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Prospects for Percutaneous Valve Therapies

Ted Feldman, MD; Martin B. Leon, MD

Developmental efforts to achieve percutaneous catheter-based therapies for cardiac valve repair and replacement have advanced rapidly over the past several years. A variety of methods to treat mitral regurgitation (MR) and to replace aortic and pulmonic valves have already been successfully employed in patients. These innovative clinical transcatheter valve therapies were anticipated more than a decade ago by creative experimentalists who helped develop predicate techniques in animal models. For example, in 1992, a catheter-delivered ball-in-cage prosthetic aortic valve was implanted in a canine model by Pavcnik¹ and a stent-mounted bioprosthetic valve was placed by Andersen, who used a retrograde transarterial approach in a swine model.² Clearly, the catheter-based technologies used in clinical studies today in patients with aortic stenosis were derived from the fusion of known successful aortic valve replacement (AVR) surgical devices and adaptive interventional modalities, first studied in experimental animal models. Similarly, approaches for transcatheter treatment of MR have also borrowed heavily from preexisting and accepted surgical techniques, such as the edge-to-edge leaflet coaptation technique and reduction ring mitral annuloplasty.³ Importantly, recognition that the coronary sinus parallels the mitral annulus has spurred unique catheter-based transvenous approaches to treat MR by indirectly reducing mitral annular dimensions.⁴ Because many of the new percutaneous approaches to valve therapy have been developed by surgeons, a collaboration has emerged between thoughtful surgeons and interventionalists, combining skill sets and experiences to accelerate the developmental pathways of less-invasive transcatheter valve therapies.

Unmet Clinical Needs

Growing recognition exists that percutaneous alternatives to surgical therapies are required in some patient subgroups with valvular heart disease. Among patients with either mitral and/or aortic valve disease, an expanding population of elderly patients with significant comorbidities may benefit from traditional surgical methods, but these methods are associated with unacceptable perioperative mortality or prolonged postoperative recoveries. In the EuroHeart Survey on Valvular Heart Disease,⁵ which monitored treatment patterns in >5000 patients from 25 countries, almost one third of symptomatic patients with mitral or aortic valve disease who met accepted guidelines for valve replacement or repair were

never referred for surgery. Even more disturbing was an echocardiography laboratory report of 740 consecutive patients with severe aortic stenosis.⁶ Surprisingly, 62% of the patients with severe aortic stenosis were treated conservatively without surgical AVR, and these medically managed patients had a dismal prognosis (1-, 5-, and 10-year survival was 60%, 32%, and 18%, respectively). The clinical efficacy of surgical therapy for MR in patients with congestive heart failure and for those with ischemic MR has remained uncertain, and perioperative risks are clearly increased. Therefore, given the poorly characterized risk-benefit profile in these patients, surgical mitral annuloplasty is rarely employed as a stand-alone therapy and is used most commonly in conjunction with coronary artery bypass graft procedures. An increasing patient cohort also exists with congenital heart disease, which is treated with surgical right heart conduit procedures, in whom degeneration of bioprosthetic pulmonic valves is common and presents formidable long-term clinical challenges.⁷ These patients often undergo repetitive operative procedures with progressively increasing risk, or bare stent placement, or both.⁸ In these compelling circumstances, the addition of percutaneous pulmonic valve replacement to the treatment armamentarium affords a highly attractive alternative. It should be clearly articulated that the principle intention of the new transcatheter valve therapies is initially to expand the pool of patients with valvular heart disease who may become treatment candidates and not to replace current successful low-risk surgical therapies.

Preclinical Assessments

Preclinical development and testing of catheter-based devices for valvular heart disease has been hampered by difficulty in developing appropriate animal models. The best attempts to simulate human valvular heart disease have been the creation of functional or ischemic MR lesions in dogs, pigs, and sheep. Pacing tachycardia models (at heart rates of 200 to 220 bpm for several weeks), which induce a dilated congestive cardiomyopathy with associated MR, have been used to assess coronary sinus indirect annuloplasty procedures. In these models, reduction in mitral annular dimensions has been demonstrated with improved MR, but extrapolation to human clinical scenarios using the same devices has been problematic. Similarly, coronary artery ligation techniques have been used in sheep models to produce ischemic MR, but the

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reproducibility of the model can be difficult and making the transition to the more complex human anatomy has resulted in less consistent efficacy. Even more frustrating has been the inability to approximate the pathoanatomy of mitral valve prolapse (degenerative MR) and calcific aortic stenosis outside of the human clinical setting. Therefore, animal models have been used primarily to examine early and late healing responses of implanted devices, to test catheter delivery systems, and to refine operator implantation techniques. All transcatheter valve replacement therapies are subjected to careful finite element analysis and long-term durability testing on conventional *ex vivo* pulse duplicators (200 to 600 million cycles) to characterize device failure modes.

Clinical Trial Methodologies

The clinical trial pathways for emerging catheter-based valve therapies are still in a state of rapid evolution. Often a delicate balance must be struck between the requirements to satisfy the rigorous US Food and Drug Administration standards for a permanent transcatheter valve therapy and the economic realities of small start-up device companies. Initial first-in-humans experiences in 10 to 30 patients are necessary to establish safety and general operator use principles and to determine proof-of-concept feasibility. Next, larger, more rigorous multicenter registries (30 to 100 patients) are recommended to encourage device design iteration, to improve and standardize operator technique, to uncover device failure modes, and to compare clinical safety and efficacy outcomes with natural history data and surgical series. Finally, pivotal randomized controlled trials are performed in several hundred patients with a frozen device design versus an appropriate surgical or medical therapy control group. At every stage problems abound, including agreement on the target patient population and control group therapy, definitions of end points, duration of follow-up, and physician training requirements. Finally, one can legitimately raise the question of whether percutaneous catheter-based valve therapies in a morbid elderly patient cohort should be held to the same high standards as surgical therapies performed in younger and healthier patients.

Most assuredly, to propose transcatheter valve alternatives will require the demonstration of incremental clinical benefits in well-characterized patient cohorts studied with the use of rigorous clinical trial methodologies. Thus, these new therapy approaches must have substantive clinical value and cannot simply be the fashionable extrapolation of previous catheter-based treatments for vascular disease.

Percutaneous Pulmonary Valve Replacement

The first successful human percutaneous implantation of a catheter-based stent valve was accomplished in the pulmonic position by Bonhoeffer in 2000.⁹ A bovine jugular vein valve was sutured onto a platinum stent and the stent-valve device was compressed on an 18-mm balloon catheter and enclosed within an 18F sheath. The stent valve was delivered percutaneously via the femoral vein in a 12-year-old boy with a severely stenosed pulmonary valve in a right ventricle-to-pulmonary artery conduit. After sheath retraction, the stent valve was deployed by balloon inflation at the point of greatest

obstruction within the degenerated Carpentier-Edwards prosthetic valve and immediate hemodynamic improvement was observed. This created a functional pulmonic valve in a case where a bioprosthetic valve had failed, which otherwise would have required a repeat high-risk cardiac operation. The trileaflet bovine jugular vein valve used in this landmark case was well suited to the lower-pressure right heart circulation and proved ideal as a valve material for this first application in humans. Subsequently, this device in a variety of similar formulations has been employed in ≈ 200 patients worldwide with congenital heart disease. Seventeen of these have been stent-within-stent procedures. Infrequent procedural complications ($\approx 6\%$ of cases) have included homograft rupture, device dislodgement, coronary compression, and jailing of the right pulmonary artery. One- and 5-year freedom from subsequent surgical procedures to treat device failures has been 90% and 80%, respectively (Philipp Bonhoeffer, MD, personal communication, 2007). In addition to sparing these patients the rigors of an additional or repeat high-risk surgical cardiac procedure, pulmonic valve replacement in this population has been shown to have a profound impact on the physiology of right ventricular outflow tract obstruction occurring late after repair for other congenital heart defects, with improvements in symptoms, aerobic and anaerobic exercise capacity, right ventricular volumes, and systolic and diastolic function.^{10,11}

Surgical Aortic Valve Replacement—The “Gold Standard,” but Not for Everyone

Few therapies in cardiovascular medicine are as accepted and standardized as the surgical treatment of symptomatic patients with severe valvular aortic stenosis. The recent American College of Cardiology/American Heart Association Guidelines for management of valvular heart disease list four class I recommendations for AVR in patients with severe aortic stenosis.¹² Surgical AVR has had an illustrious history for >40 years, with low mortality, continued improvement in operative and perioperative patient management techniques, and increased valve durability. Unlike many current therapies, we can state unequivocally that surgical AVR in symptomatic patients with severe aortic stenosis both relieves symptoms and prolongs life.^{13–15}

Despite clear benefits of AVR in patients with aortic stenosis, morbidity and mortality of valve replacement surgery remains significant in several subgroups. Average perioperative mortality reported from the recent Society of Thoracic Surgeons database is 5.5% to 6.8% for AVR combined with coronary bypass surgery.^{16,17} Surgical mortality increases by 33% in low-volume centers^{18,19} and increases to >10% in octogenarians.^{20,21} Other traditional operative risk factors include female gender, pulmonary hypertension, chronic pulmonary disease, prior cardiac surgical procedures, chronic renal insufficiency, reduced ejection fraction (especially an ejection fraction <30% with prior myocardial infarction), and New York Heart Association class III and IV congestive heart failure.^{22–24} In addition, other imponderables contribute to surgical mortality, such as heavy calcification of the thoracic aorta (so-called porcelain aorta), chest-wall radiation exposure, and chest-wall deformities. These higher

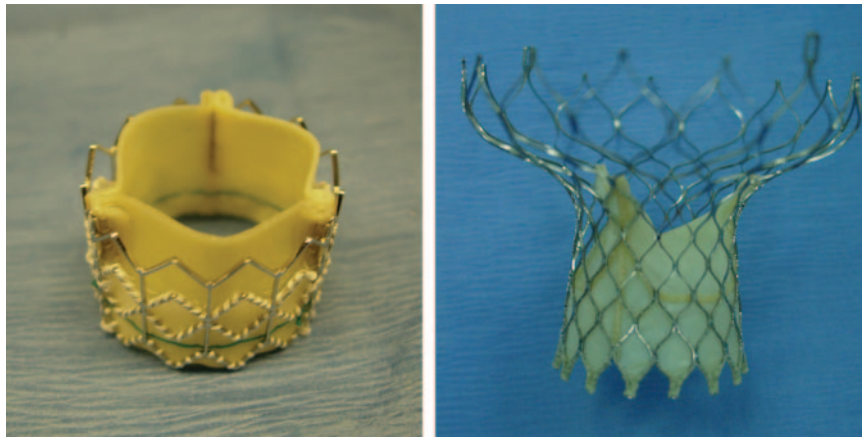


Figure 1. The Cribier-Edwards stent-mounted percutaneous aortic valve replacement prosthesis is shown on the left. The leaflets are made of equine pericardium and sutured to the stainless steel stent delivery platform. The device must be crimped on a balloon catheter to be delivered retrograde through the aorta into the aortic valve orifice. The CoreValve aortic replacement device is shown on the right. It is a fundamentally different design with a self-expanding Nitinol frame within which is mounted a trileaflet tissue valve. The geometry of the stent allows for anchoring in the aortic root above the sinuses of Valsalva. The inferior portion of this stent anchors below the aortic valve annulus in the muscular left ventricular out-flow tract.

risks are amplified in the elderly population, in which additional postoperative concerns are present, including increased neurocognitive dysfunction, prolonged hospital stays, frequent discharge to a rehabilitation facility, and high readmission rates in the first 30 days, primarily as a result of heart failure, arrhythmias, and wound infections.^{25–27} Thus, an expanding population exists of patients with severe aortic stenosis in whom aortic valve surgery is either not considered or results in disproportionate perioperative mortality and morbidity. This so-called high-risk group has been the focus for new transcatheter AVR therapies.

Transcatheter Aortic Valve Replacement

General Considerations

The current design requirements for a permanent catheter-based aortic valve system are formidable and have evolved over the past 4 years, since the first successful percutaneous aortic valve implant by Cribier.²⁸ Design engineers currently favor the use of biological trileaflet tissue valves, and pericardium has been the valve material of choice. The trileaflet valve is sewn or affixed to a circular balloon-expanding or self-expanding stent (or cage) and mounted on a catheter system for deployment. The earliest percutaneous aortic stent valves were large, stiff devices (24F to 26F in diameter), but iterative designs have reduced the system profiles of some devices to 18F. The stent valve is deployed by either balloon expansion or after withdrawal of a sheath that releases a self-expanding stent. The deployed stent valve must remain securely implanted with displacement of the diseased native valve to allow the new tissue valve to begin to function immediately. The hemodynamic performance of the catheter-based aortic valves should be similar to surgical counterparts with minimal transvalvular gradients (<10 mm Hg) and measured aortic valve areas of 1.5 to 2.0 cm². It is essential that no component of the stent valve obstruct the native coronary arteries or interfere with function of the mitral valve apparatus. Also, there must be circumferential apposition of the stent valve to the aortic annulus to prevent the occurrence of paravalvular aortic regurgitation.

Successful application of catheter-based aortic valve technology depends greatly on careful attention to operator technique and procedural methodology. All current catheter-based aortic stent valve procedures begin with conventional

balloon aortic valvuloplasty to provide an enlarged passageway for the insertion of the larger stent-valve device. Careful patient screening for vascular access and aortic annulus dimensions for correct valve sizing are critical. Because of increased periprocedural complications associated with the earlier transvenous antegrade approach, the transarterial retrograde approach is now the preferred technique. This requires femoral artery access (and usually a surgical arterial repair for closure); negotiation of the femoral, iliac, and aortic vasculature; and retrograde crossing of the calcified aortic valve. In general, the implanted catheter-based aortic valves are oversized relative to the annulus to ensure stability and immobility of the implanted stent and to minimize paravalvular regurgitation. During valve deployment, to ensure hemodynamic stability and to minimize movement effects of pulsatile aortic flow heart on stent-valve positioning, additional hemodynamic support devices or temporary rapid right ventricular pacing (to heart rates ≥ 200 beats per minute) may be necessary. After implantation of the stent valve, postdilatation with slightly larger balloon catheter may be needed to reduce paravalvular regurgitation.

The Cribier-Edwards Valve

The Cribier-Edwards Aortic Bioprosthesis (Edwards Lifesciences Inc., Orange, Calif) has been in development for 8 years.²⁹ The leaflet material is currently thin, durable equine pericardium. The 3 valve leaflets are hand-sewn to a stainless steel, tubular, slotted balloon expandable stent (Figure 1, left). Currently stent valves are available that are 23 mm and 26 mm in diameter and that accommodate aortic annulus sizes between 18 mm and 24 mm. At the time of implantation, the sterile stent valve is carefully mounted and crimped (with a specialized crimping tool) onto conventional balloon dilatation catheters. At present, during retrograde procedures, the balloon catheter and stent valve assembly are placed within a tip-deflecting catheter, which is then inserted into a 22F to 24F flexible arterial sheath.³⁰ Active flexion of the tip-deflecting catheter navigates aortic tortuosity and assists with native valve crossing. After successful balloon valvuloplasty and retrograde positioning of the stent valve, rapid ventricular pacing is initiated and balloon inflation deploys the stent valve in the subannular position.

An alternative to the percutaneous access approach for the Cribier-Edwards bioprosthesis involves the use of a transthoracic, transapical device access strategy.³¹ A left anterolateral intercostal incision is used to expose the left ventricular apex. Using direct needle puncture, a 33F sheath is inserted into the left ventricle. The stent valve, which is identical to the percutaneous transfemoral version, is mounted in the antegrade direction on a shorter catheter and is positioned in either a catheterization laboratory or an operating room with the use of fluoroscopy, aortography, and echocardiography. This technique encourages a close collaboration between surgeons and interventionalists and avoids the sometimes forbidding iliofemoral arterial access anatomy that may preclude the percutaneous retrograde approach.

The first successful percutaneous aortic stent valve implantation was performed by Cribier on April 16, 2002, in a patient with critical aortic stenosis and cardiogenic shock, multiple comorbidities, and no therapy options because he was refused surgical AVR.²⁸ The antegrade approach was used to implant a 23-mm bovine pericardial stent valve. The valve performed flawlessly, and the patient experienced dramatic hemodynamic improvement, but he died 17 weeks later after a lower limb amputation for peripheral vascular disease. After 3 additional “compassionate use” cases performed by Cribier’s team in Rouen, France, a European registry was initiated for patients without surgical options (Initial Registry of EndoVascular Implantation of Valves in Europe (I-REVIVE)). This was followed by another single-center registry in Rouen that used the antegrade approach in high-risk patients who had been refused surgical AVR (Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST)). Cribier recently reported the procedural results, clinical outcomes, and impressions from the 36 patients treated in his center who enrolled in these registries.³² In 3 patients, because of procedural complications, valve implantation was never attempted. Overall, successful stent-valve placement was achieved in 27 patients (75%); 23 patients were treated using the antegrade approach and 4 were treated using the retrograde approach. Reasons for failure to successfully implant the stent valve included hemodynamic instability, stent-valve embolization into the aorta after deployment, and failure to cross the native valve from the retrograde direction. Hemodynamic results after successful stent-valve implantation were uniformly excellent; echocardiography mean aortic valve gradients decreased from 37 to 9 mm Hg ($P<0.0001$) and mean aortic valve areas increased from 0.6 to 1.7 cm² ($P<0.0001$). Ejection fraction increased from 45% pretreatment to 53% at 1 week ($P=0.02$). Postprocedural aortic regurgitation (moderate or severe) was present in 17 patients (63%) and was always paravalvular in origin. Aortic insufficiency was more common when the only available device size was 23 mm in diameter. Aortic insufficiency has been diminished with the availability of the larger, 26-mm diameter device and the use of additional balloon dilatation after initial prosthesis deployment when needed. Procedure-related in-hospital complications were disturbing, including 6 deaths and 1 stroke (26%). An additional 10 patients died in the ensuing 6 months. In all cases, out-of-hospital mortality was noncardiac and caused by comorbid conditions. Importantly,

extended follow-up in the surviving patients shows continued excellent valve function and maintained symptom relief. The longest survivor from this series received the stent valve >3 years ago.

An important advance in transcatheter Cribier-Edwards AVR was led by Webb and colleagues, who refined the retrograde implantation approach with the use of improvements in equipment and procedural techniques. The availability of a 26-mm valve prosthesis has reduced the likelihood of valve embolization and the severity of paravalvular regurgitation. The use of a supportive tip-deflecting loading catheter assists with catheter navigation and native valve crossing. Webb et al reported the initial 18 cases performed with the retrograde technique.³⁰ Fourteen successful stent valve implants occurred, with 2 procedure-related deaths (1 death as a result of complications from an iliac artery rupture and the other related to inadvertent obstruction of the left main coronary artery by the prosthesis). In the expanded patient series from Webb et al in Vancouver of >40 retrograde cases (John Webb, MD, unpublished observations, 2007), procedure-related 30-day mortality has been <10%. In the United States, a 3-center phase I safety and feasibility study, Percutaneous Endovascular Implantation of Valves (RE-VIVAL), is ongoing in patients with severe aortic stenosis and high-surgical risk characteristics as determined by a logistic EuroSCORE of >20% and independent surgical assessments of risk profile. Thus far, in the first 55 patients,³³ in whom the retrograde approach was used, there have been 47 successful valve implants (87%) and 4 (7.3%) procedure-related deaths at 30 days (1 death was caused by procedural valve embolization, 1 death was caused by refractory heart failure 2 weeks after failed valve implantation, and the other 2 deaths were caused by complications of acute thoracic aorta dissection during failed valve crossing). Other periprocedural complications have included stroke (5 patients) and iliac artery rupture (5 patients). The major limitation of the current Cribier-Edwards aortic bioprosthesis resides in the large device profiles rendering transfemoral access treacherous in patients with diseased arterial vasculature. As in prior series, short-term hemodynamic results have been excellent and the frequency of moderate or severe paravalvular regurgitation has been markedly reduced (to <10%).

The major limitation of the current Cribier-Edwards aortic bioprosthesis is the large device profile. Nevertheless, the clinical trial process using this device has evolved significantly over the past 4 years and current clinical outcomes are sufficiently encouraging to justify a randomized clinical trial versus an appropriate control group in critical aortic stenosis patients who are at high risk for standard surgical AVR.

The CoreValve System

The ReValving System (CoreValve, Paris, France) consists of 3 components: a self-expanding frame with a trileaflet porcine pericardial valve, a delivery catheter that has been reduced in size from 25F to most recently 18F, and a loading system.³⁴ The self-expanding nitinol support frame (total length 45 mm) has a diamond-cell configuration and incorporates 3 different areas of radial force (Figure 1, right). The upper-frame portion anchors in the aorta above the coronary

sinuses with low radial force, the middle portion contains the valve leaflets, and the lower portion has high radial force and implants in the subannular region. Despite crossing the coronary ostia, the frame geometry is narrowed and unopposed to the aortic wall in its middle portion, thus allowing normal flow and free access to the coronary ostia through the stent struts. The single-layer porcine pericardial tissue valve is sewn to the frame with polytetrafluoroethylene (PTFE) sutures. The present system can be used in patients with distal aortas <45 mm in diameter and with aortic annulus sizes <23 mm in diameter. After balloon aortic valvuloplasty, the CoreValve ReValving system is positioned in a transaortic valve location and the overriding sheath is withdrawn over several minutes to expose and anchor the frame-valve unit. During the critical several minutes of valve deployment, percutaneous external hemodynamic support is used to maintain patient stability. Because of the self-expanding nature of the nitinol frame, continuous further expansion of the system occurs over 30 to 60 minutes, which provides apposition at the proximal and distal implantation zones, minimizing paravalvular regurgitation.

Since the initial report of the first successful implantation of the CoreValve stent valve prosthesis in 2005,³⁵ significant progress has been made in device design, operator technique, and clinical outcomes. The largest reported clinical series of CoreValve cases³⁶ includes 25 cases; the initial 10 cases used the first-generation 25F system (bovine pericardial valve material), and the subsequent 15 patients were treated with the second-generation 21F system (porcine pericardial valve material). The average baseline peak and mean transvalvular aortic pressure gradients were 69.3 mm Hg and 44.2 mm Hg, respectively, and after successful CoreValve implantation, gradients were reduced to 21.3 mm Hg and 12.4 mm Hg, respectively (both $P<0.0001$). Postprocedure aortic regurgitation grade was unchanged (0.9 preprocedure and 0.7 postprocedure), and no cases of moderate or severe paravalvular regurgitation occurred. Major in-hospital cardiovascular and cerebral events occurred in 8 (32%) patients, including death in 5 patients (20%). Among the 8 patients with device success who survived to discharge, no adverse events occurred within 30 days after discharge.

An informal report of the complete CoreValve clinical experience includes the aforementioned Siegburg series and the international ongoing multicenter trial (unpublished CoreValve company records, 2007). A total of >100 patients have been treated; 14 were treated with the 25F first-generation device and 63 were treated with the 21F second-generation device, and the remainder with the most recent 18F device. Patients were at high risk for surgical AVR (either compassionate use or logistic EuroSCORE >20%), and significant improvement occurred between first- and second-generation patient cohorts with device success increasing from 86% to 93% and 30-day death rate decreasing from 43% to 15%. The third-generation 18F device is now in use and promises to expand the treatment potential of this prosthesis. A limitation of the CoreValve approach has been the requirement for extracorporeal cardiopulmonary support during deployment. An alternative has been the use of a percutaneous left ventricular assist device for ventricular

unloading, which obviates the need for ventilatory support and extracorporeal oxygenation. The lower-profile 18F device may not require as much dependence on temporary cardiopulmonary support, thus simplifying the procedure.

Other New Technologies

Several other new percutaneous AVR technologies are being developed. These new devices offer creative design features and attempt to address some of the deficiencies of the first generation technologies. Common characteristics include retrograde valve crossing, reduced profiles, pericardial tissue valve leaflets, and the ability to retrieve and reposition the device before final deployment and release. Some of the most promising of these new aortic valve technologies are described below.

The Direct Flow percutaneous aortic valve (Santa Rosa, Calif) is a stentless, inflatable, fabric-cuff, equine pericardial tissue valve. After advancement across the diseased native aortic valve, the distal ring is positioned and inflated with contrast to secure fixation. Tethers are used to align the valve correctly and the proximal ring is then deployed. Once valve position, function, and sealing are confirmed, a permanent polymer is infused to replace the contrast, followed by detachment of the control tethers (Figure 2, left).

The Lotus percutaneous aortic valve by Sadra Medical (Saratoga, Calif) comprises a nitinol continuous braid frame with a bovine pericardial trileaflet tissue valve (Figure 2, middle). The 19F outer diameter catheter is delivered across the aortic valve and unsheathed. The self-expanding nitinol prosthesis passively shortens and self-centers with low radial force, which allows the valve to begin functioning. When it is optimally located, the nitinol frame is actively shortened and locked to its final height (19 mm), which increases the radial force and secures the bioprosthesis. The frame-valve assembly is attached to the catheter deployment system by 15 arms and the device can be re-elongated, retrieved, and repositioned at any time before final release from the catheter.

Finally, the AorTx percutaneous aortic valve (Palo Alto, Calif) consists of a low-profile, folded, metallic frame that incorporates a pericardial tissue valve (Figure 2, right). The frame is positioned, springs open to unfold the trileaflet valve, and with high radial force is securely implanted. As with the previously mentioned designs, the system is fully retrievable and can be repositioned before final detachment from the catheter delivery system.

Transcatheter Aortic Valve Replacement Clinical Trial Considerations

Given the success of surgical AVR for normal-risk patients, the focus for new transcatheter AVR technologies has been on high-surgical risk patients. Optimal characterization of patient risk requires a combination of clinical judgment and application of standard quantitative risk assessment algorithms. The 2 most commonly applied risk assessment tools are the EuroSCORE and the Society of Thoracic Surgeons risk scoring systems. In general, high surgical risk for AVR is defined as the upper 10% risk decile or, alternatively, as a 30-day procedure death rate in excess of 15%. Less tangible risks, such as patient frailty, chest-wall pathology, and



Figure 2. Three novel percutaneous aortic valve prosthesis designs. On the left is the Direct Flow valve. The device is positioned in the aortic annulus with an inflatable cuff. After a test with the cuff inflated using contrast or saline, an epoxy can be used to permanently implant the device. In the middle is the Sadra Lotus self-expanding prosthesis. The valve can be recaptured and repositioned before finally being released. On the right is the AorTx valve, which has a collapsible metal frame that also has the potential to be recaptured and repositioned.

thoracic aorta calcification are often omitted from these risk assessment algorithms and must be considered separately when overall patient risk is determined.

Undoubtedly, successful validation of transcatheter AVR as a meaningful clinical procedure will require appropriately designed randomized clinical trials. A template clinical trial pathway might involve randomization of high surgical risk patients to either transcatheter versus surgical AVR by use of a noninferiority methodology and a primary end point of all-cause death at 1 year. In critical aortic stenosis patients deemed inoperable by current standards, a different randomized clinical trial design would be appropriate, using best medical therapy and/or balloon aortic valvuloplasty as the control arm (versus transcatheter AVR). Nevertheless, secondary quality-of-life measures and other death end points would be important in such clinical trials, and long-term follow-up should be required to assess valve durability of these new devices. In the future, if transcatheter AVR is proven to be safe and effective in the high surgical risk patients, additional clinical trials comparing transcatheter AVR to analogous surgical procedures in lower risk aortic stenosis patients, patients with aortic stenosis and coronary disease, and patients with aortic regurgitation may be considered.

Surgical Mitral Valve Repair

Surgical treatment of MR remains controversial and includes mitral valve replacement and various combinations of mitral leaflet repair procedures and reduction ring annuloplasty. The choice of operation depends on both the etiology of MR and the experience of the operating surgeon. Because MR can have various causes, no single treatment approach can be applied broadly, and a complete understanding the pathophysiology of MR is essential for selection of the optimal surgical therapy. Patients with degenerative MR, caused by mitral valve prolapse, are usually treated with direct leaflet repair therapies, such as leaflet resection plus sliding repair or direct edge-to-edge repair, almost always combined with an annuloplasty ring. Patients with functional MR caused by

dilated cardiomyopathy and resulting in incomplete leaflet coaptation are typically treated with annuloplasty approaches. Ischemic MR, a subcategory of functional MR, is often caused by varying amounts of incomplete leaflet coaptation and leaflet tethering, and it is surgically managed by a combination of coronary revascularization and annuloplasty procedures. Importantly, the beneficial impact of MR surgery in patients with reduced left ventricular function and congestive heart failure has not been well established. In particular, long-term surgical outcomes after annuloplasty procedures are discouraging in patients with ischemic MR.^{37–40} Nevertheless, given these caveats, a multitude of percutaneous technologies have been developed to mimic the various aforementioned surgical procedures for treatment of MR in defined patient populations.

Transcatheter Mitral Valve Therapies

Leaflet Repair

Direct leaflet repair has been accomplished using a surgical approach pioneered by Alfieri in the early 1990s.^{41,42} Suturing of the free leaflet edges of the mid-part of the line of coaptation results in a double-orifice mitral valve. This edge-to-edge, or “bow tie,” repair can be successful as an isolated surgical approach in patients with regurgitation localized to the middle 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.^{43,44} It has been used as a bail-out procedure in cases of both functional and degenerative MR when more conventional surgical approaches had suboptimal outcomes. Isolated edge-to-edge surgical repair in a patient cohort with optimal leaflet morphology had 90% freedom from reoperation and recurrent MR >2+ at 5 years, and almost 80% freedom from reoperation and recurrent MR >2+ after 12 years.⁴⁵ This



Figure 3. The Evalve Mitraclip. The clip has 2 arms that can be opened and closed by a control mechanism. When the clip is closed, the leaflets are captured between the clip arms and the gripping element, seen on the far left with barbs resting against the shaft of the delivery catheter. On the right is the clip with the delivery catheter and guide catheter tip. The clip is covered with polyester fabric to facilitate tissue ingrowth.

latter report clearly demonstrates that isolated surgical edge-to-edge repair can be durable in selected patients.

Edge-to-edge repair has been duplicated using percutaneous clip- and suture-based devices.^{46–50} After transseptal puncture, MitraClip (Evalve, San Francisco, Calif) is delivered to the left atrium via a 24F guide catheter and positioned in the mid-left atrial cavity above the mitral orifice (Figure 3). 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 MitraClip guide catheter into optimal position is accomplished using steering knobs on the guide catheter and clip-delivery catheter, using 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 opened 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, with results at 6 and 12 months reported recently.^{51,52} Surgical candidates with moderately severe or severe MR and cardiac symptoms or no symptoms with signs of left ventricular dysfunction were included in the clinical Endovascular Valve Edge-to-Edge Repair Study (EVEREST-I). Patients fulfilled the American Heart Association/American College of Cardiology guidelines criteria for surgical treatment of MR,¹² and echocardiograms were evaluated using the American Society for Echocardiography methods for assessment of MR severity.⁵³ 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 ≥ 2 mm and ≤ 11 mm, respectively. When flail segments are present, the flail gap must be <10 mm and

the flail width <15 mm. These rigorous clinical and morphological criteria effectively exclude patients with severe annular dilatation. Less than 20% of echocardiograms evaluated by the core laboratory are considered appropriate for treatment with the MitraClip device.

A total of 70 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 27 patients. Compared with results from the most recent Society of Thoracic Surgeons database, patients referred for this percutaneous procedure were significantly older; median age was 71 years for the clip procedure compared with 59 years for surgical repairs. In these 70 patients, clips were successfully implanted in 90% and no intraprocedural major complications occurred. Acute procedure success, defined as successful clip placement with reduction in MR severity to $\leq 2+$, was 73%. Major adverse events within 30 days included partial clip detachment without embolization in 7% of patients, all of whom underwent successful elective valve surgery, and a postprocedure stroke in 1 patient, which resolved in 1 month. Average length of hospital stay was <2 days. Even when a clip was placed and the results were suboptimal and required surgery afterward, mitral leaflet repair using standard surgical techniques has been possible as late as 18 months after the index interventional procedure.⁵⁴ Actuarial 2-year freedom from death, mitral valve surgery, or recurrent MR $>2+$ has been 80% among patients discharged with successful clip therapy.⁵² The mitral clip procedure may be difficult to generalize to most interventional operators, as a significant operator learning curve is required to reduce procedure time and achieve consistent results, in addition to a familiarity with transesophageal echocardiographic techniques for therapy guidance.

The encouraging success of the Evalve clip procedure, particularly the favorable procedural safety results, has led to a randomized trial comparing this device with mitral valve surgery in the United States. EVEREST II is currently randomizing patients to percutaneous repair versus a standard surgical approach (2:1 allocation), with clinical and echocardiographic safety and efficacy end points. Importantly, in the

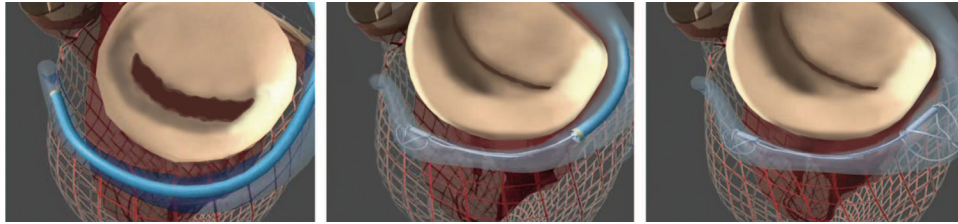


Figure 4. Coronary sinus annuloplasty. On the left, a guide catheter has been placed via transjugular venous puncture distally in the coronary sinus. The regurgitant orifice of the mitral valve can be seen. In the middle, a coronary sinus annuloplasty device is anchored in the distal coronary sinus, and the guide catheter is withdrawn, placing tension on the mitral annulus via the coronary sinus. On the right, the device is in place, the guide catheter has been withdrawn, and the regurgitant orifice has been reduced.

surgical literature there has never been a prospective, echocardiography core laboratory–evaluated, intention-to-treat trial of mitral valve repair therapy. 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.

The edge-to-edge mitral valve repair can also be accomplished using the Mobius percutaneous suture device (Edwards Lifesciences Inc., Orange, Calif). A 16F guide catheter is used to deliver a 10F therapy catheter. The therapy catheter uses suction to capture and immobilize a portion of the mitral leaflet, and then deliver a suture. The device is rotated and the procedure is repeated on the second leaflet. A nitinol fastener is delivered over the suture and the suture is clipped. Early first-in-man experiences that use this suture-based edge-to-edge approach at multiple investigator sites are accumulating. Percutaneous suture-based edge-to-edge mitral valve repair has been successful in reducing MR and creating a double-orifice mitral inlet, but additional device enhancements and refinement in patient selection and operator technique are required to achieve consistent procedure results.

Coronary Sinus Annuloplasty

The mainstay of surgical therapy for MR has been ring reduction annuloplasty, either as a stand-alone treatment for MR or in conjunction with mitral leaflet repair. A simplified interventional approach to simulate surgical annuloplasty has been to work from within the coronary sinus to geometrically deform the anteroposterior dimension of the mitral annulus. This procedure is dependent on the anatomic juxtaposition of the mitral annulus and the circumnavigating coronary sinus.⁵⁵ Anchors or stents can be placed in both the distal coronary sinus or great cardiac vein and in the coronary sinus ostium, with a bridging connector, which either immediately or over time constrains the coronary sinus and reduces the cross-sectional area of the mitral annulus, thereby improving MR.

The Monarc device (Edwards Lifesciences Inc.) has been implanted in >80 patients outside the United States. 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 that are separated by a connecting bridge element. The connecting bridge is a coiled spring, held in an open position by biodegradable material in the spring interstices. Thus, tension on the coronary sinus (and mitral annulus) develops over 3 to 6 weeks as the spring shortens as a result of biodegradation of the embedded material. This device is in early phase I clinical

trials, with published reports on only the first few patients treated. In the earliest experience, bridge fractures between the 2 anchors occurred in 3 of the 4 implanted patients (detected at days 22, 28, and 81 after device implantation) but were not associated with clinical sequelae other than worsening MR.⁵⁶ After a redesign of the bridge element, >80 additional procedures have been performed without fractures or other device failures. Importantly, because tension on the mitral annulus is slow and gradual (coincident with bridge shortening), the efficacy in reducing MR can only be determined during follow-up assessments.

The Carillon mitral contour system (Cardiac Dimensions, Kirkland, Wash) consists of a nitinol wire shaping ribbon between proximal and distal anchors that are placed in the coronary sinus.^{57–59} Tension applied to the shaping ribbon between the 2 anchors deforms the coronary sinus geometry, thereby reducing the mitral annulus dimensions (Figure 4). The Carillon device, delivered via a transjugular puncture and requiring a 9F guiding catheter, is progressively shortened before final deployment of the proximal anchor on the basis of the reduction in MR measured using echocardiography. This device has been inserted successfully in a small number of patients both outside and inside the United States and has already undergone a device redesign to improve coronary sinus securement and fixation. The first treated patient had ischemic MR, with sustained reduction of MR after 2 years. A continuation of the first-in-humans clinical trial is underway.

The percutaneous transvenous mitral annuloplasty system (Viacor, Wilmington, Mass) is the third in this genre of coronary sinus shape deforming devices. Percutaneous transvenous mitral annuloplasty was invented by cardiac surgeons and consists of a 7F multilumen polytetrafluoroethylene catheter, within which variable stiffness rods are inserted. The rods deform the shape of the midportion of the coronary sinus, which diminishes the septal to lateral dimension of the mitral annulus and reduces the severity of MR in animal models.⁶⁰ After the optimal number and stiffness of rods have been inserted in a temporary diagnostic catheter, a permanent version of the device is implanted. Importantly, 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. Presently, a 30-patient clinical trial is ongoing at 3 centers outside the United States.

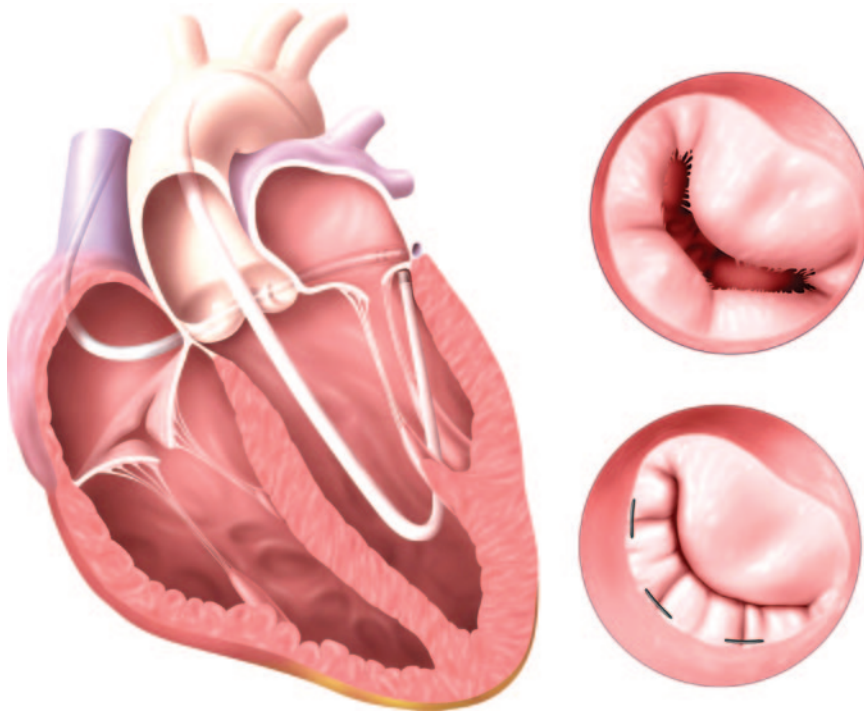


Figure 5. Direct annuloplasty can be accomplished by retrograde catheterization of the left ventricle from the aorta. A catheter is placed behind the posterior leaflet adjacent to the annulus. At the top right, the incompetent mitral valve with poor apposition of the anterior and posterior leaflets is shown. As seen at the lower right, anchors are placed directly through the mitral annulus and tethered together, analogous to a draw-string, with reduction of the regurgitant orifice.

Another similar coronary sinus approach is the so-called percutaneous septal-sinus shortening procedure. An anchor is placed in the coronary sinus and a cord traversing the left atrium is attached to a septal occluder in the fossa ovalis and tensioned to modify mitral annulus geometry.⁶¹ This system is in the process of initiating first-in-humans clinical trials.

Important limitations may be associated with coronary sinus annuloplasty as a methodology to reduce MR. The coronary sinus does not directly parallel the mitral annulus in many patients, but rather is positioned about 1 cm cranial and somewhat tangential to the annulus plane.⁶² Thus, tension created within the coronary sinus is transmitted imprecisely and indirectly to the annulus and might dissipate into the surrounding tissues over time, reducing the efficacy of MR reduction. Moreover, the coronary sinus crosses over branches of the circumflex coronary artery in approximately half of the patients. It remains unclear whether any of the aforementioned devices will induce important circumflex artery compression and ischemia. The coronary sinus has become a frequently utilized anatomic space over the past several years and it would be important to maintain access for lead placements during procedures such as resynchronization therapy. Finally, issues of erosion and thrombosis of the coronary sinus with these devices can only be ascertained after increased clinical experiences. Despite these potential disadvantages, if a safe and predictable device reduces MR by use of a simple transvenous coronary sinus implant, this would become a worthwhile therapy for many patients.

Direct Mitral Annuloplasty

To overcome some of the potential limitations of indirect annuloplasty via the coronary sinus, direct approaches to the mitral annulus are being developed. The Mitralign device (Mitralign, Tewksbury, Mass) uses anchor pledgets that are

placed directly into the mitral annulus, and a drawstring to cinch the annulus in a manner analogous to surgical plication annuloplasty (Figure 5). A relatively small (20%) reduction of the posterior annulus can normalize the septal–lateral dimension and eliminate ischemic MR.⁶³ The surgical version of this approach was initially described in 1977,⁶⁴ and acceptable clinical surgical results have been reported recently.^{65,66} The Mitralign annuloplasty system places anchors directly into the mitral annulus from the left ventricular side and tethers them with a plication suture. Transventricular access to the periannular space on the left ventricular side of the posterior leaflet is achieved with retrograde left ventricular catheterization by use of standard guiding catheter shapes. Clinical studies with the Mitralign device will commence in the next several months.

Transpericardial Annulus and Left Ventricular Remodeling

The Coapsys surgical system (Myocor, Maple Grove, Minn) uses pads placed on either side of the ventricle with a cord passing through the left ventricular cavity to apply tension to both the mitral annulus and the basal left ventricular cavity (Figure 6).⁶⁷ Uniquely, 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 in patients with ischemic MR during coronary revascularization, have shown sustained reductions in MR and improved ventricular chamber dimensions for as long as 1 year after the procedure. A percutaneous transpericardial method to simulate this surgical procedure (iCoapsys) is under development in preclinical models.⁶⁸

Percutaneous Mitral Repair Trial Considerations

Patient selection and trial design for the development of these novel technologies remains challenging.⁶⁹ There have been

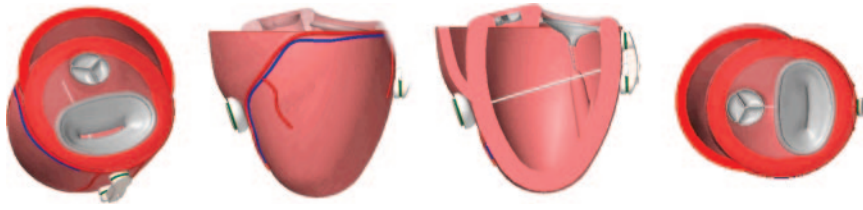


Figure 6. A surgical approach using external pads and a transventricular cord has been developed by Myocor. This technique has been adapted to transpericardial percutaneous use in animal models. The tether places tension on the septal-lateral dimension of the mitral valve and also remodels the basal left ventricle with reorientation of the papillary muscles.

no prior randomized trials and little organized follow-up to evaluate surgical approaches to treat MR. Thus, no established methods exist to compare percutaneous and surgical valve therapy approaches. Percutaneous therapy is inherently different, and the standards for measuring clinical outcomes after percutaneous therapy may not be comparable to surgery. Clinical trials designed to demonstrate noninferiority for efficacy end points and superiority for safety end points may be reasonable goals for catheter-based versus surgical mitral valve procedures.

It has been demonstrated that asymptomatic patients with severe MR have a poor prognosis compared with those with less severe MR.⁷⁰ A clinical trial is urgently needed 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, evidence exists to indicate favorable outcomes with watchful waiting in this patient group; 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.⁷¹ Indirect or direct annuloplasty approaches are better suited to patients with functional MR as a result of heart failure or coronary ischemia. This population is often not treated surgically, and comparisons with medical therapy may be more appropriate.

A paucity of data on the results of mitral repair surgery complicates comparisons with catheter-based technologies. There have been no prospective intention-to-treat trials to define the rate of prosthetic replacement when valve repair is intended, and this conversion rate will impact the relative merits of surgical and percutaneous methods. The usual end point in long-term surgical reports is freedom from reoperation rather than the combination of freedom from death, reoperation, and recurrent MR. Patient selection and surgical outcomes have never been reported with the use of rigorous intention-to-treat principles, core laboratory evaluation of baseline echocardiograms, use of American Society for Echocardiography criteria for grading severity of MR, or prospective echocardiographic follow-up.

Combinations of mitral annuloplasty and leaflet repair approaches may ultimately be necessary for optimal percutaneous therapy in some patients with MR. The use of device combinations will be extremely difficult to evaluate from a clinical trial perspective. The potential for novel nondevice therapies is also just being recognized. Recently, autologous myoblast transplantation that results in left ventricular remodeling has been used to reduce MR in a sheep myocardial infarction model designed to induce chronic ischemic MR.⁷²

Conclusions

The field of percutaneous valve replacement and repair is clearly developing rapidly. Transcatheter aortic and pulmonic

valve replacement and a variety of mitral valve therapy approaches have been successfully performed in hundreds of patients. A variety of operator technique and device-related problems have been encountered and solved.⁷³ Significant challenges in patient selection and clinical trial design have yet to be resolved. The patient populations who may ultimately benefit most from treatment using these new technologies will be better defined during the course of the clinical trial process. In aggregate, these creative new transcatheter approaches may change the face of valve therapy and promise to extend treatment to a larger proportion of the valve disease population.

Disclosures

Dr Feldman is on the scientific advisory board of Myocor and has received grant support from Cardiac Dimensions, Edwards Lifesciences, and Myocor. He is principal investigator for the Evalve EVEREST trial. Dr Leon is on the scientific advisory boards of Edwards Lifesciences, Guided Delivery Systems, Mitralign, and Sadra Medical. He has received grant support from Edwards Lifesciences and owns equity in Guided Delivery Systems, Mitralign, and Sadra Medical. He is principal investigator for the Edwards Lifesciences PARTNER trial.

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