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Percutaneous Mitral Valve Repair

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Percutaneous Mitral Valve Repair Therapies

The first uses of percutaneous catheter based therapy for mitral valve lesions began in 1982 with the introduction of percutaneous transvenous mitral commissurotomy (PTMC) for treatment of mitral stenosis by Inoue.[1] A variety of approaches and devices for variations on the theme of PTMC developed of the next decade[2], but no attempts to treat mitral regurgitation (MR) using cather methods have been reported until recently. During most of that time catheter treatment for regurgitant lesions remained a distant concept.

Over the last few years a variety of catheter based, percutaneous approaches to valve repair for MR have been developed. These technologies are based on existing surgical procedures, though some of the predicate surgical techniques are not in wide use by surgeons, and some are novel new procedures for surgical mitral repair.

The percutaneous approaches to mitral repair include coronary sinus annuloplasty, direct annuloplasty, and leaflet repair, and a combination of annular remodeling together with chamber remodeling (Table 1).

Coronary Sinus Annuloplasty: The most frequent and ubiquitous surgical therapy has been annuloplasty with a ring, either as a stand-alone treatment for MR or in conjunction with some form of mitral leaflet repair. It has been recognized that the coronary sinus parallels the mitral annulus.[3] A device can be placed in the coronary sinus to deform the mitral annulus and diminish the annular circumference. This approach relies on the anatomic relationship of the mitral annulus and the coronary sinus. Anchors or stents can be placed in the distal coronary sinus and the coronary sinus ostium, with a connector which constrains the coronary sinus and reduces the circumference of the mitral annulus.

The Monarc device (Edwards Lifesciences Inc., Orange, CA) has been implanted in more than eighty patients outside the U.S. The coronary sinus and anterior interventricular vein are cannulated via the right internal jugular vein with deployment of distal and proximal self-expanding stent anchors which are separated by a connecting bridge element. The connecting bridge is a spring, held in an open position by biodegradable material in the spring spaces. Tension on the coronary sinus and mitral annulus develops as the spring shortens. Shortening occurs over 3-6 weeks in animal models, but may be more gradual in humans. This device is in phase I clinical trials. In the first few patients treated, fractures of the

bridge between the two anchors occurred in three of the four implanted patients (detected at days 22, 28 and 81 after device implantation). These were not associated with clinical sequellae other than worsening MR.[4] After a redesign of the bridge element, a rapidly growing number of additional procedures have been performed without additional device failures. Evaluation of the efficacy of this device to reduce MR is ongoing, since the device acts slowly on the mitral annulus. Reductions in MR can only be determined after weeks to months.

Another coronary sinus device is the Carillon mitral contour system (Cardiac Dimensions, Kirkland, WA). It is a nitinol wire shaping ribbon between proximal and distal anchors.[5-7] Tension is applied to the wire element between the two anchors to constrain the coronary sinus, reducing annulular circumference. The device is delivered via a transjugular puncture with a 9 French guiding catheter. During deployment it is progressively shortened and the reduction in MR is measured using echocardiography. This device has been inserted successfully in patients both outside and inside the U.S. The first generation had cases of failure of the distal coronary sinus anchor to hold adequately and it has undergone a redesign, which has successfully improved anchoring. Implantation has resumed. Early results have demonstrated improved six minute walk test times and decreases in MR grade.

The percutaneous transvenous mitral annuloplasty (PTMA) system (Viacor, Wilmington, MA) is another coronary sinus shape deforming device. PTMA was invented by cardiac surgeons and consists of a 7 French multi-lumen PTFE catheter , within which are inserted variable stiffness rods. The rods compress the mid-portion of the coronary sinus which diminishes the septal to lateral dimension of the mitral annulus and reduces the severity of MR in animal models.[8] After the optimal number and stiffness of rods have been tested in a temporary diagnostic catheter, a permanent version of the device is implanted. The system shape and stiffness can be adjusted over time by addition or substitution of rods, depending on the patient response and changes in the severity of MR. A small series of temporary implants were inserted in the operating room to establish proof of concept[9,10].

Another similar coronary sinus approach is the percutaneous septal-sinus shortening procedure (PS3). An anchor is placed in the coronary sinus and a cord traversing the left atrium is attached to a anchor in the fossa ovalis. The cord is tensioned to diminish the mitral annulus septal-lateral dimension.[11] This system is in the process of initiating first-in-man clinical trials.

There may be important limitations associated with coronary sinus annuloplasty. The magnitude of MR reduction, predicting non-responders vs responders, and the durability of MR reductions will be defined by the ongoing trials.

The coronary sinus does not directly parallel the mitral annulus in many patients, and is often about a centimeter above the annular plane.[3] The coronary sinus crosses over branches of the circumflex coronary artery in about half of patients. In some cases these devices cause important circumflex artery compression or ischemia, necessitating either repositioning or removal of the device in the case of the Carillon device. The Monarc approach involves placing the device without any assessment of efficacy at the time of implantation, since it's spring element shortens over a period of weeks or months. Thus, the potential to compress the circumflex is harder to gauge with this device. Coronary compression of a prior circumflex lesion has been described the Monarc. The degree to which coronary compression limits the use of the coronary sinus approach remains to be determined. These devices occupy the space often used for biventricular pacing leads. Access for lead placements during procedures such as resynchronization therapy will ultimately probably be possible, but use of new devices in trials precludes multiple types of concomitant coronary sinus implants. The potential for erosion and thrombosis of the coronary sinus can only be ascertained after increased clinical experience with these devices, but have not yet been encountered.

Direct Mitral Annuloplasty: Direct approaches to the mitral annulus are in development, both because of the appeal of a direct method, and also to address the potential limitations of indirect annuloplasty via the coronary sinus. The Mitralign device (Mitralign, Tewksbury, MA) uses anchor pledgets placed directly into the mitral annulus, and a "drawstring" to cinch the annulus. This approach is similar to surgical plication annuloplasty which was described in 1977.[12] Good surgical results with suture annuloplasty have been reported recently.[13,14] A 20% reduction of the posterior annulus circumference can normalize the septal-lateral dimension and eliminate ischemic MR[15]. The Mitralign annuloplasty system places anchors directly into the mitral annulus from the left ventricular side, and tethers them with a plication suture. A catheter is used to access the space on the ventricular side of the side of the posterior mitral leaflet. Retrograde left ventricular catheterization using standard guiding catheter shapes for left ventricular access to the peri-annular space has been accomplished reliably. The

procedure has been reproducibly successful in pre-clinical models. Clinical studies with the Mitralign device are being planned.

Leaflet Repair: Leaflet repair methods include various forms of resection, sliding "plasty", and chordal replacement. A novel form of leaflet repair has been performed using a surgical approach first reported by Alfieri in the early 1990s.[16,17] Suturing of the free leaflet edges of the mid part of the line of mitral coaptation results in a double orifice mitral valve. This double orifice, or edge-to-edge, or "bow tie" repair, can be successful as an isolated surgical approach in patients with regurgitation localized to the mid segments of the anterior or posterior leaflets, in the absence of a grossly dilated annulus. The edge-to-edge repair, often combined with an annuloplasty ring, obliterates the gap in coaptation caused by the redundant leaflets.

Surgical edge-to-edge repair has had mixed clinical results.[18,19] It has been used as a "bailout" procedure in cases of both functional and degenerative MR when more conventional surgical approaches had suboptimal outcomes. A report of isolated edge-to-edge surgical repair in patients with optimal leaflet morphology had five-year 90% freedom from reoperation and MR>2+, and after 12 years, freedom from reoperation and MR>2+ was almost 80%.[20] This demonstrates that isolated surgical edge-to-edge repair can be durable in selected patients.

The edge-to-edge repair has been duplicated using percutaneous clip.[21-25] After transseptal puncture, a MitraClip (Evalve, SanFranciso, CA) is delivered to the left atrium via a 24 French guide catheter, and positioned in the mid left atrial cavity above the mitral orifice. The clip must be aligned in the center of the valve orifice, with the clip arms perpendicular to the line of coaptation. The process of steering the guide catheter into optimal position is accomplished using steering knobs on the guide catheter and clip delivery catheter, utilizing both fluoroscopic and transesophageal echocardiographic guidance. When the clip is centered above the origin of the regurgitant jet, along the line of leaflet coaptation, the clip is opened. The open clip arms are passed through the mitral orifice; the open arms minimize the chance for chordal entanglement. After the clip is passed into the left ventricle, below the mitral leaflets, it is pulled back, the leaflets are grasped, and the clip arms are closed to create a double orifice. The device can be repositioned if control of the MR is not adequate, and removed if it appears to

be unsuccessful. A second clip can also be placed if a first clip appears inadequate in decreasing the magnitude of MR.

This device approach has been successfully used in a phase I clinical trial in the United States, and results at 12 months have been reported.[26,27] Surgical candidates with moderately severe or severe MR and cardiac symptoms or no symptoms with signs of LV dysfunction, were included in the EVEREST-I clinical trial (Endovascular Valve Edge-to-edge REpair STudy). Patients fulfilled the AHA-ACC guidelines criteria for surgical treatment of MR[28] and echocardiograms were evaluated using the American Society for Echocardiography methods for assessment of MR severity.[29] Mitral leaflet morphology and MR jet origin must be suited to this approach. The regurgitant jet must arise from the central two-thirds of the line of coaptation. Leaflet coaptation length and depth must be $\geq$2mm and $\leq$11mm respectively. When flail segments are present, the flail gap must be <10mm and the flail width <15mm. These rigorous clinical and morphologic criteria effectively exclude patients with severe annular dilatation. Less than 20% of echocardiograms evaluated by the core lab are considered appropriate for treatment with the Mitraclip device.

Over 100 patients were enrolled in this Phase I trial and in the run-in portion of the subsequent EVEREST-II trial (see below) with > 6 months follow-up in about 80 patients. Compared to results from the most recent STS database, patients referred for this percutaneous procedure were significantly older; median age was 71 years for the clip procedure compared to 59 years for surgical repairs. Clips were successfully implanted in 90% and there were no intra-procedural major complications. Acute procedure success, defined as successful clip placement with reduction in MR severity to $\leq$ 2+, was >70%. Major adverse events within 30 days included partial clip detachment without embolization in 8% of patients, all of whom underwent successful elective valve surgery, and a post procedure stroke in one patient, which resolved in one month. Average length of hospital stay was less than two days. When a clip was placed and the results were suboptimal, mitral leaflet repair using standard surgical techniques has been possible as late as 18 months after the index interventional procedure.[30] Two-year freedom from death, mitral valve surgery, or recurrent MR >2+ has been 80% among patients discharged with successful clip therapy[27].

The encouraging success of the Evalve clip procedure in the Phase I experience, in terms of both safety and effectiveness, has led to a randomized trial comparing this device with mitral valve surgery in the U.S. EVEREST II is currently randomizing patients to percutaneous repair vs a standard surgical approach (2:1 randomization scheme), with clinical and echocardiographic safety and efficacy endpoints. Importantly, there has never been a prospective, echocardiography core lab evaluated, intention-to-treat trial of mitral valve repair therapy in the surgical literature. The EVEREST II trial will be important not only in the assessment of a new percutaneous mitral valve therapy, but also in defining the contemporary results of surgery for mitral valve disease.

Annulus and Left Ventricular Chamber Remodeling: This percutaneous technology is based on a novel surgical device. The Coapsys surgical system (Myocor, Maple Grove, MN) places pads on either side of the left ventricle with a cord passing through the left ventricular cavity to apply tension to the mitral annulus and the basal left ventricular chamber.[31] This off-pump surgical procedure is a direct approach to achieve both left ventricular remodeling and an associated mitral annuloplasty. Initial results of the Coapsys surgical system implanted during coronary revascularization in patients with ischemic MR, have shown sustained reductions in MR and improved ventricular chamber dimensions for as long as one year after the procedure. A percutaneous transpericardial method to simulate this surgical procedure (iCoapsys) is under development in preclinical models.[32]

Comparisons of Percutaneous and Surgical Mitral Repair: Surgery is the established standard for treatment of MR, and comparisons of percutaneous approaches with surgery are both inevitable and necessary. It is thus critical to understand some of the surgical background. The surgical literature has many limitations (Table 2). There have been no prior randomized trials or prospective, intention to treat reports on surgical approaches for MR. Percutaneous therapy is fundamentally different.[33] Outcome measurement after percutaneous therapy is not easily comparable to surgery. It has been infrequent to report composite endpoints that include death, recurrent MR and freedom from reoperation. The assessment of MR severity has been subjective.

There have been no intention to treat trials of mitral valve repair surgery. Most reports are single center, self-reported, and retrospective. Thus the frequency of conversion for mitral repair to mitral valve replacement has been variable and is not well defined. The quantitation of conversion to replacement is

important in manner analogous to its importance for carotid endarterectomy surgery. For symptomatic patients to benefit from carotid endarterectomy, the 30 day combined risk of stroke and death must less than 6%. Asymptomatic patients derive net benefit only when the major surgical complication rate at 30 days is less than 3%. It has been demonstrated that asymptomatic patients with severe MR have a poor prognosis compared to those with less severe MR.[34] There is a compelling need for a clinical trial to demonstrate that early mitral valve therapy might benefit these patients. The lower morbidity of percutaneous therapies may be well suited for such an asymptomatic, lower risk population. Alternatively, there is evidence to indicate favorable outcomes with “watchful waiting” in this patient group[35]; thus, a randomized clinical trial versus either medical or surgical therapy would be critical to evaluate the utility of any therapy in this patient population. Mitral repair surgery may be analogous, with a lower tolerance for complications in asymptomatic patients, but these threshold numbers for justifying surgical intervention are undefined. For the asymptomatic patient population, this is a necessary piece of information for acceptable judgments regarding the use of repair surgery.

In clinical practice, the severity of MR has not been evaluated using the American Society for echocardiography quantitative criteria for grading. Thus, the measure of MR severity has been "eyeball" evaluation. Furthermore, core laboratories have not been used to evaluate the severity of MR. Self-reported subjective measures are clearly suboptimal. Surgical series often include patients with moderate MR. The valve disease guidelines recommend moderate to severe or severe MR as the threshold for intervention. The EVEREST trial includes only patients with moderate-to-severe or severe MR and thus, is not comparable to populations reported previously or in the STS database. For example, the mean age for mitral valve repair patients in the STS database is 59 years compared to 71 years in the Everest trial non-randomized cohort. Core lab evaluation of baseline echocardiograms, use of American Society for Echocardiography criteria for grading severity of MR[29], or prospective echocardiographic follow-up are being introduced with percutaneous device trials, but have not part of the development of traditional surgical therapies.

The clinical endpoint reported in most surgical series is primarily freedom from re-operation. While this is an important measure, procedure mortality is not always clearly reported. Differences

between cardiac and non-cardiac mortality are often not clear in retrospective reports. Overall, mortality must be stated clearly.

Recurrent MR greater than 2+ is rarely reported as an endpoint in the surgical literature. The combined clinical endpoint of freedom from overall death, re-operation, and recurrent MR should be the standard and is part of trials evaluating the percutaneous therapies.

Functional vs degenerative MR: It is important to distinguish between functional and degenerative MR. Functional MR from ischemic disease or dilated cardiomyopathy has distinctly different challenges for both surgical and percutaneous repair. The outcomes of surgical repair for functional MR have been poor compared to repair for degenerative disease. The patients with ischemic disease and heart failure generally undergo annuloplasty, with no manipulations of the leaflets or chordae directly. Degenerative MR has been treated with a combination of annuloplasty and a variety of leaflet and chordal approaches. The results for repair of posterior leaflet prolapse have been excellent, and afford long term relief from re-operation in the degenerative disease population. Bileaflet prolapse and anterior leaflet prolapse have substantially better results then functional MR but have not been as successful as posterior leaflet prolapse repair outcomes. It is notable that repair is not successfully performed in half of patients undergoing isolated mitral valve surgery in the STS database, despite the advantages of repair. Repair techniques are often described as teachable and reproducible, despite the persistent high frequency of mitral valve replacement in apparently repairable patients.

Indirect or direct annuloplasty approaches are better suited to patients with functional MR due to heart failure or coronary ischemia. This population is often not treated surgically, and comparisons with medical therapy may be more appropriate. The expectations for repair therapy for functional MR with percutaneous techniques cannot be the same as for degenerative MR. It will take some time to define whether patients with functional MR truly derive benefit from any form of repair, especially using only classic annuloplasty techniques, which address the annulus but not the primary problem of ventricular dilatation and dysfunction. One recent report suggests no long term benefit from annuloplasty in ischemic MR[36]. The evaluation of functional MR percutaneous repair techniques will be similar to heart failure trials for many of these devices, with comparisons to medical therapy rather than surgical therapy.

Conclusion: Surgical therapy for MR has been developing since the mid 1950s. Annuloplasty was introduces in the early 1970s. The refinements in leaflet repair, and the development of current generation annuloplasty rings have occurred over a period of decades. Despite this time course, few prospective and almost no randomized trial evaluations of these therapies have occurred. The very new field of percutaneous mitral valve repair is developing rapidly, with organized, prospective Phase I safety trials, a high level of scrutiny, and now randomized Phase 2 trials. The role of these new techniques and technologies will be developed by clinical research, and ultimately the utility of both surgical and percutaneous approaches will be better defined. Patients will be the clear benefactors.

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Table 1 **Percutaneous mitral repair therapies grouped by approach and company**

Coronary sinus annuloplasty

Edwards Monarc
Cardiac Dimensions Carillon
Viacor Shape Changing Rods
St. Jude Annulus Reshaping

Direct annuloplasty

Mitralign Suture-Based Plication
Guided Delivery Anchor-Cinch Plication
QuantumCor RF Annulus Remodeling
MiCardia variable size ring

Leaflet repair

EValve Mitraclip
Edwards Mobius stitch

Chamber + annular remodeling

Myocor iCoapsys
Ample PS3

Table 2: **Requirements for evaluation of mitral repair**

Prospective
Randomized
Intention to treat
Echocardiographic core lab
Quantitative MR scoring
Pre-specified MR severity for inclusion
Endpoints: reoperation, death, recurrent MR