FOCUS ISSUE: VALVULAR HEART DISEASE

Transcatheter Mitral and Pulmonary Valve Therapy

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As the percentage of seniors continues to rise in many populations around the world, the already challenging burden of valvular heart disease will become even greater. Unfortunately, a significant proportion of patients with moderate-to-severe valve disease are refused or denied valve surgery based on age and/or accompanying comorbidities. Furthermore, because of advances in pediatric cardiology, the number of adult patients with congenital heart disease is on the rise and over time, these patients will likely require repeat high-risk surgical procedures. The aim of transcatheter valve therapies is to provide a minimally invasive treatment that is at least as effective as conventional valve surgery and is associated with less morbidity and mortality. The objective of this review was to provide an update on the clinical status, applicability, and limitations of transcatheter mitral and pulmonary valve therapies. (J Am Coll Cardiol 2009;53:1837–51) © 2009 by the American College of Cardiology Foundation

The prevalence of moderate-to-severe valvular heart disease is highly age-dependent, ranging from an estimated 0.7% in 18- to 44-year-olds in the U.S. to 13.3% among those 75 years of age or older (1). Given the aging population in many developed countries, the percentage of seniors with significant heart valve disease is projected to rise substantially in coming years. Moreover, an increasing number of adult patients with congenital heart disease will contribute further to the growing number of patients who will require high-risk surgical procedures in the future (2).

Although surgical heart valve repair or replacement remains the standard of care for patients with hemodynamically significant valvular heart disease, the European Heart Survey demonstrated that up to one-third of patients with symptomatic severe valve disease are denied surgery (3). This includes about one-half of patients with severe symptomatic mitral regurgitation (MR) and one-third of elderly patients with severe, symptomatic aortic stenosis who are denied or refused surgery (4,5). Compared with those who underwent surgery, these patients were typically older, had moderate impairment of ejection fraction (31% to 60%), and had more noncardiac comorbidities than did patients undergoing valve surgery. Whether denying surgery in these patients was justified or not, the challenges of managing these patients will only increase in the coming years as the number of patients considered for surgery continues to rise. Finally, the situation is further complicated by the increasing prevalence of adults with congenital heart disease. It is safe to assume that some of these patients will require high-risk surgical valve procedures in the future (2). In an effort to address the challenges ahead, researchers have been developing new options for a rapidly growing pool of patients in whom heart valve replacement or repair may be beneficial, but for whom surgical intervention is considered too high risk. The goal of transcatheter valve therapy is to provide a treatment modality that is less invasive, associated with equal or greater efficacy compared with standard surgery, and is potentially safer than more invasive procedures.

Conceptualization of a catheter-mounted heart valve emerged 3 decades ago (6,7). In 1992, investigators proposed transcatheter deployment of a stent-mounted porcine bioprosthetic valve in an animal model (8). In 2000, Bonhoeffer et al. (9) reported the first percutaneous implantation of a stent-mounted bovine jugular vein valve in the pulmonary position. Soon thereafter, Cribier et al. (10) described the first-in-man percutaneous aortic valve implantation and subsequently, the first percutaneous mitral valve repair was performed.

Historically, randomized controlled trials are not required by the U.S. Food and Drug Administration for the approval of surgical heart valve prostheses. Instead, objective performance criteria, established by large retrospective observational studies, have been used to assess the safety and efficacy of surgical valve prostheses (11). The Food and Drug Administration, however, views percutaneous valve technology as enough of a departure from the current standard of clinical care that randomized controlled clinical trials will be required to evaluate safety and effectiveness.

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Generally speaking, a trial comparing transcatheter valve therapy to surgical therapy will require superiority assessment for safety and noninferiority or even superiority assessment for efficacy. On the other hand, a trial comparing transcatheter valve therapy with medical therapy in nonoperative patients will require proof of superiority for both safety and efficacy.

The objective of this review was to provide a comprehensive update on the current clinical status, applicability, and limitations of transcatheter mitral and pulmonary valve therapies.

**Transcatheter Mitral Valve Repair**

One of the most common forms of valvular heart disease (1,3), MR affects an estimated 9.3% of the population age ≥75 years (1). Furthermore, 15% to 20% of patients with heart failure and 12% of patients 30 days after myocardial infarction (MI) have moderate to severe MR (12,13). Even mild-to-moderate degrees of MR that occur after an acute MI will adversely affect 5-year survival, yet the potential benefits of surgically or percutaneously treating mild or moderate degrees of MR are unknown.

Proper functioning of the mitral valvular complex depends on the structural and functional integrity of its individual components (i.e., the mitral annulus, leaflets, chordae tendineae, papillary muscles, left atrial and left ventricular [LV] walls in continuity with the leaflets, and papillary muscles, respectively). MR can be classified as primary, that is, an abnormality of the mitral valve apparatus (e.g., degenerative mitral valve disease), or secondary (or functional), as a result of an ischemic or nonischemic dilated cardiomyopathy in the setting of anatomically normal mitral valvular leaflets and chords. It is axiomatic that a thorough understanding of the mechanisms of MR and its surgical treatment are essential to the conceptualization, development, and understanding of transcatheter mitral valve techniques. Despite the superior long-term outcomes associated with mitral valve repair rather than mitral valve replacement (14), mitral valve repair is performed in only one-third of patients undergoing mitral valve surgery (15).

Annuloplasty is the cornerstone of mitral valve repair and is essential for the surgical correction of functional MR. For repair of degenerative mitral valve disease, failure to perform a concomitant annuloplasty procedure adversely affects the long-term durability of the repair (16,17). Annuloplasty may be used concomitantly with leaflet repair (resection, sliding annuloplasty) or chordal reconstruction (transposition, artificial chords).

The Alfieri procedure involves suturing the free edges of the middle anterior (A2) and posterior (P2) leaflets of the mitral valve. This produces a double orifice mitral valve. The procedure can be used to treat degenerative or functional MR. Like leaflet repair, the Alfieri procedure requires concomitant annuloplasty to avoid repair failure (18,19). This concept, however, has been challenged by Maisano et al. (20), who reported that isolated surgical edge-to-edge repair performed intentionally without annuloplasty has acceptable midterm results for degenerative and functional mitral regurgitation (5-year freedom from recurrent MR grade >2+ and reoperation 90 ± 5%). The results support the use of an isolated transcatheter edge-to-edge repair technique. After mitral valve surgery, 15% to 30% of patients have persistent/recurrent MR ≥2+ (17,21–24), yet a significant proportion of these patients remains asymptomatic and does not require reoperation (93% to 96% freedom from reoperation at 10 years) (16,25).

Strategies for transcatheter mitral valve repair (reviewed in Table 1) include: 1) creation of a double orifice mitral valve using percutaneous edge-to-edge techniques with a clip device (e.g., MitraClip [Evalve, Inc., Menlo Park, California]) or stitch (e.g., MOBIUS [Edwards Lifesciences Corp., Irvine, California]); 2) remodeling of the annulus of the mitral valve by suture-based techniques (e.g., Percutaneous Suture Annuloplasty [Mitralign, Inc., Tewksbury, Massachusetts], AccuCinch [Guided Delivery Systems, Santa Clara, California]), or application of radiofrequency energy (e.g., QuantumCor Endovascular Device [QuantumCor, San Clemente, California]); 3) remodeling of the mitral valvular complex by transventricular (e.g., iCoapsys [Myocor, Maple Grove, Minnesota]) or transatrial (e.g., Percutaneous Septal Sinus Shortening [PS3] system [Amped Medical, Foster City, California]) devices; and 4) remodeling of the annulus of the mitral valve by devices implanted in the coronary sinus (e.g., Percutaneous Mitral Annuloplasty [PTMA] device [Viacor, Wilmington, Massachusetts]; CARILLON Mitral Contour System [Cardiac Dimensions Inc., Kirkland, Washington]; and MONARC System [Edwards Lifesciences Corp.]).

There are 2 important points. First, unlike pulmonic valve disease, treatment of MR has the potential to have an extraordinary impact on clinical practice due to the higher prevalence of the disease. Second, as opposed to the endoluminal treatment of aortic valve disease, significant and robust clinical results from transcatheter mitral valve therapies cannot be expected in the short term, due both to the complexities of the anatomy and the pathophysiology of MR. In addition, as with conventional surgery, a combination of more than 1 transcatheter mitral valve technique may be required to achieve satisfactory results.

**Edge-to-Edge Techniques**

**Mitraclip.** The Mitraclip (Evalve, Inc.) uses a tri-axial catheter system with a clip device at its distal tip (Figs. 1A and 1B). The goal of the procedure is to create a double-orifice mitral valve similar to the Alfieri surgical technique.
raphy confirm adequate reduction of MR (grade 3 to 1) and favorable positive remodeling indexes after acute procedural success, 73% of patients had improvement in New York Heart Association functional class at 12 months. To resort to surgery for device failure. Among patients with partial clip detachment and 9 of these occurred within 30 days, 97 patients (91%) were free from major adverse events. Ten patients (9%) experienced partial clip detachment and 9 of these occurred within 30 days, but without any major adverse events. Length of hospital stay averaged 3.2 days, and 104 patients (97%) were discharged without the need for home care. After a median follow-up of 386 days, 75 patients (70%) did not have to resort to surgery for device failure. Among patients with acute procedural success, 73% of patients had improvement in New York Heart Association functional class at 12 months. The 2-year follow-up of the first patient showed a sustained decrease in the severity of mitral regurgitation (reduced from grade 4 to 1) and favorable positive remodeling indexes after Mitraclip implantation (29). To date, approximately 400 patients (EVEREST I and II) have been implanted with the Mitraclip. Initial results

(Fig. 1C). The guide catheter is 24-F at its proximal end, tapering to 22-F at its distal end. The system is delivered via a standard transseptal approach into the left atrium. The 2–arm clip is a polyester-covered device. Each clip arm opposes against a multipronged friction element that allows 2–arm clip device is detached from the delivery catheter. Use of standardized echocardiographic protocols can greatly improve procedural times and ease of clip placement (26). The safety and feasibility of the Mitraclip in a porcine model has been reported (27,28). The EVEREST (Endovascular Valve Edge-to-Edge Repair Study) phase I clinical study is completed and EVEREST phase II is currently enrolling patients with degenerative or functional MR (moderate-severe [3+] or severe [4+]). Patients are being randomized to Mitraclip versus mitral valve surgery (2:1). Preliminary results from the initial 107 patients—55 patients from the EVEREST I and 52 patients from the ongoing EVEREST II study—indicated that 84 patients (79%) had degenerative mitral valve disease and 23 patients (21%) had functional MR. One or more clips were implanted in 96 patients (90%) (65 patients, 1 clip; 31 patients, 2 clips). Acute procedural success, defined by clip placement and MR grade ≤2+, was observed in 81 of 96 patients (84%) (Table 2). There was 1 in-hospital death (0.9%) unrelated to the clip device. At 30 days, 97 patients (91%) were free from major adverse events. Ten patients (9%) experienced partial clip detachment and 9 of these occurred within 30 days, but without any major adverse events. Length of hospital stay averaged 3.2 days, and 104 patients (97%) were discharged without the need for home care. After a median follow-up of 386 days, 75 patients (70%) did not have to resort to surgery for device failure. Among patients with acute procedural success, 73% of patients had improvement in New York Heart Association functional class at 12 months. The 2-year follow-up of the first patient showed a sustained decrease in the severity of mitral regurgitation (reduced from grade 4 to 1) and favorable positive remodeling indexes after Mitraclip implantation (29). To date, approximately 400 patients (EVEREST I and II) have been implanted with the Mitraclip. Initial results

### Table 1: Overview of Transcatheter Mitral Valve Therapies

<table>
<thead>
<tr>
<th>Technology (Manufacturer)</th>
<th>General Approach</th>
<th>Indication</th>
<th>Vascular Access</th>
<th>Study Phase</th>
<th>Technical Demand*</th>
<th>Coronary Artery Compromise†</th>
<th>Dependency on Imaging for Implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitraclip (Evalve)</td>
<td>Edge-to-edge repair (“percutaneous Alfieri stitch”)</td>
<td>Degenerative or functional MR</td>
<td>Standard transseptal</td>
<td>Phase II</td>
<td>(+++)</td>
<td>(-)</td>
<td>Echocardiography &gt; fluoroscopy</td>
</tr>
<tr>
<td>MOBIUS Leaflet Repair System (Edwards)</td>
<td>Edge-to-edge repair (“percutaneous Alfieri stitch”)</td>
<td>Degenerative or functional MR</td>
<td>Standard transseptal</td>
<td>Phase I</td>
<td>(+++)</td>
<td>(-)</td>
<td>Echocardiography &gt; fluoroscopy</td>
</tr>
<tr>
<td>Mitralign (Accelerated Technologies)</td>
<td>“Suture” annuloplasty</td>
<td>Degenerative or functional MR</td>
<td>FA (retrograde access to LV)</td>
<td>Phase I</td>
<td>(+++)</td>
<td>(-)</td>
<td>Echocardiography = fluoroscopy</td>
</tr>
<tr>
<td>AccuCinch (Guided Delivery Systems)</td>
<td>“Suture” annuloplasty</td>
<td>Functional MR</td>
<td>RU vein (access to CS) and FA (retrograde access to LV)</td>
<td>Pre-clinical</td>
<td>Not available</td>
<td>(-)</td>
<td>Echocardiography = fluoroscopy</td>
</tr>
<tr>
<td>QuantumCor radiofrequency technology</td>
<td>“Radiofrequency” annuloplasty</td>
<td>Functional MR</td>
<td>Under investigation</td>
<td>Pre-clinical</td>
<td>Not available</td>
<td>(-)</td>
<td>Under investigation</td>
</tr>
<tr>
<td>iCoapsys (Myocor)</td>
<td>Transventricular remodeling</td>
<td>Functional MR</td>
<td>Subxiphoid pericardial approach</td>
<td>Phase I</td>
<td>(+++)</td>
<td>(+)</td>
<td>Echocardiography = fluoroscopy</td>
</tr>
<tr>
<td>Percutaneous Septal Sinus Shortening Device (Ample Medical)</td>
<td>Transatrial remodeling</td>
<td>Functional MR</td>
<td>RU vein (access to CS) and standard transseptal</td>
<td>Phase I</td>
<td>(+++)</td>
<td>(-)</td>
<td>Fluoroscopy &gt; echocardiography</td>
</tr>
<tr>
<td>MONARC System (Edwards)</td>
<td>Coronary sinus device</td>
<td>Functional MR</td>
<td>RU vein (access to CS)</td>
<td>Phase II</td>
<td>(+)</td>
<td>(+++)</td>
<td>Fluoroscopy &gt; echocardiography</td>
</tr>
<tr>
<td>Percutaneous Mitral Annuloplasty (PTMA) device (Viacor)</td>
<td>Coronary sinus device</td>
<td>Functional MR</td>
<td>RU vein (access to CS)</td>
<td>Phase II</td>
<td>(+)</td>
<td>(+++)</td>
<td>Fluoroscopy &gt; echocardiography</td>
</tr>
<tr>
<td>The CARILLON Mitral Contour System (Cardiac Dimensions)</td>
<td>Coronary sinus device</td>
<td>Functional MR</td>
<td>RU vein (access to CS)</td>
<td>Phase I</td>
<td>(+)</td>
<td>(+++)</td>
<td>Fluoroscopy &gt; echocardiography</td>
</tr>
</tbody>
</table>

*The number of + symbols indicates the relative technical demands of the procedure; 3 + symbols indicate the most demanding and 1 + symbol indicates the least demanding. †The number of + symbols indicates the potential for coronary artery occlusion with the device; 3 + symbols indicates the greatest risk and a + symbol indicates no risk.

CS = coronary sinus; FA = femoral artery; LV = left ventricle; MR = mitral regurgitation; RU = right internal jugular.
are encouraging, but they remain inferior to surgical results. Importantly, clip failure is well tolerated and does not preclude surgical mitral valve repair. In rare instances, excessive fibrous reaction around the clip device may prohibit mitral valve repair and lead to the necessity for mitral valve replacement.

**MOBIUS Leaflet Repair system.** Although similar in concept to the Mitraclip device, the Edwards MOBIUS Leaflet Repair system (Edwards Lifesciences Corp.) uses a “percutaneous” stitch to create a double-orifice mitral valve (Fig. 2). The procedure is performed under intracardiac echocardiography and fluoroscopy (30). A standard transeptal approach is used to access the left atrium with a 10-F catheter. The therapy catheter is used to vacuum, capture, and deliver a 4-0 polypropylene suture to the free edges of the mitral valve. Finally, a 7-F fastener catheter deploys a nitinol suture clip and cuts the excess suture. In case of inadequate results, it is possible to remove the suture before deploying the clip.

Feasibility studies in animals provided encouraging results (31). Outcomes from the initial 15 patients treated with the MOBIUS Leaflet Repair system demonstrated acute procedural success in about two-thirds (9 of 15) of patients, with the remainder undergoing successful mitral valve surgery (Table 2). The degree of MR improved from a mean grade of 4+ to 2+ at discharge. At 30-day follow-up, fewer than one-half of the total patients enrolled (6 of 15) had a successful stitch in place. Of the 6 stitch responders, 3, 2, and 1 patients had a 1+, 2+, and 3+ reduction in the severity of MR, respectively. The poor intermediate durability results led investigators to suspend further experimentation with the device for this particular indication.

**Direct Annuloplasty Techniques**

The gold standard for surgical annuloplasty is to implant an undersized, rigid, and complete prosthetic ring (21), but both semi-rigid and flexible rings abolish normal annular dynamics and freeze the posterior mitral leaflet in the semi-open position. Surgical suture annuloplasty was developed to reduce the size of the annulus while maintaining physiological annular and leaflet motion. Evidence suggests that a 20% relative reduction of the septal-lateral dimensions of the mitral annulus can significantly reduce the severity of regurgitation (32). This approach has acceptable 7-year durability results, including an 82% rate of freedom from significant MR, a 95% rate for freedom from reoperation, and an actuarial survival rate of 87.2% at 6.4 years (33). **Mitralign.** In an effort to imitate a surgical suture annuloplasty procedure, the Mitralign system (Mitralign, Inc.) relies on a single 14-F femoral arterial access whereby a therapy catheter with a deflectable end is inserted retrograde across the aortic valve into the LV and positioned in a subvalvular mitral position (Fig. 3A). The deflectable catheter helps direct guidewires and anchors pledgets across the
mitral annulus from the LV to the left atrium. The anchors are tethered and put into tension to decrease the septal-lateral dimensions of the mitral annulus (Figs. 3B and 3C). Outside of the U.S., a small number of patients have undergone preliminary studies examining only catheter positioning and wire placement. A European-based pilot implant study in humans was recently initiated in the last quarter of 2008. **AccuCinch.** The AccuCinch device (Guided Delivery Systems) uses a commercially available catheter with a proprietary design allowing retrograde access to the subannular space of the mitral valve. The goal is to deliver anchors

<table>
<thead>
<tr>
<th>Technology</th>
<th>Study Phase</th>
<th>Procedural Success</th>
<th>% of Patients With Procedural Success and Reduction in Severity of MR</th>
<th>Clinical Improvement</th>
<th>30-Day Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evalve Mitraclip</td>
<td>Phase II (n = 107)</td>
<td>84%</td>
<td>≤ grade 2 MR: 84% (immediate)</td>
<td>73% of patients had at least 1 grade improvement in NYHA functional class</td>
<td>91% free of major adverse events</td>
</tr>
<tr>
<td>MOBIUS Leaflet Repair System</td>
<td>Phase I (n = 15)</td>
<td>60%</td>
<td>≤ grade 2 MR: 83% (immediate) and 50% (30 days)</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Edwards MONARC System</td>
<td>Phase I (n = 79)</td>
<td>82%</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Viacor Percutaneous Mitral Annuloplasty device</td>
<td>Phase I (n = 19)</td>
<td>68%</td>
<td>≤1 grade reduction in MR: 68% (immediate)</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>CARILLON Cardiac Dimensions Coronary Sinus Annuloplasty Device</td>
<td>Phase I (n = 43)</td>
<td>70%</td>
<td>≤1 grade reduction in MR: 80% (immediate)</td>
<td>75% of patients had at least 1 grade improvement in NYHA functional class</td>
<td>Not available</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; MR = myocardial regurgitation; NYHA = New York Heart Association.

**Table 2 Clinical Results**

**Figure 2 The MOBIUS Leaflet Repair Suture Delivery System (Edwards Lifesciences Corp.)**

(A) A 17-F guide catheter, (B) a 10-F therapy catheter, and (C) a 7-F fastener catheter designed to deploy the suture clip and cut the suture. (D) Animal pathology specimen of the mitral valve with suture clip resulting in a double-orifice mitral valve. (E) Zoomed view of the end of therapy catheter showing an orifice (white arrow) that is used to suction the mitral leaflet and deliver the suture. (F) Nitinol suture-clip that is delivered over the suture before the suture is cut above the suture-clip. The * and ** denote the anterior and posterior mitral valve leaflets, respectively.
across the mitral annulus and use a cinching cable to reduce the septal-lateral dimensions of the mitral annulus. The investigational strategy has been to demonstrate efficacy in humans using a surgical approach before developing fully a percutaneous delivery system.

Acute and chronic animal studies of the AccuCinch device have shown no evidence of acute trauma to the leaflets of the mitral valve or LV outflow tract obstruction. Histological studies observed normal tissue healing surrounding the site of implantation of the device. Two surgical patients treated with the device so far have shown sustained reductions in MR severity (2+ to 0) at 6- and 12-month follow-up. In both cases, the surgery was adjunctive to primary coronary artery bypass surgery. The company is performing human cineangiographic studies with its guide catheter to understand the shapes, angles, and views. First-in-man studies of the AccuCinch device are planned for 2009.

QuantumCor. The QuantumCor device (QuantumCor) uses subablative radiofrequency energy to induce heating and shrinkage of the collagen of the mitral annulus. This results in remodeling and reduction of the septal-lateral dimensions of the mitral annulus. The initial prototype of the QuantumCor device involves a catheter with an end-loop diameter of 40 mm that has 7 electrodes along with 14 thermocouples measuring 3 mm in length with 2-mm spacing (Fig. 4). Acute and chronic studies in sheep have shown relative reductions in septal-lateral dimensions of up to one-fifth (34). Acute histopathology specimens have documented no injury to the mitral leaflets or coronary sinus. First-in-man studies are planned.

Indirect Annuloplasty Techniques

Coapsys. The Coapsys or iCoapsys (Myocor) LV reshaping device was designed to be delivered surgically via an open-chest procedure (Coapsys) or percutaneously through a subxiphoid pericardial approach (iCoapsys). (Editor's note: On October 30, 2008, Myocor sold its intellectual property to Edwards Lifesciences Corp., which, according to news reports, has no plans to continue trials of the Coapsys surgical system. However, the devices represented an important concept and are included in this discussion.)

The Coapsys surgical system consists of an externally placed epicardial posterior pad and an anterior pad bridged by a cord that is covered with polytetrafluoroethylene (Fig. 5). The posterior pad has 2 heads, 1 positioned at the level of the mitral annulus and 1 at the level of the papillary muscles. The Myocor device results in: 1) reshaping of the LV and reduction in the dimensions of the septal-lateral dimensions of the mitral annulus; and 2) superior displacement of the papillary muscles in a more subvalvular position. These changes address the 2 main pathophysiological mechanisms of functional MR: annular dilatation and LV remodeling associated with
papillary muscle displacement, leaflet tethering, and leaflet malcoaptation.

A prospective, nonrandomized feasibility study in humans with functional ischemic MR (TRACE study [TRAndolapril Cardiac Evaluation]) has been completed, demonstrating significant acute and midterm reductions in MR grade (3+ to 1+) and reductions in anteroposterior dimensions of the mitral annulus (3.45 ± 0.39 cm to 2.34 ± 0.37 cm vs. 3.40 ± 0.27 cm to 2.85 ± 0.34 cm) with either approach.

The iCoapsys system is delivered through a subxiphoid pericardial approach under fluoroscopic and angiographic guidance. A specifically designed needle, guidewire, and sheath are used to obtain controlled access into the pericardial space. A needle is passed transventricularly to allow passage of a flexible wire and eventually, a transventricular cord is passed and exteriorized. Once implantation is complete, the sizing cord is used to alter the geometry of the LV until the desired reduction in mitral regurgitation is achieved (36).

A prospective, nonrandomized, single-arm feasibility evaluation of the iCoapsys System (the VIVID [Valvular and Ventricular Improvement Via iCoapsys Delivery] study) was initiated in 2008 for patients with functional MR.

**Percutaneous septal sinus shortening.** This device, also known as PS3 (Ample Medical), consists of an atrial septal occluder device and T-bar element that act as anchors in the interatrial septum and coronary sinus, respectively (Fig. 6A). A bridging element traversing the left atrium connects the 2 anchors (Fig. 6B). Specialized catheters, known as Magnecaths, incorporate corresponding shaped magnets at their distal tip; these are placed in the coronary sinus and left atrium. After magnetic linking of both Magnecaths, a crossing catheter is advanced from the left atrial catheter into the coronary sinus catheter. The T-bar element is advanced into the coronary sinus and the bridging element, attached to the T-bar, is pulled back across the transseptal puncture. Finally, the atrial septal occluder device is deployed over the bridging element and tension is applied to displace the coronary sinus toward the atrial septum. This includes reduction in MR severity and change in indices of LV remodeling. To date, 138 patients have undergone randomization, and preliminary acute results have shown similar improvements in MR grade (3+ to 1+) and reductions in anteroposterior dimensions of the mitral annulus (3.45 ± 0.39 cm to 2.34 ± 0.37 cm vs. 3.40 ± 0.27 cm to 2.85 ± 0.34 cm) with either approach.

RESTOR-MV (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve) is a prospective, multicenter, pivotal U.S. Food and Drug Administration trial randomizing patients with coronary artery disease and functional MR to surgical revascularization and reduction annuloplasty or surgical revascularization and Coapsys annuloplasty. The primary end point at 1-year follow-up (35).

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The iCoapsys system is delivered through a subxiphoid pericardial approach under fluoroscopic and angiographic guidance. A specifically designed needle, guidewire, and sheath are used to obtain controlled access into the pericardial space. A needle is passed transventricularly to allow passage of a flexible wire and eventually, a transventricular cord is passed and exteriorized. Once implantation is complete, the sizing cord is used to alter the geometry of the LV until the desired reduction in mitral regurgitation is achieved (36).

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results in reduction of the septal-lateral dimensions of the valve annulus.

Studies using the PS3 in a sheep model of functional MR demonstrated acute and chronic reductions in septal-lateral dimensions of the mitral annulus by up to one-quarter and reductions in MR from 2+/H1 to 1/\(H1\) (37). Subsequently, 2 patients have undergone temporary implantation of the PS3 device before clinically indicated mitral valve repair surgery (38). In the first patient, with severe aortic insufficiency and moderate functional MR, a reduction in MR grade from 2+ to 1+ and a decrease in septal-lateral dimensions from 38 to 27 mm (29% relative change) were observed. The second patient, who had severe functional MR and multivessel coronary artery disease, also experienced significant reductions in MR grade from 3+ to 1+ and a decrease in septal-lateral dimensions of the mitral annulus from 36 to 25 mm (31% relative change). In both patients, no procedural complications were observed and removal of the device at surgery was uneventful. The final generation device has been tested in animals and the company plans to initiate phase I clinical trials in late 2008 and early 2009.

Transcatheter Coronary Sinus Techniques

Transcathether coronary sinus techniques use a reshaping device implanted in the coronary sinus to reduce the septal-lateral dimensions of the mitral annulus. The spatial relationship between the coronary sinus and mitral valve annulus plays a crucial role in these procedures (39).

Several aspects of the coronary sinus–mitral valve annulus are of note. In the majority of cases, the coronary sinus is located superior to the level of the mitral annulus, often in direct contact with the posterior left atrial wall (40–42). The smallest and largest separation distance between the coronary sinus and mitral annulus is usually located near the anterolateral commissure (i.e., distal coronary sinus) and anteromedial commissure (i.e., proximal coronary sinus), respectively (40–44). The crossover frequency between the left circumflex coronary artery and coronary sinus can range from 63.9% to 80.8%. Thus, the coronary sinus device can potentially compress and limit flow in the coronary artery (41,42,45). It is important to note, however, that crossing of the coronary arteries does not necessarily result in compromised coronary atrial flow. Last, variability exists in the branching points of the coronary venous tree. Although not yet confirmed, these subtleties can result in suboptimal deformation of the mitral annulus and inadequate reductions in MR.

MONARC. The Edwards MONARC device (Edwards Lifesciences Corp.) is implanted in the coronary sinus via the right internal jugular vein. The support frame is constructed of nitinol. Intervening between the proximal and distal stent anchors is a spring-like bridging segment that contains biodegradable material (Fig. 7). A few weeks after implantation, resorption of the biodegradable material causes shortening of this bridging segment, bringing the proximal and distal anchors closer together and displacing the posterior mitral annulus more anteriorly. The net effect is a reduction in the septal-lateral dimension of the mitral valve annulus.

Human experience with the first-generation Viking annuloplasty device (Viking Systems, La Jolla, California) was reported by Webb et al. (46); 4 of 5 patients with chronic
ischemic MR $\geq 2+$ underwent successful implantation and 1 patient had perforation of the anterior interventricular vein. In those with a functioning device at last follow-up, mean MR grade decreased from $3.0 \pm 0.7$ to $1.6 \pm 1.1$. Three patients had separation of the nitinol bridge segment at 22, 28, and 81 days post-implantation.

The now completed EVOLUTION phase I study enrolled patients with functional MR and heart failure. The MONARC device used in this study was designed with a reinforced bridging segment. Implantation success was achieved in 59 of 72 patients (82%) (47). Freedom from death, MI, and cardiac tamponade at 30 days was 91% ($n = 57$). At 90 days, freedom from death, MI, cardiac tamponade, coronary sinus thrombosis, device migration, device embolization, or pulmonary embolus was 86%. Of note, 3-month follow-up angiography revealed coronary artery compression in 15 of 50 patients (30%); 3 patients experienced an MI resulting in 1 death. Major adverse events at 18-month follow-up included 1 death, 3 MIs, 2 coronary sinus perforations, 1 anchor displacement, and 4 anchor separations.

Based on the evidence, the MONARC system is feasible to implant. Although efficacy data are encouraging, coronary compression and anchor separation are important safety concerns. Screening of patients and design iterations may solve these problems. A nonrandomized, multicenter, prospective safety and efficacy study (EVOLUTION phase II) is planned for the near future.

PTMA device. The Percutaneous Mitral Annuloplasty device (PTMA) (Viacor) consists of a 7-F multilumen delivery catheter that is placed in the coronary sinus. Up to 3 rods of varying stiffness, length, and tapers can be inserted into the parallel lumens of the delivery catheter to vary the tension of the delivery catheter (Fig. 8). In contrast to the MONARC system and CARILLON Cardiac Mitral Contour system (see the following text), this device exerts an outward force at its proximal and distal segments (i.e., commissural points) resulting in anterior displacement of the P2 segment and a decrease in the septal-lateral dimensions of the mitral annulus.

The PTMA device has been tested in animal models of ischemic MR (48,49), with evidence of significant reductions in the septal-lateral dimensions of the mitral annulus, mitral valve tenting area, and mitral regurgitation. In a temporary implant study of 4 patients with ischemic cardiomyopathy and MR, successful device implantation was achieved in 3 patients (50). There was a reduction in the effective regurgitant orifice area (0.25 $\pm$ 0.06 cm$^2$ to 0.07 $\pm$ 0.03 cm$^2$), regurgitant volume (45.5 $\pm$ 24.4 ml to 13.3 $\pm$ 7.3 ml), and septal-lateral dimensions of the mitral annulus (40.75 $\pm$ 4.3 mm to 35.2 $\pm$ 1.6 mm).

The phase I PTOLEMY (Percutaneous TransvenOus Mitral AnnuloplastY) trial enrolled 27 patients with heart failure (New York Heart Association functional class II to IV) and moderate to severe functional mitral regurgitation from 5 centers in Europe and Canada (51). Eight patients were excluded before implantation because of unsuitable coronary sinus anatomy. Of the 19 patients who underwent implantation, 13 had a reduction in MR severity and in 6, the device was ineffective (Table 2). Four patients subsequently required removal of the device: 1 patient at day 7 for device fracture and 3 patients referred to surgery because of device migration and/or diminished efficacy. Five patients (18.5%) had long-term implants with reductions in MR severity. Following the completion of the phase I studies and the ensuing device iterations, the PTOLEMY II trial is currently underway and will treat up to 60 patients at investigational sites in Europe, Canada, and the U.S. Patients with moderate to severe mitral regurgitation, NYHA functional class II to IV, and LV dysfunction (LV ejection fraction 25% to 50%) will be included.

CARILLON. The CARILLON Mitral Contour System (Cardiac Dimensions) consists of a proximal and distal helical anchor connected by a curved nitinol bridge that is implanted in the coronary sinus (Fig. 9). The right internal jugular vein is cannulated with a 9-F catheter to access the coronary sinus. After deployment of the distal anchor in the great cardiac vein, tension is applied by pulling on the system, resulting in cinching of the mitral annulus. After the desired effect is achieved, the proximal anchor is deployed and the device is uncoupled from the delivery catheter system. The proximal and distal anchors may be deployed and subsequently recaptured in the event of malpositioning or inadequate efficacy.

Animal safety and feasibility studies demonstrated acute and chronic reductions in the diameter of the mitral annulus and reductions in the ratio of MR to left atrial area (16 $\pm$ 4 to 4 $\pm$ 1) (52–54).

In the European phase I AMADEUS (CARILLON Mitral Annuloplasty Device European Union Study) trial (55), implantation success was achieved in 30 of 43 patients (70%) and 80% of patients had at least a 1-grade reduction.
in MR severity (Table 2). Major adverse events at 1-month follow-up included 1 death, 2 MIs, 2 coronary sinus perforations, 1 dissection, 1 anchor displacement, and 1 contrast nephropathy. Coronary arteries were crossed in 36 patients (84%). Arterial compromise contributed to lack of implantation in 6 patients (14%). All unsuccessful implants were recaptured and removed in these patients without complications. Of note, not all crossed coronary arteries resulted in compromised coronary artery flow.

**A Glimpse Into the Future**

A number of transcatheter mitral valve therapies are currently in developmental stages: transcatheter mitral valve...
replacement (e.g., EndoValve Hermann or Lutter mitral valve), percutaneous neochordal implantation (56), and hybrid surgical-transcatheter strategies (e.g., a surgically implanted prosthetic annular ring that can, in case of future need, be adjusted mechanically in the catheterization laboratory percutaneously).

**Pulmonary Valve Therapies**

The pulmonary valve, often thought to be the least important valve in the heart, has long been ignored in the adult population. Disease of this valve was believed to have little impact on patient morbidity and mortality. This is, in fact, not the case, particularly in the subset of patients with congenital heart disease. Tetralogy of Fallot accounts for approximately 10% of all forms of congenital heart disease and is associated with varying degrees of pulmonary obstruction ranging from pulmonary atresia to right ventricular outflow tract (RVOT) obstruction. Reparative options in these patients have focused on increasing pulmonary blood flow using various surgical techniques including homograft conduits and transannular patches.

Unfortunately, long-term follow-up suggests that these techniques are associated with serious complications once thought to be benign. Severe pulmonary insufficiency, for example, results in right ventricular (RV) volume overload, dilation, and failure, thereby increasing the risk of arrhythmias and sudden death. In addition, homograft pulmonary valve stenosis is associated with the development of RV hypertension and arrhythmias. These complications often require further surgical intervention that comes at the cost of additional morbidity and mortality. In this group of young patients, multiple additional procedures may be required during their lifetimes, which has led to interest in developing a nonsurgical technique for percutaneous placement of a biological valve in the pulmonary position.

**Early work.** Development of a percutaneous pulmonary valve was pioneered by Bonhoeffer and his group’s work with lambs. They used a biological valve harvested from the jugular veins of fresh bovine cadavers. These valves were bicuspid or tricuspid, with extremely thin leaflets. The valves were prepared by trimming the venous wall to eliminate any extraneous tissue and reduce the valve profile. These valves were then sutured to a vascular stent composed of platinum and iridium. For implantation the valve was hand-crimped onto a balloon catheter ranging from 18 to 22 mm in length. The balloon catheter was chosen to approximate the size of the pulmonary artery as measured on angiography. The position of the valued stent was easily visualized using fluoroscopy and the stent was then balloon-expanded and deployed in the native pulmonary valve of the lamb to fix the device on the pulmonary wall. The balloon was subsequently deflated and the catheter removed, leaving the replacement valve in the desired position. The procedure was carried out successfully in 5 animals with no complications, demonstrating that percutaneous pulmonary valve implantation was possible in animals and perhaps humans (57).

The first implantation of a pulmonary valve in a human was carried out by Bonhoeffer et al. (58) in 2000. The patient was a 12-year-old boy with a history of congenital heart disease and a previous RV-to-pulmonary artery conduit that had become stenotic with moderate insufficiency leading to moderate RV dilation. The procedure, performed under general anesthesia, used hemodynamic and angiographic evaluation of the conduit was used to determine the severity and location of stenosis. A right coronary catheter was placed in a distal branch pulmonary artery, and a super-stiff exchange guidewire (Amplatz, Meditech, Watertown, Massachusetts) was positioned in the distal pulmonary artery. The valve assembly, composed of the valved-stent and balloon-in-balloon catheter, was then passed over the guidewire and advanced into the pulmonary artery. Once in an acceptable position, the sheath was withdrawn to expose the stent crimped on the balloon. The inner balloon was initially inflated followed by the outer balloon, thus deploying the valved stent. The inner and the outer balloons were then rapidly deflated and the balloon catheter was removed, leaving the guidewire in place (Fig. 10). The procedure was uncomplicated and the patient was discharged home the following day. On follow-up, the child was asymptomatic with complete relief of conduit insufficiency and mild residual stenosis secondary to severe conduit calcification.

After this initial successful implant in a human being, Bonhoeffer et al. (59) reported the first series of percutaneous pulmonary valve implantations in 8 patients with surgically repaired congenital heart disease and resultant conduit pulmonary valve disease. All patients were symptomatic with effort intolerance and breathlessness, and needed conduit replacement because of significant stenosis.
and/or pulmonary regurgitation. The procedures were performed in the manner discussed previously with the exception that manual inflation of a balloon (Zmed II 1 \( \times \) 4, Numed Inc., Nicholville, New York) was performed in the RVOT to determine whether there was sufficient room to implant a pulmonary valve without creating additional obstruction in the conduit.

The valved stent was successfully implanted in all 8 patients. After implantation, angiographic evaluation confirmed competence of the newly implanted valve in 6 patients. Two patients had suboptimal valve placement resulting in an insignificant paraprosthetic leak. Hemodynamic improvement was seen in 5 of 8 patients, with partial relief of obstruction in 3 patients. There were no major procedural complications and all patients were discharged between 1 and 5 days after the procedure. Echocardiographic follow-up at a mean of 10 months demonstrated good valve function, with improvement in RV size and function as well as clinical improvement based on relief of symptoms and improved functional capacity in those with complete relief of obstruction.

This study demonstrated the feasibility and safety of the percutaneous approach for replacement of the pulmonary valve and, in this group of patients, demonstrated that relief of pulmonary insufficiency was associated with improvements in RV function, perhaps leading to subsequent beneficial effects on arrhythmia reduction.

Certain limitations remain; in particular, the procedure may not provide adequate relief of obstruction in patients with severely calcified or small conduits. In addition, for those with large or aneurysmal conduits, there may be an upper limit of size for which this procedure will be suitable. The longevity of such valves is also unclear and will require long-term follow-up studies.

**Congenital heart disease.** This successful initial series prompted further study of percutaneous pulmonary valve replacement in congenital patients with a history of RVOT. A larger series of 59 patients with pulmonary regurgitation with or without stenosis after repair of congenital heart disease followed in 2005 (60). Patients were considered for participation if they had previously undergone RVOT surgery during repair of congenital heart disease and had symptoms or RVOT dysfunction of a sufficient degree to warrant surgical intervention on the basis of conventional indications: RV hypertension (two-thirds of systemic blood pressure or greater) with outflow tract obstruction, significant pulmonary insufficiency, RV dilation, or RV failure. Exclusion criteria included patients <5 years of age or weighing <20 kg, pregnancy, occluded central veins, active infection, and outflow tracts with RVOT diameter >22 mm on angiography, or conduits <16 mm in diameter at surgical insertion.

Fifty-nine patients were recruited for percutaneous pulmonary valve implantation with the Melody bovine jugular vein valve (Medtronic, Minneapolis, Minnesota). The median age was 16 years (range 9 to 43 years) and median weight 56 kg (range 25 to 110 kg); 36 patients (61%) had variants of tetralogy of Fallot, the majority of whom had pulmonary atresia (n = 18), 3 with absent pulmonary valve syndrome, and the rest with severe pulmonary stenosis. Most patients had a homograft conduit after surgery to the RVOT (46 of 59, 78%). Three patients had a “native” RVOT that had been augmented with a pericardial or homograft patch.

Pulmonary valve implantation was successful in 58 of 59 patients. There were 3 significant early complications. In 2 patients, the stent dislodged over the guidewire, and both had successful surgical homograft implantation. There was 1 life-threatening bleed due to dissection of the homograft that required emergent surgical intervention. Minor complications included minor dissection of the homograft (n = 1, treated conservatively), detachment of the distal tip of delivery system (n = 2) into the branch pulmonary artery (snared successfully and retrieved), and local bleeding (n = 4).

Mean follow-up was 9.8 ± 1.4 months and there was no reported mortality. Follow-up echocardiography demonstrated sustained hemodynamic improvements in all patients with a history of stenosis. The improvement in regurgitation also was sustained, with only 1 patient having moderate regurgitation because of endocarditis of the valve. Magnetic resonance imaging showed significant reduction in pulmonary regurgitant fraction and in RV end-diastolic volume as well as a significant increase in LV end-diastolic volume and effective RV stroke volume.

There were device-related problems during follow-up in 14 patients. In-stent stenosis was observed in 7 patients because of a problem with valve apposition within the stent. The problem may have been secondary to failure to suture the valve to the entire length of stent in the initial design of the device. This led to device explantation in 3 patients; however, with further experience, these patients were later treated with a second percutaneous valve implantation. Stent fracture was observed in 7 patients at a median of 9 months after the procedure, but this was associated with only 2 clinical events. There was 1 incident of late stent embolization to the right pulmonary artery 9 months after the procedure.

Recently published data on the previous cohort, now expanded to 155 congenital heart disease patients, illustrated the impact of changing technology and operator learning curve on the success of this procedure (61). Between 2000 and 2007, 163 patients were evaluated for percutaneous pulmonary valve replacement, with 155 patients eventually undergoing the procedure. Median age of the cohort was 21.2 years (range 7 to 71 years); 37% of patients were <16 years old, and 42% were female. The majority of patients had a diagnosis of tetralogy of Fallot (61%) and the anatomic substrate was an RV-pulmonary artery conduit in 92% of patients.

All patients were assessed using transthoracic echocardiography, magnetic resonance imaging, or angiography. In some cases simultaneous coronary angiography was per-
formed at the time of balloon sizing of the conduit to evaluate the risk of coronary compression by percutaneous valve implantation.

Results of the cohort were divided into 2 groups (the first 50 patients and the remaining 105 patients) in order to demonstrate a difference in the learning curve and improved technology. The first 50 patients were believed to represent the learning curve because many design and protocol changes took place with this initial group of patients. The procedure was successful in the majority of these early patients; however, there were 7 major complications including homograft rupture, coronary compression, device dislodgment, and embolization with obstruction of the right pulmonary artery. None of these complications resulted in mortality, although 5 patients required surgical intervention of the RVOT.

Median follow-up was 28.5 months (range 0 to 83.7 months) and data were available on all patients with respect to mortality, reoperation, and repeat transcatheter intervention. Four of 155 patients who underwent percutaneous pulmonary valve implantation died, and survival at 83 months was 96.6%. Freedom from transcatheter reintervention decreased from 95 ± 2% at 10 months to 73 ± 6% at 70 months. Repeat interventions included balloon dilatation and placement of a second valve within a valve. Reasons for reintervention included stent fracture, residual gradient, and valve restenosis. Follow-up echocardiography demonstrated good valve function with, at worst, mild regurgitation and predominantly trivial or absent pulmonary regurgitation in more than 100 patients.

Analysis of the data with respect to the impact of the learning curve suggested improved patient selection, lower occurrence of a residual gradient due to aggressive post-dilatation of the device after deployment, and treatment of device failures with a second device as opposed to reoperation. The incidence of procedural complications also decreased, from 6% in the earliest group of patients to 2.9% in the second (3 of 50 patients vs. 3 of 105 patients). However, there was no difference in transcatheter reintervention between the 2 groups. This was attributed to the requirement of additional interventions due to stent fracture, a complication not related to the learning curve of the procedure. These studies illustrate the success of percutaneous valve implantation in patients with both stenotic and regurgitant lesions, as well as the problems that can be associated with this technology and the work that remains.

One of the obvious current limitations of this procedure is the size of the RVOT. This study excluded patients with an outflow tract larger than 22 mm in diameter due to concerns over valve stability and competence if implanted in a larger outflow tract. Work is already underway in animal models to develop a nitinol stent housing a bioprosthetic valve that can be implanted in larger outflow tracts without compromising valve function (62). In addition, complications such as stent fracture, which occurred in 21% of patients, will require monitoring with serial radiographs and echocardiography after valve implantation. Research has identified the following factors associated with a higher risk of stent fracture: implantation into a “native” RVOT, the absence of calcification along the RVOT, and recoil of the percutaneously implanted pulmonary valve after deployment (62).

Finally, the question of valve longevity remains. Current data confirm that the bovine jugular valve functions well at a median of 29 months, yet this valve will likely suffer from the same degenerative processes that affect other biological valves. Until longer-term data are available, patients will have to be closely monitored for signs of valve failure.

Overall, these initial results in percutaneous pulmonary valve replacement are encouraging for the field of transcatheter intervention, but long-term follow-up is essential to understand the overall impact of this technology on patients.

Conclusions

Transcatheter valve therapy provides a minimally invasive approach compared with existing alternatives, with the ability to address a significant number of patients and have a positive impact on their lives. However, many questions remain: What are the indications/contraindications for these procedures? What are the patient selection criteria? What are the short- and long-term complications (safety)? What are the short- and long-term benefits (efficacy)? What are the cost implications? What type of pivotal study designs are needed to adequately evaluate these therapies?

One thing is certain: The widespread implementation of transcatheter technology will require a heart team approach (i.e., interventional cardiologists and cardiac surgeons) to understand where these new therapies will fit into the management of valvular heart disease. Fortunately, both the knowledge and limitations of the cardiac surgeon and interventional cardiologist are complementary; consequently, when they perform as a team, it is the patient who ultimately benefits the most.

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