MitraClip for Functional MR

A review of MitraClip use and the COAPT trial in the heart failure population.

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Mitral regurgitation (MR) is the most common type of heart valve insufficiency in the United States. There are more than 4 million patients with significant MR, and the prevalence increases with increasing age, occurring in 9.3% of the population over 75 years.1 Surprisingly, only 2% (approximately 30,000 patients per year) are being surgically treated,2 and a large portion of MR patients are left untreated due to ineligibility for surgical treatment or concerns about surgical risk.3

MitraClip therapy (Abbott Vascular, Menlo Park, CA) is a percutaneous treatment option for MR, derived from the edge-to-edge surgical technique pioneered by Alfieri et al.4 The MitraClip system received CE Mark approval in March 2008, and as a result of promising initial clinical experiences with this procedure, this device has been implanted as a less invasive treatment alternative to surgery in more than 10,000 patients worldwide (Figures 1 and 2).

In the United States, after the EVEREST I feasibility trial,5 the EVEREST II randomized trial was conducted and compared treatment with the MitraClip device to treatment with surgery for MR in a relatively low-risk group of patients. At 1 year, the rate of death was similar in both groups, whereas the degree of residual MR was higher with the percutaneous approach compared with surgery. However, major adverse events at 30 days were lower overall for percutaneously treated subjects. Certain patient groups, such as older patients and

Figure 1. A fluoroscopic view showing detail from the working end of the MitraClip repair system is shown. Note that because cardiac valve tissue is generally invisible with fluoroscopy, this imaging modality is of lesser importance compared to echocardiography for the procedure.

Figure 2. Echocardiographic imaging demonstrates a patient with two MitraClip devices placed side by side on the central portions of what was once a regurgitant valve, leaving a double inflow.
those with functional MR, experienced effectiveness of the percutaneous treatment that was comparable to surgery at 1 year in an exploratory analysis.\textsuperscript{6} The EVEREST II High-Surgical-Risk cohort included patients enrolled in the multicenter EVEREST II High Risk registry and the REALISM continued-access study. This cohort was designed to include symptomatic patients with 3+ to 4+ MR for whom the surgical risk for perioperative mortality was estimated to be $\geq 12\%$, using either the Society of Thoracic Surgeons (STS) calculator or a surgeon coinvestigator-estimated mortality rate based on prespecified criteria. The observed 30-day mortality rate in this cohort of high-risk patients was significantly lower than predicted for surgery, and a majority of patients were discharged to home with a short length of hospital stay. The MitraClip device reduced MR in a majority of patients deemed high risk for surgery, resulting in improvement in clinical symptoms and significant left ventricular reverse remodeling over 12 months.\textsuperscript{7} These data suggested a role for the MitraClip device in treating patients who are at high risk of mortality with mitral valve surgery. MitraClip device placement is feasible and effective in reducing symptoms of heart failure and improving clinical status, and is relatively safe in patients who otherwise have no safe option to reduce MR.

Beginning in June 2012, to confirm the safety and effectiveness of the MitraClip system for the treatment of significant functional MR in heart failure patients, the COAPT randomized trial (clinicaltrials.gov #NCT01626079) was initiated.

**OUTCOMES IN FUNCTIONAL MR**

Although much has been written about functional MR,\textsuperscript{8-11} no randomized controlled studies focusing on functional MR have been published to date. Additionally, while the majority of the patients enrolled in the EVEREST II High-Surgical-Risk cohort had functional MR, it was a heterogeneous group and was not compared to the medical standard of care. The data from this cohort did demonstrate positive and consistent results for high-surgical-risk patients in terms of safety, reduction of MR, reverse left ventricular remodeling, improvement in heart failure symptoms, improvement in quality of life, and reduced rates of rehospitalization, albeit in a small number of patients.\textsuperscript{7} Interestingly, recent European registries, such as ACCESS EU,\textsuperscript{8} TRAMI\textsuperscript{9} and the French registry,\textsuperscript{10} have demonstrated a shift in patient selection from the low-risk degenerative MR patients seen in EVEREST II to a high-risk and mainly functional MR subset of patients. The ACCESS EU trial has demonstrated procedural safety with a low rate of hospital mortality, low rates of short-term adverse events, and clinical hemodynamic improvement, with objective improvement in quality of life and functional status in the high-risk population with prevalence of functional MR.\textsuperscript{8}

**DIFFERENTIATION BETWEEN MR ETIOLOGY SUBTYPES**

The differentiation between degenerative and functional MR (Figures 3 and 4) is the most widely used classification to date and accounts for many important aspects when assessing patients with MR. Degenerative MR most commonly involves structural abnormalities of the mitral leaflets with either prolapse or flail of the posterior leaflet.
and less commonly the anterior or both leaflets. These structural abnormalities may be due to myxomatous or fibroelastic changes of the leaflets and chordae. In contrast, functional MR results from geometric remodeling of the left ventricle from dilated or ischemic cardiomyopathy, whereas the leaflets are structurally normal. Leaflet tethering, papillary muscle dysfunction, and annular dilation are causes in functional MR that lead to mechanical malcoaptation of the leaflets. There are important differences between these two cohorts in morphology and function of the left ventricle and mitral valve, as well as with respect to patient characteristics (eg, age, comorbidities).

Degenerative MR and functional MR are completely different diseases with a common final endpoint of MR. Strict differentiation between the two etiologies of MR may reflect a diverging disease process. Degenerative MR is a leaflet disease, and the only curative option recommended is surgery for repair or replacement (class I or IIa indication for symptomatic degenerative MR), whereas functional MR is a disease of the left ventricle and medical therapy, including cardiac resynchronization therapy, is the standard of care, with data supporting this management. The role of surgery remains debated in patients with functional MR (class IIb recommendation, level of evidence C), with a high rate of MR recurrence.

THE COAPT TRIAL

The COAPT trial, which is now underway in multiple sites, will be the first randomized controlled trial to evaluate the safety and efficacy of the use of the MitraClip device in such patients with functional MR (Figure 5).

The COAPT trial is a prospective, multicenter, randomized controlled trial comparing MitraClip therapy to the medical standard of care to reduce the burden of heart failure in patients with functional MR. The safety and effectiveness of the MitraClip system will be evaluated in this group of patients with symptomatic functional MR who are at high surgical risk. The study was approved by the Food and Drug Administration and started in June 2012.

The COAPT trial design includes 420 patients enrolled at up to 75 sites in the United States with a 1:1 randomization between the MitraClip arm and the control arm with standard heart failure care. Primary endpoints include effectiveness at 1 year, defined as patients without recurrent heart failure hospitalizations, and a primary safety endpoint defined as freedom from all-cause mortality, stroke, worsening kidney function, and ventricular-assist device implantation or cardiac transplantation. Secondary endpoints for effectiveness are defined as MR severity at 12 months, change in 6-minute walking distance, change in quality-of-life score (Kansas City Cardiomyopathy Questionnaire) at 12 months, change in left ventricular end-diastolic volume, and reduction in New York Heart Association (NYHA) functional class I/II at 12 months. Secondary safety endpoints are defined as death, stroke, myocardial infarction, nonelective cardiovascular surgery for device-related complication in device group at 30 days, and all-cause mortality at 12 months.

Patients are eligible for this trial if they have grade 3+ or more chronic MR due to cardiomyopathy of either ischemic or nonischemic etiology, confirmed by an echocore lab. Study subjects must be symptomatic with a New York Heart Association functional class of 2 or greater. The STS online risk calculator is used primarily to determine high-risk status, with a predicted surgical mortality risk of ≥ 8% for inclusion, or if the patient has comorbidities that result in a prohibitive predicted operative risk of stroke or death by the site heart team.

Patients enrolled must also have demonstrated that they are at high risk for continued heart failure exacerbation, as evidenced by a recent heart failure hospitalization in the past 12 months before enrollment, or natriuretic peptide levels consistent with some degree of decompensation (either a brain natriuretic peptide level of > 400 pg/mL or NT-proBNP > 1,600 pg/mL measured within 90 days before enrollment), despite being adequately treated per heart failure standards (revascularization of coronary artery disease, medical therapy of heart failure, or device therapy of left ventricular dysfunction cardiac resynchronization therapy).

The patient’s MR must also be amenable to transcatheter mitral valve repair with the MitraClip device, such that the primary regurgitant jet originates from malcoaptation of the A2 and P2 scallops of the mitral valve. If secondary MR jets exist, they must be considered clinically insignificant.

Key exclusion criteria include (1) severe left ventricular dysfunction (left ventricular end-systolic volume ≥ 55 mm, or left ventricular ejection fraction < 20%); (2) MV area < 4 cm²; (3) recent myocardial infarction; (4) unvascularized significant coronary artery disease; (5) recent cerebro-
vascular accident or severe carotid stenosis; (6) recent percutaneous coronary, carotid, or endovascular intervention or surgery; (7) recent cardiac resynchronization therapy; (8) adverse mitral leaflet anatomy; and (9) severe right ventricular failure or severe tricuspid regurgitation.

The COAPT trial will be the first to study percutaneous transcatheter valve therapy as a heart failure treatment modality and seeks to generate clinical and economic data of its use in this population.

**FUTURE CONSIDERATIONS**

As previously demonstrated by the randomized EVEREST II trial, as well as the high-risk EVEREST study, transcatheter mitral valve repair with the MitraClip device is effective and safe for treating degenerative MR, especially in high-risk and elderly patients who are at prohibitive risk for open surgical repair. However, in lower-risk subsets of patients, open surgical valve repair of primary leaflet pathology remains a more attractive option at experienced centers due to lower rates of recurrent MR despite a higher adverse event rate. Because a smaller number of patients studied had functional etiology of their MR, the need remains for the COAPT trial to determine its utility in this heart failure population. For either subset of patients with MR, to balance the safety and efficacy of the different treatment modalities, approaching the decision from an interdisciplinary heart team approach has become of pivotal importance.

Open surgical repair of functional MR centers on the use of an annuloplasty ring in most cases but has been plagued with a significant rate of MR recurrence along with a lack of evidence for improved survival or heart failure treatment benefit. Despite this, a number of transcatheter approaches have attempted to adopt a percutaneous mitral annuloplasty approach in functional MR. As with most innovation in medical device therapies, these approaches will first be studied in isolation, although surgical approaches often combine multiple therapies tailored to an individual patient’s needs. It may well turn out that a similar combination of therapeutic approaches, such as a MitraClip in combination with an annuloplasty device, will offer the best combination of efficacy and durability to the MR patient. Other mitral repair devices utilize either cinching mechanisms to force septolateral annular reduction through the approximation of two devices connected by a bridge, or by working in the subannular ventricular space. It is likely that an evolution of a number of different therapeutic devices would be required to meet the challenge to eliminate MR completely by percutaneous therapy to the same degree as by surgery.

The ongoing RESHAPE-HF trial (clinicaltrials.gov NCT01772108) in Europe, evaluating MitraClip therapy in patients with heart failure who have more severe cardiomyopathic disease than that studied by COAPT, will also give us additional insights into the MitraClip safety and efficacy at a further end of the disease spectrum. Both the COAPT and RESHAPE-HF trials may support a higher recommendation class in the forthcoming guidelines, and MitraClip is likely in the near future to become the first alternative therapeutic option in high-risk patients with functional MR.

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