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STATE-OF-THE-ART PAPERS

Percutaneous Approaches to Valve Repair for Mitral Regurgitation

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Percutaneous therapy has emerged as an option for treatment of mitral regurgitation for selected, predominantly high-risk patients. Most of the percutaneous approaches are modifications of existing surgical approaches. Catheter-based devices mimic these surgical approaches with less procedural risk, due to their less-invasive nature. Percutaneous annuloplasty can be achieved indirectly via the coronary sinus or directly from retrograde left ventricular access. Catheter-based leaflet repair with the MitraClip (Abbott Laboratories, Abbott Park, Illinois) is accomplished with an implantable clip to mimic the surgical edge-to-edge leaflet repair technique. A large experience with MitraClip has been reported, and several other percutaneous approaches have been successfully used in smaller numbers of patients to demonstrate proof of concept, whereas others have failed and are no longer under development. There is increasing experience in both trials and practice to begin to define the clinical utility of percutaneous leaflet repair, and annuloplasty approaches are undergoing significant development. Transcatheter mitral valve replacement is still in early development. (J Am Coll Cardiol 2014;63:2057–68) © 2014 by the American College of Cardiology Foundation

Novel transcatheter therapies for valvular heart disease have developed tremendously over the past decade. These innovative interventional methods are largely modeled from established surgical heart valve procedures, which have started to evolve to less-invasive approaches. Until a decade ago, interventional valve procedures included only balloon pulmonic, aortic, or mitral valvuloplasty, serving highly-selected patients. In 2000 and 2002, percutaneous valve therapy advanced greatly with the first catheter-based pulmonic and aortic valve replacement procedures (1,2). Since then, tens of thousands of high-risk patients have had percutaneous pulmonic and aortic valve replacement worldwide. Although a variety of mitral valve (MV) transcatheter therapies grew in parallel with aortic valve therapies, the MV therapies have had a slower development path. Challenges arising from the complex anatomy of the MV and mitral apparatus and the interplay of the MV with the left ventricle (LV) contribute to the greater difficulty in conceiving of and evaluating mitral devices.

Severe mitral regurgitation (MR) is an insidious disorder that develops gradually over many years and carries an annual mortality rate of at least 5% (3,4). Medical therapy relieves symptoms but does not reverse the underlying mitral pathology. Those with degenerative MR have excellent outcomes with repair surgery (5). The long-term benefits of surgical treatment of functional MR are harder to demonstrate and remain controversial (6–9).

A number of transcatheter MV therapies have been adapted from surgical techniques and are being applied in patients at high-risk for surgery as a result of coexisting comorbidities, among whom there is a large unmet clinical need (10). Catheter device approaches for leaflet repair, indirect and direct annuloplasty, chordal replacement, and LV remodeling for the treatment of MR are under development for these patients who otherwise do not have a good therapy option.

Leaflet Repair

In 1991, Alfieri et al. (11) described a simple surgical technique for suturing leaflets together to reduce MR in patients with degenerative MR. This repair technique, also known as the edge-to-edge leaflet repair, involves suturing the anterior and posterior mitral leaflet edges together near their midpoints, creating a double-orifice valve, and thereby reducing MR. Alfieri performed this surgical procedure in combination with mitral annuloplasty in most cases (12,13). In a select group of patients who underwent isolated surgical edge-to-edge repair without annuloplasty, longer-term outcomes up to 12 years were excellent (14). This concept is the basis of a catheter-based approach to mimic the edge-to-edge surgical repair.

MitraClip. The MitraClip (Abbott Laboratories, Abbott Park, Illinois) is a novel transvenous percutaneous device

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Abbreviations and Acronyms

CRT = cardiac resynchronization therapy

EuroSCORE = European System for Cardiac Operative Risk Evaluation

LV = left ventricle/ventricular

MR = mitral regurgitation

MV = mitral valve

NYHA = New York Heart Association

STS = Society of Thoracic Surgeons

that creates an edge-to-edge repair for MR (15). The MitraClip remains investigational in the United States. It received CE mark approval in 2008. Catheter-based mitral repair with the MitraClip system was first performed in patients in 2003. To date, of the various transcatheter MV therapies, the largest clinical experience is with the MitraClip system, which has been implanted in over 10,000 patients worldwide.

The MitraClip is a mechanical clip that permanently opposes the middle of the anterior and posterior mitral leaflets (Fig. 1). A double-orifice is formed, and the subvalvular apparatus is spared. The procedure is performed in the cardiac catheterization laboratory in the beating heart, under general anesthesia, and with fluoroscopic and transesophageal echocardiographic guidance. The MitraClip system consists of the clip delivery system, to which the device is mounted at its distal end, and steerable guide catheter. The MitraClip comes in 1 size, made of cobalt-chromium metal alloy covered by polypropylene fabric. The clip delivery system and clip are passed through the steerable guide. The steerable catheter is 24-F at the skin and 22-F when it gains access to the left atrium at the level of the atrial septum through a transseptal puncture. The arms of the MitraClip are 8 mm long. With the arms extended, the MitraClip is navigated from the left atrium, across the mitral orifice, and into the LV at a point above the origin of the MR jet (Fig. 2). Once across the orifice, the open clip is slowly pulled back, allowing the leaflets to fall into the arms. The arms are closed to grasp the leaflet edges. Successful grasping results in immediate reduction in the degree of MR. An assessment of leaflet insertion is made to ensure stability of the device and leaflets, and then the clip is closed. The operator may release and re-adjust the position of the clip to optimize MR reduction. In approximately 40% of the cases a second clip might be required to achieve sufficient reduction in MR if the degree of MR reduction from the first device is insufficient. Three clips are used in approximately 1% of cases, and the use of as many as 4 clips has been described (16). The use of 2 clips is an integral part of the strategy of the procedure. The device manufacturer currently charges for the device on a per-procedure rather than a per-clip basis, so the expense of the procedure is not different when multiple clips are used.

The MitraClip device was used in carefully-selected patients in the initial trial experience. In addition to clinical selection criteria based verbatim on the valve guidelines (9), careful anatomic criteria were also required. These anatomic features were originally designed for degenerative MR. Subsequently, it has been recognized in real-world practice that patients with functional MR might be treated with less concern for the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) criteria. Specifically, a jet origin that extends beyond the central scallops of the line of coaptation, or is even pan-orificial, might respond to MitraClip therapy in patients with functional MR. The anatomic criteria are ideal in approximately 20% to 35% of patients with severe degenerative MR and acceptable in a larger proportion with functional MR.

The EVEREST I clinical trial established safety of the device and feasibility of the procedure (17). In the phase II EVEREST trial, 279 patients selected by the guideline criteria for mitral operation were randomized in a 2:1 ratio to undergo percutaneous repair with MitraClip (n = 184) or conventional MV repair or replacement surgery (n = 95) (Table 1) (18). Most patients (73%) had degenerative MV as the etiology of MR. In the intention-to-treat analysis, the rates of death (6%) were similar for MitraClip and surgery at 1 year. The frequency of 2+ MR was significantly higher after MitraClip, but the proportion of patients with grade 3+ or 4+ MR was not significantly different between the 2 groups at 2 years of follow-up (20% percutaneous group vs. 22% surgical group). The rate of surgery for MV dysfunction was 20% for percutaneous group as compared with 2.2% in the surgical group. The combined primary efficacy endpoint of freedom from death, from surgery for MV dysfunction, and from grade 3+ or 4+ MR was 55% in the percutaneous-repair group and 73% in the surgery group ($p = 0.007$). This difference was driven largely by the high rate of surgery after the initial intervention in the MitraClip group. The EVEREST II trial showed superior safety in the percutaneous-repair group as compared with the surgery group in an intention-to-treat analysis (19). This was driven primarily by a higher rate of bleeding requiring transfusion in the surgery group. Importantly, the safety of the procedure even in high-risk patients has been a large part of the acceptance of the therapy in commercial use around the world. Device embolization was not observed, and mitral stenosis was not reported. Having a MitraClip in place did not take away the option for surgical MV reconstruction (20).

A number of studies have established favorable changes in LV dimensions, loading conditions, and MR severity after MitraClip implantation (21–24). Baseline versus 24-h echocardiographic measurements demonstrated significant reductions in MR grade (mean 3.3 to 1.6), regurgitant fraction (mean 46% to 28%) and volume (mean 51 to 27 ml), and LV end-systolic and -diastolic dimensions and volume (25). Other signs of significant reversal in LV remodeling include decrease in LV mass and LV wall stress (26). Left atrial volume reduction was associated with reduction in vena contracta area >50% (27). A novel mechanism for how the MitraClip might alter LV remodeling has been proposed (28). Tissue growth into the clip forms a bridge between the anterior and posterior mitral leaflets. The anatomic formation of this bridge might interact with adjacent myocardial tissue to enhance the