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Defining the Role of MitraClip Therapy for Mitral Valve Regurgitation

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Mitral valve regurgitation (MR) often occurs in patients who are poor candidates for conventional cardiac surgery, particularly in those with advanced heart failure (HF) who are at increased risk of perioperative surgical complications. Catheter-based therapies for mitral valve (MV) repair, such as the MitraClip (Abbott), have been developed.[1] We discuss a conceptual framework for classifying MR by etiology and morphology; techniques, risks, and benefits of surgical and MitraClip repair; and indications for MitraClip therapy.

Mitral Valve Regurgitation and Carpentier Classification

When functioning well, the MV ensures unidirectional diastolic flow between the left atrium and left ventricle (LV). However, this function is affected by stenosis and, far more often, by regurgitation. Mitral regurgitation creates a vicious cycle of progressive LV dilation and systolic dysfunction that ultimately results in clinical HF. Heart failure and myocardial infarction (MI) each have a worse prognosis when associated with MR.[2,3] In patients with HF, clinical outcomes deteriorate as MR becomes more severe. Conversely, treating MR before the onset of clinical HF improves HF-related and overall outcomes.[4,5] Therefore, current American College of Cardiology/American Heart Association guidelines recommend treatment of MR when it is associated not only with clinical HF, but also with LV systolic dysfunction or LV dilation (class I recommendations).[6]

Mitral valve regurgitation can be classified by etiology or morphology. These approaches are complementary. Etiologically, MR may be primary or secondary. The primary type arises from *intrinsic* structural pathology of the annulus, leaflets, or subvalvular apparatus (namely, the chordae tendineae and papillary muscles). In most cases, primary MR involves intrinsic leaflet pathology. In contrast, the secondary or "functional" type arises from the interplay between LV contractility (intrinsic systolic function) and loading conditions, resulting in net LV systolic dysfunction (impaired contractility relative to afterload). Morphologically, MR can be classified according to the Carpentier system, which encompasses both regurgitation and stenosis. Type I disease is characterized by dilation of the MV annulus and generally results from LV dilation due to LV systolic dysfunction. Type II disease is characterized by increased leaflet mobility, which may be due to leaflet perforation, degeneration, or redundancy; chordal redundancy or rupture; or papillary muscle dysfunction or rupture. Type III disease is characterized by decreased leaflet mobility in either diastole (IIIa) (namely, MV stenosis) or systole (IIIb). Type IIIb disease, like type I disease, generally results from LV dilation due to LV systolic dysfunction. It is important to note that, in the Carpentier classification, MR can have more than one cause and more than one morphologic presentation.

Surgical Repair

Open surgical repair, when technically and physiologically feasible and safe, remains the primary treatment option for MR. The advantages of MV repair over replacement are well established.[7] These include decreased perioperative mortality, better preservation of LV systolic function (although chordal-sparing replacement has improved outcomes), decreased risk of endocarditis, generally no need for anticoagulation, greater durability and less need for reoperation when compared with bioprosthetic (but not mechanical prosthetic) MV replacement, and potentially better long-term survival.

Surgical techniques for MV repair vary widely. Annuloplasty, usually involving rigid or semirigid rings, is used to treat annular dilation and provide support for the MV leaflets and subvalvular apparatus.[8] Patch closure, typically with biological materials, is used to treat leaflet defects.[9] Redundant leaflet tissue may be resected if necessary,[10] although resection is increasingly less popular[11] with the wider use of artificial chordal (or neochordal) techniques.[12] The Alfieri edge-to-edge repair approximates the anterior and posterior leaflets of the MV, thereby creating a double orifice.[13,14] Chordal transfer or artificial chordae placement is used to treat ruptured chordae or redundant leaflet tissue having insufficient chordal support. Papillary muscle bands may be used to realign displaced papillary muscles.

These surgical repair techniques also vary in effectiveness. More than one technique may be needed to effectively and durably eliminate regurgitation in individual patients; in fact, this is the norm (for example, annuloplasty plus artificial chordae placement).[12] Most have no easily implemented catheter-based equivalent. The Alfieri edge-to-edge repair is easily and rapidly performed; however, without concomitant annuloplasty, the repair is not as effective or durable.[15] The MitraClip was developed as a catheter-based analogue to the Alfieri repair.

MitraClip Therapy: Background and Current Status

The MitraClip is a 2-arm mechanical device deployed across the atrial septum, under fluoroscopic and echocardiographic guidance. A 24F sheath is inserted into the common femoral vein and advanced into the right atrium; transseptal puncture through the fossa ovalis gives access to the left atrium.[16] The MitraClip is advanced through the sheath, positioned, and deployed at the defect site. The effectiveness of the repair and the degree (if any) of iatrogenic MV stenosis are ascertained by means of follow-up imaging of the MV and measurement of left atrial and LV pressures.

The MitraClip was initially evaluated in candidates for surgical MV repair in a phase I safety and feasibility trial—the Endovascular Valve Edge-to-Edge Repair Study (EVEREST I).[1,16] Most of the trial's 27 patients (93%) had degenerative MR (primary and Carpentier type II). Twenty-two patients were discharged with a MitraClip in place; 14 had moderate MR at one month; and 6 needed conversion to surgery (repair in 5 and replacement in 1).

In the follow-up EVEREST II trial,[17] 279 patients with chronic MR (primary in 204 [73%] and secondary in 75 [27%]) were randomly assigned to either MitraClip therapy or MV surgery. They were compared in terms of the primary composite endpoint—freedom from death, reoperation due to MV dysfunction, and moderate-to-severe (grade 3+) or severe (grade 4+) MR at 12 months. (Note, however, that withdrawal of consent to therapy was considered a therapeutic failure, and that 3% of patients assigned to MitraClip therapy and 16% of those assigned to surgery withdrew consent.) Surgery was more effective than MitraClip therapy (73% vs 55%), mainly because it resulted in a significantly lower rate of reoperation for MV dysfunction (2% vs 20%; P <0.001). Both groups had similar rates of grade 3+ or 4+ MR (21% for MitraClip vs 20% for surgery) and death (6% for both groups). However, among patients who actually underwent their assigned treatment, those who underwent MV surgery had significantly lower rates of grades 3+ and 4+ MR than did those who underwent MitraClip therapy (4% vs 18%; P <0.001); this was also true for moderate (grade 2+) MR (13% vs 27%; P <0.001). In subgroup analyses, surgery was superior to MitraClip therapy with respect to the primary endpoint in patients without preoperative LV systolic dysfunction (an LV ejection fraction [LVEF] <0.60), in those with primary MR, and in those younger than 70 years.

The efficacy of the MitraClip in patients with secondary MR has been evaluated in 2 randomized controlled trials: COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation)[18] and MITRA-FR (Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation).[19] Of note, the COAPT trial incorporated 4-dimensional transesophageal echocardiography; the EVEREST I and II trials did not.[18] Better imaging has enabled better implant techniques.

The COAPT trial enrolled 614 patients with HF who had moderate-to-severe functional MR refractory to guideline-directed medical therapy, an LVEF of 0.20 to 0.50, and a high risk of surgical complications. Patients were randomly assigned to either MitraClip therapy or ongoing medical therapy. The resulting 2-year mortality rate was substantially lower in the MitraClip group (29.1% vs 46.1%). The MITRA-FR study enrolled patients with HF who had severe functional MR (assessed differently than in COAPT) but were not necessarily receiving maximal medical therapy and who had an LVEF of 0.15 to 0.40. They too were randomly assigned to either MitraClip therapy or ongoing medical therapy. The mortality rate was similar in both groups (24.3% vs 22.4%).

What accounts for these disparate results? MitraClip therapy may have provided more benefit in the COAPT trial because its patient population had relatively more severe MR, with greater calculated regurgitant volumes despite relatively smaller LV end-diastolic volumes when compared with the MITRA-FR study population. Moreover, patients included in the COAPT trial had to be receiving maximal guideline-directed

medical therapy; those in the MITRA-FR study did not. Consequently, patients in the MITRA-FR study may have had more room for augmenting conventional medical therapy. Yet, these seemingly discrepant findings underscore the importance of optimized guideline-directed medical therapies for HF.

In light of these trials, MV surgery—particularly MV repair—remains the primary treatment option for MR in appropriate operative candidates. However, transcatheter MitraClip therapy may be a reasonable option in patients with primary MR (predominantly Carpentier type II) who are poor candidates for MV surgery and in patients with secondary MR (Carpentier types I and IIIb).

The overall effectiveness (technical success relative to operative/procedural risk) of MV surgery and MitraClip therapy for different types of MR can be evaluated within our conceptual framework of the Carpentier system. In type I MR, annular dilation secondary to LV dilation is successfully treated by annuloplasty, but operative risk is high because of LV systolic dysfunction. MitraClip therapy is less successful when LV dilation is more severe, but its procedural risk is substantially lower. In type II MR, excess leaflet mobility is effectively treated with a range of specific surgical techniques, and operative risk is typically low. In contrast, MitraClip therapy is much less technically successful, but its procedural risk is also low. In type IIIb MR, surgical techniques are technically successful, but less so than in types I and II (because of a relative deficiency of leaflet/chordal tissue); operative risk is high because at least some degree of LV systolic dysfunction is present. In contrast, MitraClip therapy is reasonably successful, and its procedural risk is low.

Defining the Role of MitraClip Therapy

In comparing cardiac surgery and nonsurgical interventions across a wide range of diseases, a broad theme emerges. Surgical approaches often achieve technically superior and more durable outcomes, but at the cost of greater initial mortality and morbidity rates. Nonsurgical interventions often have lower periprocedural mortality and morbidity rates, but are technically inferior in the short and long terms. This applies to the treatment of MR. However, patients with secondary or functional MR are among those at highest risk of complications of conventional cardiac surgery, primarily because they have pre-existing LV systolic dysfunction. Mitral valve surgery is often complicated by intraoperative myocardial ischemia resulting from either ascending thoracic aortic cross-clamping (despite cardioplegia administration) or induced ventricular fibrillation. Consequently, even though the MitraClip was developed as a catheter-based analogue to a less effective surgical treatment for primary, Carpentier type II MR (namely, Alfieri edge-to-edge repair), its best indication is secondary, functional MR. Future studies are needed to better define the populations in which the MitraClip can most effectively treat functional MR.

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