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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

# The Evolution of Percutaneous Mitral Valve Repair Therapy

## Lessons Learned and Implications for Patient Selection

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**ABSTRACT**

Mitral regurgitation (MR) is the most common valve disease in the United States. However, a significant number of patients are denied surgery due to increased age, poor ventricular function, or associated comorbidities, putting them at high risk for adverse events. Moreover, the benefit of surgery for MR is unclear in patients with functional (secondary) MR. Recently, percutaneous repair of the mitral valve with a particular device (MitraClip, Abbott, Menlo Park, California) has emerged as a novel therapeutic option for patients with secondary MR or those deemed to be high risk for surgery. We review data from its initial concept through clinical trials and current data available from several registries. We focused on lessons learned regarding adequate patient selection, along with current and future perspectives on the use of device therapy for the treatment of MR. (J Am Coll Cardiol 2014;64:2688–700) © 2014 by the American College of Cardiology Foundation.

Mitral regurgitation (MR) is the most common valve disease in the United States (1,2). Worldwide, there are an estimated 50,000 operations for MR per year, of which about 55% are isolated mitral valve (MV) procedures (3). Patients with severe MR need to be monitored to prevent the consequences of chronic volume overload, such as: shortness of breath, heart failure, pulmonary hypertension, and reduced left ventricular (LV) function. Additionally, chronic severe MR leads to enlargement of the left atrium (LA).

MR pathogenesis can be divided into either a primary abnormality of the valve, degenerative mitral regurgitation (DMR) (**Figures 1A to 1C**), or an abnormality secondary to LV dysfunction, functional mitral regurgitation (FMR). Mixed situations, involving both a primary leaflet abnormality and a functional component, can also occur. MR may worsen or develop in the setting of atrial fibrillation. Patients with FMR usually have a worse prognosis than those with DMR. FMR is a consequence of ischemic or nonischemic LV dysfunction and remodeling, in which LV geometry becomes more spherical, leading to apical and posterior displacement of the papillary muscles and tenting of the (usually morphologically normal) MV leaflets along with dilation, and often with loss of annular contraction during systole (4,5) (**Figures 1D and 1E**). Current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend that surgery be performed (Class I) for symptomatic patients with chronic severe MR due to a primary valvular abnormality, and also state that surgery may be considered (Class IIb recommendation) as a therapeutic option for

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symptomatic patients with secondary (functional) severe MR (6). In these cases, there is no consistent data showing improved outcomes with surgery in terms of patient survival or quality of life (7,8). A recent analysis from Europe showed that about one-half of patients with severe symptomatic MR are denied surgery, mostly due to older age, impaired ventricular function, and associated comorbidities (9).

In the early 1990s, Alfieri developed the surgical edge-to-edge technique to treat MR (10,11). The edge-to-edge technique consists of suturing the free leaflet edges in the midportion of the anterior and posterior MV leaflets, creating a double orifice valve. Whether treating FMR or DMR, surgical edge-to-edge repair of the MV is generally associated with implantation of a flexible or semirigid prosthetic ring to increase the coaptation surface. Alfieri's group found this technique to be safe and durable. It is less optimal in patients with complex MR or with ischemic or functional etiology. Edge-to-edge repair with a flexible band had good short-term results in ischemic MR, but there was a high recurrence of ≥3+ MR in this patient group (12). Edge-to-edge repair's effectiveness has been debated because of variable results, a perceived nonphysiological approach, and the potential risk of causing secondary mitral stenosis.

The MitraClip System (Abbott, Menlo Park, California) was developed on the basis of Alfieri's edge-to-edge technique (**Figure 2**). The first porcine experience demonstrating feasibility was reported in 2003 (13), and the first human case was performed the same year (14). The percutaneously-delivered device (**Figure 3**) reduces MR by approximating the anterior and posterior MV leaflets. The procedure is done under fluoroscopic and echocardiographic guidance (15). **Figure 4** demonstrates the steps in device deployment. The system is introduced through the femoral vein and is advanced under fluoroscopic and echocardiographic guidance into the LA through a transseptal puncture. After being oriented perpendicular to the line of coaptation of the anterior and posterior MV leaflets in the LA, the system is advanced into the LV, where the anterior and posterior MV leaflets are grasped, creating a double MV orifice. If necessary, more than 1 clip can be deployed to achieve adequate MR reduction.

## PATIENT ELIGIBILITY CRITERIA

**Table 1** defines and **Figure 5** demonstrates the echocardiographic criteria for inclusion and exclusion of patients for the procedure on the basis of criteria used in U.S. clinical trials (16) and from additional experience in other locations (17). At present, this procedure is mostly used for central MR. However, investigators have started using the device for noncentral MR, where the medial or lateral scallops are involved, and in patients with moderate to severe MR after failed MV annuloplasty rings.

## EVOLVING EXPERIENCE

**INITIAL EXPERIENCE AND COMPARISON TO SURGERY.** Major studies and their outcomes are summarized in **Table 2** and the **Central Illustration**. The first trial to evaluate MitraClip safety, EVEREST I (Endovascular Valve Edge-to-Edge REpair Study) (18), demonstrated its safety and feasibility for treatment of MR. Hemodynamic improvement of patients was noted post-procedure; however, 30% of patients had surgery due to MR ≥3+ within 3 years of the procedure (19). Subsequently, EVEREST II, a multicenter, randomized controlled trial, compared percutaneous repair versus surgery (either replacement or repair) (15) in patients with symptomatic severe MR (≥3+) who were also candidates for MV surgery.

Of note, as this study randomized surgery-eligible patients, those with severe LV dysfunction (ejection fraction [EF] ≤25%) or LV end-systolic dimensions >55 mm were excluded. The 279 patients were randomized in a 2:1 ratio in favor of percutaneous therapy. FMR was present in 27% of patients, and 52% of patients were New York Heart Association (NYHA) functional class (FC) III or IV (16). In the intention-to-treat analysis, both groups exhibited similar MR reductions at 1 year (MR reduction to ≤2+ was 80% for surgery and 79% for percutaneous repair, p = 1). However, patients assigned to a specific arm but who did not undergo the procedure (15 of 95 patients referred for surgery, 6 for percutaneous repair) were considered to have the same degree of MR at follow-up, accounting for most patients in the surgery group with residual MR. Among those assigned to and treated with surgery, only 4% had grade 3+ or 4+ mitral regurgitation at 1 year of follow-up, compared with 19% of those assigned to and treated with the device. In retrospect, the suboptimal reduction of MR using percutaneous therapy in this study may have been due to a number of factors: lack of operator experience (only 4 of 37 centers had performed more than 20 cases); suboptimal patient selection; and, in many cases, insufficient use of a second clip. It should be noted that this procedure has a significant learning curve. Schillinger et al. (20) found that procedural times progressively decrease after 25, 50, and 75 percutaneous valve repair cases. Similar findings support the importance of the learning curve for

**ABBREVIATIONS AND ACRONYMS**

**DMR** = degenerative mitral regurgitation

**EF** = ejection fraction

**FC** = functional class

**FMR** = functional mitral regurgitation

**HRR** = high-risk registry

**LA** = left atrium

**LV** = left ventricular

**MR** = mitral regurgitation

**MV** = mitral valve

**NYHA** = New York Heart Association

**STS** = Society of Thoracic Surgeons