Percutaneous Mitral Valve Repair
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Introduction:
Regardless of the etiology of MR, functional or degenerative, traditional medical therapy relieves symptoms to a certain extent but does not reverse the underlying pathology. Surgical repair or replacement of the valve is currently the mainstay for treatment in the presence of significant symptoms, and is recommended for dilated left ventricle, new development of atrial fibrillation, or pulmonary hypertension. Based on surgical principles several less invasive, percutaneous therapies for the treatment of MR have been developed for higher risk patients who otherwise would not have an option for any mechanical treatment. Several categories of percutaneous mitral valve therapies such as the edge-to-edge leaflet repair system, indirect annuloplasty by way of the coronary sinus, and direct annuloplasty are under development.

Leaflet repair:
The MitraClip device (Abbott, Abbott Park, IL) is based on the surgical edge-to-edge repair and is a novel transcatheter device for mitral valve repair. Of the various percutaneous mitral valve therapies, the MitraClip system has the largest clinical experience and has been implanted in over 9,000 patients worldwide. The MitraClip system permanently approximates the leaflets, thereby forming a double orifice.

The initial phase I study of the MitraClip (EVEREST I) established the safety of the device and demonstrated reduction in severity of MR and improved clinical outcomes that were sustained at 6 month. EVEREST II was a randomized comparison of the MitraClip device and conventional surgical mitral valve repair or replacement in patients considered to be good surgical candidates. 279 patients with moderate to severe (grade 3+ or 4+) MR were randomly assigned in a 2:1 ratio to undergo either a percutaneous repair (n=184) or surgery (n=95). The inclusion criteria were taken directly from the AHA-ACC valve therapy guidelines. The final conclusions of the EVEREST II trial were that although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes.

Subgroup analysis of the EVEREST II trial demonstrated significant between-group differences related to age (age ≥ 70 years vs. age < 70, between etiology of MR (functional vs. degenerative MR), and LVEF (LVEF < 60% vs. LVEF ≥ 60%). Outcomes in the percutaneous-repair group were comparable to the surgery group in patients who were older, had poorer left ventricular function, and who had functional MR. This observation led to the EVEREST High Risk study in which patients with severe MR, who were high risk (estimated surgical mortality rate of ≥ 12%) for surgical repair or replacement were compared to a nonrandomized concurrent control group. At one year, improvement in mortality was demonstrated in these high-risk, predominantly functional MR, patients in comparison to the concurrent control group treated with medical therapy. The 12-month survival rate was 76% in the high-risk group and 55% in the
control group (p=0.47). Importantly, a 45% reduction in rate of repeat hospitalization in the year following MitraClip placement was demonstrated.

An additional subgroup of patients who have benefited from MitraClip therapy are cardiac-resynchronization therapy (CRT) non-responders. Patients with persistent severe MR despite placement of a CRT device have increased rates of hospitalization, increased major arrhythmic events, less reverse remodeling, and higher incidence of mortality.

Several registries have been reported from sites in Europe that are using the MitraClip in commercial practice. Broadly, they are all consistent in including patients at high risk for surgery with a 2/3-3/4 predominance of functional MR. The safety results are also highly consistent with low rates of procedure related mortality or major complications, significant reductions in MR grade and improvements in exercise capacity lasting beyond one year in most patients. The proportion of patients discharged to home is uniformly over 80%, consistent with the low morbidity of the procedure.

A pivotal randomized trial of MitraClip in a high risk for surgery heart failure population has been initiated. The COAPT trial is examining the safety and effectiveness of the MitraClip device in high surgical risk patients with MR and heart failure, who are randomized to either percutaneous mitral repair or control group with medical therapy alone. A similar trial in Europe, RESHAPE-HF, is taking place. These randomized trials will add considerably to our understanding of the role of MitraClip therapy compared to medical therapy in an FMR patient population that is too high risk to undergo mitral valve surgery, generate clinical and economic data to support reimbursement and evidence to support the development of treatment guidelines, and will be the first randomized clinical trials to compare non-surgical standard of care medical treatment to an interventional therapy for MR.

**Indirect Annuloplasty:**
Other novel catheter-based devices have made use of the coronary sinus to achieve indirect annuloplasty. The Carillon Mitral Contour System (Cardiac Dimension Inc., Kirkland, WA, USA) is implanted through a percutaneous catheter-based approach via internal jugular vein. The Transcatheter Implantation of the Carillon Mitral Annuloplasty Device (TITAN) trial, is a prospective, non-randomized study of 53 subjects with the second generation device. Patients who received the device had significant benefit in left ventricular remodeling. There were significant reductions in quantitative measures of functional MR, LV dimensions and volume, and the septo-lateral annular dimension that were sustained at 6 and 12 months. Additionally, there was significant improvement in 6-minute walk test, functional class, and quality of life sustained at 24 months. The Carillon device received CE mark approval in Europe in 2011.

**Direct Annuloplasty:**
Other novel devices to perform direct annuloplasty via transvascular implantation are currently under investigation. The Mitralign device delivers two pairs of pledgets to the posterior mitral annulus near A1-P1 and A3-P3. The pledgets are plicated together to
reduce the size of the mitral annulus and hence mitral orifice area. The Accucinch (Guided Delivery Systems, Santa Clara, California) is a direct annuloplasty device that also utilizes the retrograde transventricular approach. A series of anchors are connected by a nitinol wire. The anchors are implanted beneath the mitral valve in the basilar left ventricle. Tethering the cord cinches the basal left ventricle and mitral annulus. A percutaneous annuloplasty ring that closely resembles a surgical ring is under development and has some successful first-in-human experience.

Conclusion:
A number of novel percutaneous mitral valve devices are emerging for the treatment of MR. It is widely recognized that moderate to severe or severe MR portends a poor prognosis. Traditionally, surgery with mitral valve repair or replacement has been performed. Currently, percutaneous mitral repair devices are being used for high-risk surgical candidates. Percutaneous mitral valve repair is less invasive and safer for these very sick patients. Steady progress has been made in the past decade for percutaneous repair. The MitraClip system results in diminished MR and improved symptoms and functional class in individuals who are high-risk for surgical mitral valve repair or replacement. Other novel devices are under investigation and will add to armamentarium of catheter-based approaches to MR.

Key References:
