of symptoms, age, AF, the degree of MR, LA dilatation, LV dilatation, and low LV ejection fraction (LVEF).⁶ Optimal medical management and/or cardiac resynchronization therapy can improve symptoms and reduce MR severity in a number of patients.⁷ Recent guidelines recommend resynchronization therapy to reduce morbidity and mortality (Class IA recommendation for patients in New York Heart Association [NYHA] class III/IV, LVEF <35%, QRS >120 ms) and/or to reduce morbidity and prevent disease progression (Class IA recommendation for patients NYHA class II, LVEF <35%, QRS >150 ms).⁸

MV surgery is the standard of care for patients with symptomatic MR or asymptomatic MR with evidence of LV dysfunction or dilation. Notably, a large percentage of patients in need of valve reconstruction or replacement do not undergo surgery because of a high perioperative risk (malignancy disease, obstructive pulmonary disease, renal insufficiency, pulmonary hypertension, liver cirrhosis and dementia as comorbidities).^{9–12} Both the logistic EuroSCORE and the Society of

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Table. Indications for Surgery in Severe MR⁶

	Class
Indications for surgery in severe organic MR	
- Symptomatic patients with LVEF >30%/ESD <55 mm*	IB
- Asymptomatic patients with LV dysfunction (ESD >45 mm* ± LVEF <60%)	IC
- Asymptomatic patients with preserved LV function and AF or pulmonary hypertension (sPAP >50 mmHg at rest)	IIaC
- Patients with severe LV dysfunction (LVEF <30% ± ESD >55 mm*) refractory to medical therapy with high likelihood of durable repair and low comorbidity	IIaC
- Asymptomatic patients with preserved LV function, high likelihood of durable repair, and low risk of surgery	IIbB
- Patients with severe LV dysfunction (LVEF <30% ± ESD >55 mm*) refractory to medical therapy with low likelihood of repair and low comorbidity	IIbC
Indications for surgery in chronic ischemic MR	
- Patients with severe MR, LVEF >30% undergoing CABG	IC
- Patients with moderate MR undergoing CABG if repair is feasible	IaC
- Symptomatic patients with severe MR, LVEF <30% and option for revascularization	IaC
- Patients with severe MR, LVEF >30%, no option for revascularization, refractory to medical therapy and low comorbidity	IbC

*Lower values can be considered for patients with small stature.

MR, mitral regurgitation; LVEF, left ventricular (LV) ejection fraction; ESD, endsystolic dimension; AF, atrial fibrillation; CABG, coronary artery bypass grafting.

Thoracic Surgeons (STS) Score have shown reliable predictive value for patients undergoing cardiac surgery.¹¹

Results of Surgery

Indications for MV surgery in the current guidelines are summarized in the [Table](#). To date, there are no randomized trials comparing valve replacement and valve repair. However, valve repair is widely accepted as the optimal surgical treatment for patients with MR. When compared with valve replacement, repair has a lower perioperative mortality, improved survival, better preservation of postoperative LV function, and lower long-term morbidity.^{13–15} Predictors of poor surgical outcome are the presence of symptoms, age, AF, preoperative LV function and reparability of the valve.⁶ Moreover, progressive development of pulmonary hypertension is also a marker for poor prognosis.

Reported operative or in-hospital mortality rates for MV surgery range from 1% to 2% for low-risk, young patients undergoing MV repair to as high as 25% for high-risk or elderly patients undergoing valve replacement.¹⁶

The probability of a durable valve repair is of crucial importance.^{17,18} Degenerative MR because of segmental valve prolapse can usually be repaired with a low risk of reoperation. The reparability of extensive prolapse, rheumatic lesions, leaflet calcification or extensive annulus calcification is not as consistent, even in experienced hands. The results of valve repair are also highly dependent on the experience of the surgeon. In contrast, when repair is not feasible, MV replacement with chordal preservation is preferred.

Current Evidence on Mitraclip®

The first percutaneous MV repairs in humans were performed using either implants introduced via the coronary sinus or stitches mimicking the Alfieri operation (edge-to-edge method) introduced transseptally.^{19–21}

Recently, a variety of less invasive, percutaneous treatment options for MV repair have been developed. Most of these techniques are still at an early stage of clinical evalua-

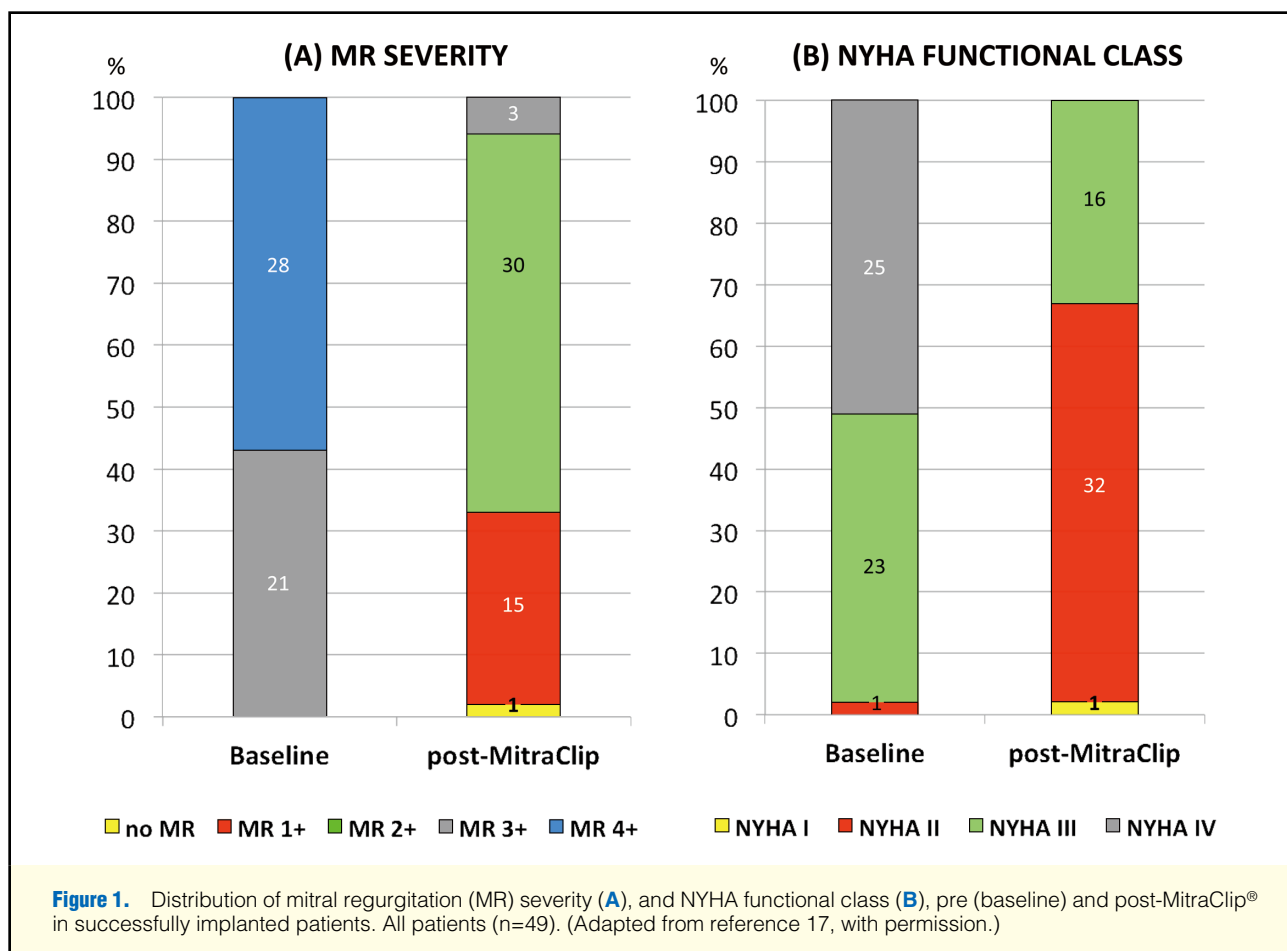
tion, but have shown promising results for “unoperable” patients.^{15,22,23}

MitraClip® (Abbot Vascular, Abbot Park, IL, USA) decreases the distance between the anterior and posterior leaflets and thus applies tension to the chordae, leaflets, and, potentially, the annulus. This may be advantageous because it stabilizes or even shortens the diameter between the anterior and posterior aspect of the mitral annulus.^{24,25}

Approximately 50 centers in Europe have been using the technique since September 2008, and 2 years later, more than 2,000 procedures have been performed. The rate of implants in Europe is accelerating, and in September 2011, more than 120 patients were being treated per month.

The Endovascular Valve Edge-to-Edge Repair Study (EVEREST I) Trial¹⁹ was a feasibility trial that enrolled 27 patients with severe MR for MitraClip® implantation; 82% patients were discharged from hospital with a clip in place and all of them were free from surgery at 6 months. Furthermore, nearly 60% of them had a significant reduction in MR severity, which was confirmed at the 6-month follow-up. In addition, 6 patients underwent MV surgery after MitraClip® implantation for persistence of severe MR. During surgery, the clips were uneventfully removed in all 5 cases in which the intention was to repair the valve with no limitation on surgical options, including 1 patient treated with 2 clips.

Patients treated in the EVEREST trial were selected using the American Heart Association/American College of Cardiology guideline recommendations²⁶ for surgical MV repair. The EVEREST II Trial¹⁵ enrolled 279 patients with moderately severe or severe (grade 3+ or 4+) MR in a 2:1 ratio to undergo either percutaneous repair or conventional surgery for repair or replacement of the MV. The primary composite endpoint for efficacy was freedom from death, from surgery for MV dysfunction, and from grade 3+ or 4+ MR at 12 months. At 12 months, the rates of the primary endpoint for efficacy were 55% in the percutaneous-repair group and 73% in the surgery group (P=0.007). The respective rates of the components of the primary endpoint were as follows: death, 6% in each group; surgery for MV dysfunction, 20% vs. 2%; and grade 3+ or 4+ MR, 21% vs. 20%. Major adverse events



occurred in 15% of patients in the percutaneous-repair group and 48% of patients in the surgery group at 30 days ($P<0.001$), which included the need for blood transfusions. At 12 months, both groups had improved LV size, NYHA functional class, and quality-of-life measures, as compared with baseline. In summary, although percutaneous repair was less effective at reducing MR than surgery before hospital discharge, at 12 and 24 months the rates of reduction in MR were similar, and percutaneous treatment was associated with increased safety, improved LV dimensions, and clinical improvements in NYHA class and quality of life. Longer term follow-up will provide additional data to better understand percutaneous treatment of MR.

The real-world ACCESS EU cohort, which included patients without exhaustive EVEREST exclusion criteria, enrolled 157 patients with severe functional MR and who were divided into 2 groups: LVEF $\leq 30\%$ or $>30\%$.²⁷ Both groups had similar mortality at 6 months' follow-up, similar reductions in MR severity and similar improvements in NYHA functional class. Franzen et al²⁴ treated 51 high-surgical-risk patients, with 96% successful implantation of MitraClip®; 90% of the treated patients exhibit improvement in NYHA functional class, and there were no procedure-related complications or in-hospital deaths (Figure 1).

Patient Selection

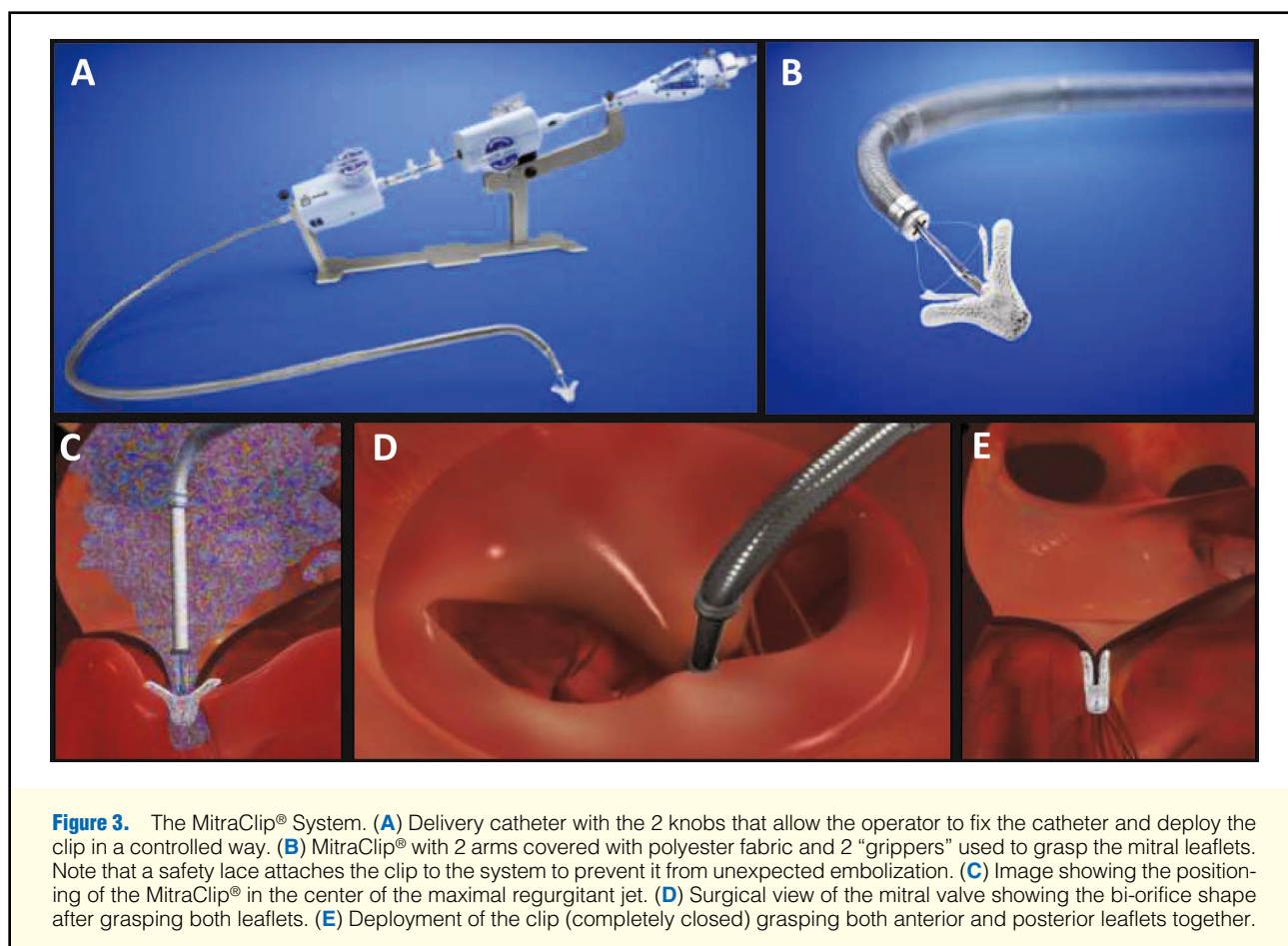
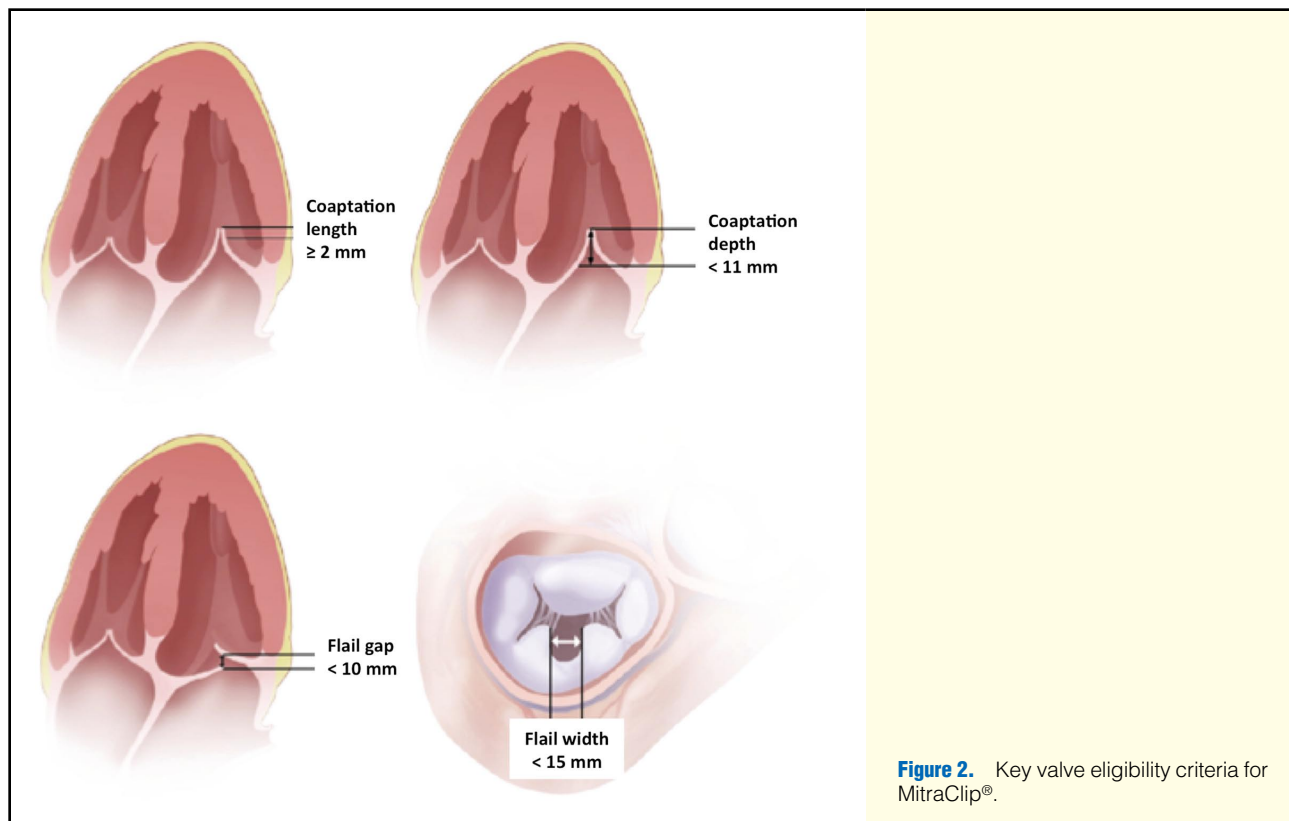
Patient selection and overall decision making is strongly influenced by anatomical and clinical factors. Transesophageal

echocardiography (TOE) evaluation of the morphology of the mitral leaflets is critical for good patient selection. A coaptation length of at least 2 mm and coaptation depth <11 mm are needed. Thus, some tissue from both leaflets should be in contact so there is some tissue to grasp with the clip. With a flail mitral leaflet, a flail gap ≥ 10 mm and a flail width ≥ 15 mm are exclusion criteria. The MR jet must arise from the central two-thirds of the line of coaptation, as seen on short-axis color Doppler examination (Figure 2).^{28–30}

Decision making in degenerative vs. functional MR can be quite different. The relative role of MitraClip® and surgery in the management of patients with MR is still unclear. From the global initial experience, MitraClip® therapy could be complementary to surgery in those patients at high risk for surgery but who have the ideal anatomical characteristics for implantation. The procedure is quite predictable in patients with favorable anatomy. In patients with suboptimal anatomy, if the risk of surgery is too high, MitraClip® could be still sometimes indicated. Our preliminary experience suggests that in patients with degenerative MR, the EVEREST anatomical criteria are strong predictors of early and mid-term success. According to it, MitraClip® therapy is appropriate in those degenerative MR patients with high surgical risk and ideal anatomy for clip implantation according to the EVEREST criteria.

Procedure Overview

Surgical leaflet repair has mainly used annuloplasty in conjunction with the techniques of leaflet resection and sliding



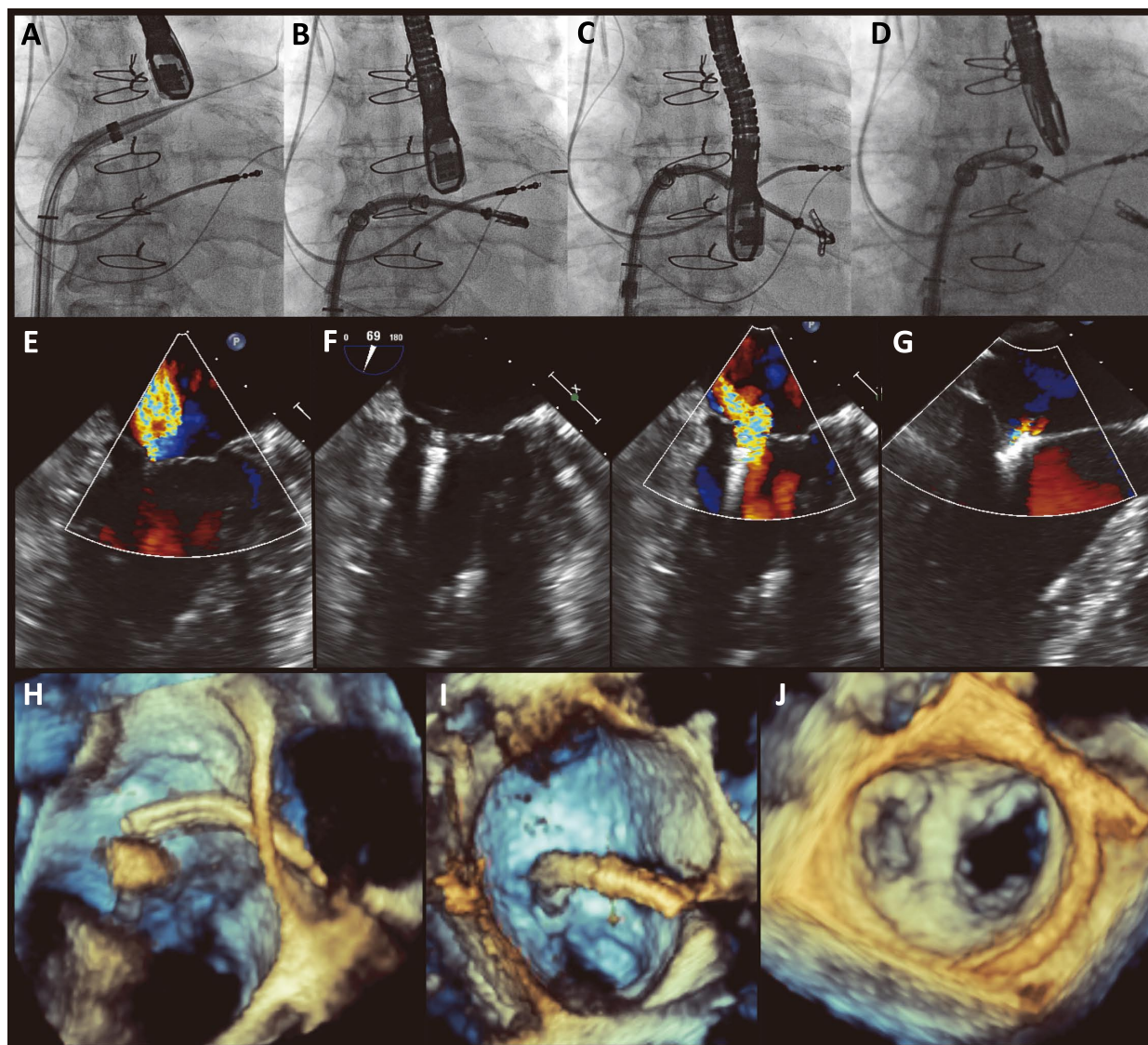
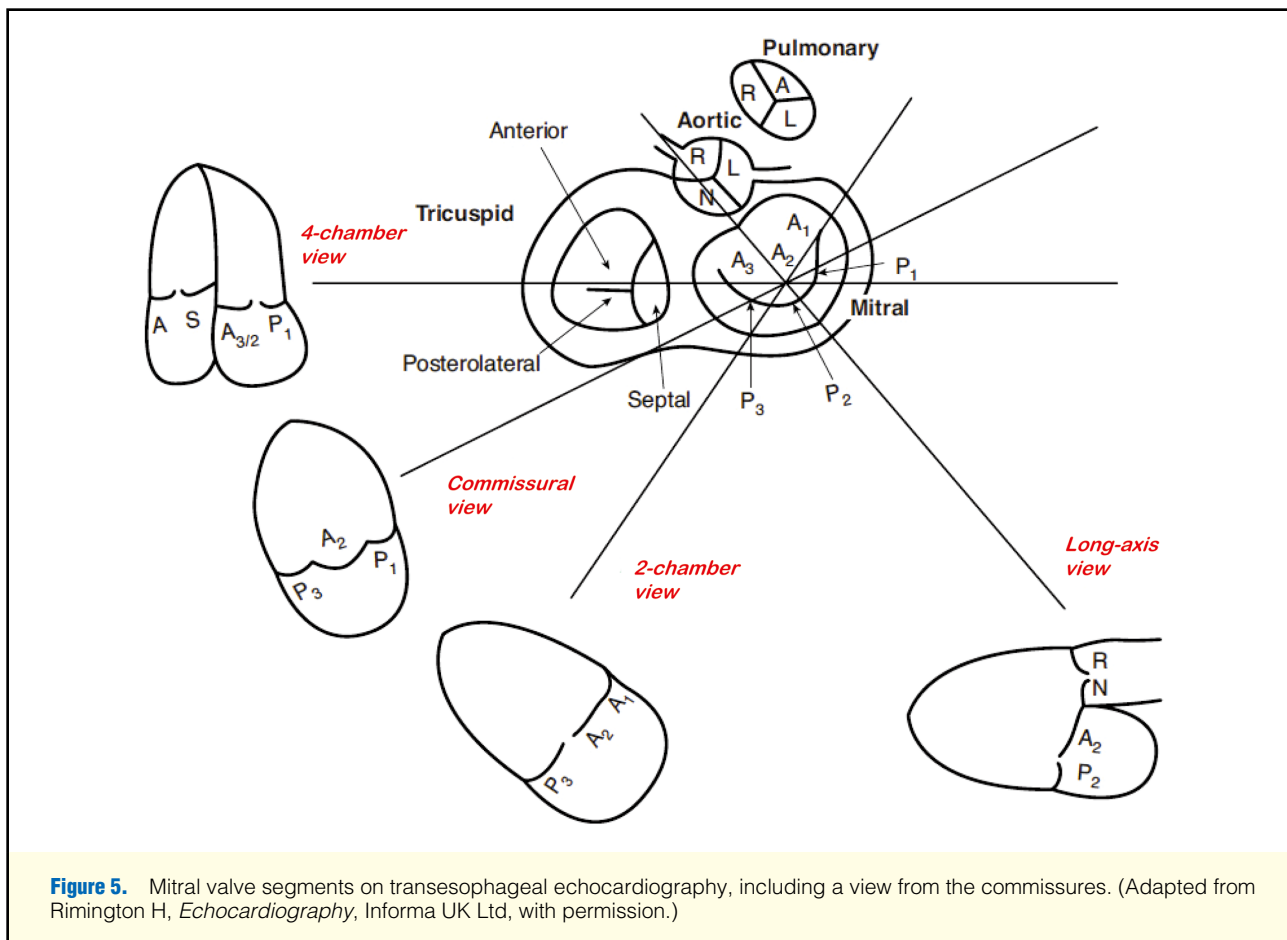


Figure 4. A 76-year-old man with severe organic mitral regurgitation (MR). (A) MitraClip® dilator is advanced through the fossa ovalis puncture, following the wire inserted in the left upper pulmonary vein. (B) MitraClip® is advanced cautiously into the left atrium. (C) After entering the left ventricle, crossing the mitral valve (MV) under TOE guidance, the clip is opened and oriented perpendicular to the MV orifice. (D) The clip is released completely closed, grasping both anterior and posterior leaflets. (E) TOE image in 2-chamber view showing severe MR caused by P2 prolapse. (F) Positioning the clip under TOE guidance, centered in the area of maximal regurgitation. (G) TOE demonstration of reduction in MR to grade 1 after complete grasping of the anterior and posterior leaflets. (H) 3D-TOE image illustrating the MitraClip® catheter advanced through the interatrial septum. (I) 3D-TOE image from the surgical view (from the left atrium) showing correct position of the clip 90° from the longitudinal axis of the MV. (J) Bi-orifice view after edge-to-edge plication with the Mitraclip®, from the left atrium towards the LV. TOE, transesophageal echocardiography.

annuloplasty. Surgical leaflet approaches are used for MV prolapse to remove some of the redundant leaflet tissue, and to help restore leaflet coaptation. No percutaneous version of leaflet resection is currently available and has yet to be developed. A less commonly used surgical leaflet repair approach is the edge-to-edge, or double orifice, repair.^{31–34}

The MitraClip® is 4-mm wide cobalt chromium device with 2 arms designed to grasp both mitral leaflets and mimic edge-to-edge surgical repair (Figure 3), a procedure that was described by Alfieri et al^{31,35} and is accomplished by suturing the

free edges of the mitral leaflets together to form a double orifice. In most cases, annuloplasty is performed in conjunction with leaflet surgical repair. Isolated use of edge-to-edge repair has been controversial, because most surgical experience has been with the combination of annuloplasty and leaflet repair. Follow-up for as long as 12 years in a small group of patients who underwent isolated surgical edge-to-edge repair without annuloplasty has demonstrated durable clinical outcome, and thus proof of principle, with this surgical technique.^{36,37}



Transseptal Puncture

A key step of the procedure is adequate transseptal puncture. TOE guidance in this procedural step is crucial, in order to guide the catheter to the correct position on the interatrial septum, and subsequently during the puncture. Moreover, precise measurement between the tenting on the septum and the annulus plane (or leaflet coaptation) is necessary for a perfect puncture. Depending on the MV anatomy, the operator might chose a more posterior or superior position for the puncture to enable a better maneuvering of the delivery device. For patients with small LA volume, a conscious selection of the site of puncture precludes failure in positioning the clip towards the mitral orifice. By far the most important structure to avoid puncturing is the aortic valve and root (TOE guidance avoids this risk). Most operators therefore use a catheter in the aortic root to provide an anatomical marker of the aortic valve. With the X-ray positioned at 30° left anterior oblique, the sheath and catheter are rotated so that both are pointing approximately to the 4–5 o'clock position as previously described.^{38,39} Once satisfied that the needle is in the LA it is fixed with the right hand while the dilator and sheath are advanced with the left hand. Once the LA is entered with the 8Fr sheath, the left pulmonary vein is cannulated using a multipurpose catheter and a stiff guidewire is left in place. Then the 24Fr deflectable MitraClip® guiding catheter is introduced into the LA and the dilator is carefully and slowly retrieved. It is 24Fr proximally and tapers to 22Fr at the level of the atrial septum (Figure 4).

Positioning the MitraClip®

The MitraClip® system uses a guide catheter, a clip delivery catheter, and an implantable clip (Figure 3). The delivery catheter passes coaxially through the guide, and has the MitraClip® attached to its distal end.^{40,41} This delivery system uses 2 knobs to control mediolateral and anteroposterior steering. The clip arms are opened and closed by a knob on the delivery catheter handle. The clip has a locking mechanism to maintain closure. On the inner portion of the clip are small barbs or “grippers” to secure the leaflets when the clip arms are closed. Through the guide catheter, the clip delivery system is maneuvered to center the clip over the mitral orifice. The clip is partially opened and passed across the leaflets, through the chordae tendineae, and into the LV. The open clip is pulled back to grasp the mitral leaflets. When the leaflets have fallen into the clip arms, the grippers are lowered, and the clip is closed. A key step at that point is evaluation of the insertion of leaflet tissue into the clip. If the leaflets have been adequately grasped, a determination of the degree of reduction in MR can be made by TOE. If needed, a second clip can be placed. However, TOE measurements of the MV gradient are recommended at this stage. If the transvalvular gradient is higher than 4–5 mmHg, the risk of mitral stenosis with a second clip increases. The clip may be opened and closed to grasp the mitral leaflets several times. If the leaflet insertion is not adequate, or if the reduction of MR is insufficient, the clip is opened, withdrawn into the LA, and repositioned before crossing the leaflets and attempting another grasp. If after several attempts it appears that the degree of MR cannot be

effectively reduced, the clip can be completely removed. For patients with complex anatomy and difficult positioning, adenosine-induced asystole at this stage has been proposed.⁴² Thus, the ability to assess the results of the procedure in real time is an important asset of this therapy.

Guidance for the Operator

The procedure is performed with general anesthesia, using fluoroscopy and TOE guidance. Most of the maneuvering of the system is done using TOE.

An echocardiographer experienced in TOE is highly recommended, helping the interventionist throughout the stepwise procedure.⁴³

TOE guidance during transseptal puncture is obtained mainly from the bicaval view, which will also be helpful to analyze the septum after removing the catheter delivery system. The short-axis view will guide the posterior puncture of the septum. The long-axis TOE view helps position the clip in an anteroposterior plane. In addition, the commissural view will guide the medial/lateral movements (Figures 4,5). The LV outflow tract view will help with steering the clip to the center of the valve, positioning the clip, opening the clip arms, advancing the clip into the LV, grasping the leaflets, continuing to visualize the opened clip arms and confirm grasping, closing the clip and assessing the result. Moreover, 3-dimensional reconstructions from the LA are essential to confirm the clip arms are perpendicular with the MV opening.

Potential Complications

During the procedure, pericardial effusion/tamponade might occur during transseptal puncture. A rare but serious complication is an incidental aortic puncture. Thus, a pericardial drainage set should always open and ready to use. Other complications are related to manipulation of catheters in the left heart cavities (thrombus formation) or acute cardiac decompensation (arrhythmia, acute pulmonary edema). Other rare complications have been described (hanging the device in the MV chords, damage to the atrial free wall). Minor bleeding or hematomas after 24Fr catheter insertion in the femoral vein can occur, but manual compression or a clamp usually solves this complication.³⁸

A particular concern for operators is a partial clip detachment. Clinical and echocardiographic follow-up may reveal a significant increase in the degree of MR. If the patient is highly symptomatic, a second procedure for new MitraClip® implantation might be considered.

Anticoagulation Protection

The introduction of sheaths and catheters into the left side of the heart exposes the patient to a significant risk of ischemic embolism. This is minimized by effective anticoagulation, usually with intravenous heparin and meticulous attention to de-airing and flushing of sheaths. A critical step is removal of the stylet, when the needle is aspirated and attached to a continuously flushing heparin saline bag that is transducing pressure. Intracardiac echocardiography images of transseptal sheaths have demonstrated that thrombus can build up within a few minutes, so anticoagulation needs to be given promptly.^{44,45} Our protocol includes an initial dose of 2,000–3,000 IU unfractionated heparin after groin sheath placement before septal puncture and adding up to total 70–100 IU/kg after septal puncture (alternative: no heparin before septal puncture). The activated clotting time is checked at 15 min and then every 30 min throughout the procedure, aiming to keep it between 250 and 300 s. Protamine can be administered after

sheath removal, weighing the risk of bleeding and thrombus formation. After the procedure, preloading with aspirin 300 mg and clopidogrel 300 mg if no prior treatment, then aspirin 75 mg for 6 months and clopidogrel 75 mg for 1 month. If the patient is under chronic anticoagulation, no additional treatment is required (continue with a target INR of 2–3).

Conclusions

The MitraClip® procedure is rapidly evolving as an important option among the current therapies for patients with MR. The safety profile of this device appears to be excellent, despite the high-risk profile of the patients treated.

The MitraClip® procedure is a promising new therapy, but new ways must continue to be found to refine its application and establish ever more meaningful clinical indications for its use. Cumulative research and experience will help develop this first-generation technique, and the MitraClip® will evolve and change in the future.

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Disclosures

The authors have declared no potential conflicts of interest.

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