Defining the Role of MitraClip Therapy for Mitral Valve Regurgitation

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. 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.

MitraClip Therapy 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. 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. 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).

MitraClip 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. 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. Anu-
uloplasty, 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 increas-
ing less popular11 with the wider use of artificial chordal 
(oriﬁcium), and death (6% for both groups). However, 
among patients who actually underwent their assigned 
treatment, those who underwent MV surgery had sig-
ificantly 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 youn-
ger than 70 years.

The efficacy of the MitraClip in patients with sec-
ondary MR has been evaluated in 2 randomized con-
trolled trials: COAPT (Cardiovascular Outcomes 
Assessment of the MitraClip Percutaneous Therapy for 
Heart Failure Patients with Functional Mitral Regur-
gitation)18 and MITRA-FR (Multicentre Randomized 
Study of Percutaneous Mitral Valve Repair MitraClip 
Device in Patients with Severe Secondary Mitral Re-
gurgitation).19 Of note, the COAPT trial incorporated 
4-dimensional transesophageal echocardiography; the 
EVEREST I and II trials did not.14 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 mortal-
ity rate was substantially lower in the MitraClip group 
(29.1% vs 46.1%). The MITRA-FR study enrolled pa-

tients 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? Mitra-
Clip therapy may have provided more beneﬁt in the 
COAPT trial because its patient population had rela-
tively more severe MR, with greater calculated regurgi-
tant 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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