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REVIEW

Innovations in Therapies for Heart Valve Disease

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The burden of heart valve disease among adults is enormous in the developed world. Increased life expectancy and age-related valvular degeneration remain the predominant contributors to heart valve dysfunction, which if uncorrected lead to congestive heart failure and increased morbidity and mortality. Clinical evidence on the detrimental impact of valve disease on both pediatric and adult populations has fueled growing interest in diagnosis and therapy for heart valve disease, and also significant financial investment from hospitals and medical device manufacturers in hybrid operating rooms and novel medical device technologies. A wide array of surgical, minimally invasive and percutaneous heart valve technologies are available today, which have significantly enlarged the surgeon's armamentarium, and revolutionized the traditional role of a surgeon in correcting such lesions. Amid this revolution in heart valve technologies, we present recent advances in heart valve therapies, critically appraise their clinical need, and finally discuss the clinical experience and outcomes of some of these technologies. The expected outcome of this review is to provide the clinical reader with a reasonable scientific basis to enable appropriate adoption of these technologies into their clinical practice. (*Circ J* 2011; **75:** 1028–1041)

Key Words: Annuloplasty rings; Heart valve; Minimally invasive valve repair; Replacement valves; Transcatheter valve repair

Heart valve disease is the most prevalent structural heart disease among adults, and is associated with high morbidity and mortality.[1] Traditional approaches using valve replacement or repair are invasive procedures that usually require a median sternotomy and cardiac arrest. Long-term patient outcomes for aortic valve replacement,[2,3] mitral valve replacement/repair[4] and tricuspid valve repair[5] are now available. The advent of minimally invasive methods for surgical repair, and the more recent thrust towards transcatheter approaches has revolutionized this long-established field in cardiothoracic surgery. Heart valve technologies tailored to catheter approaches are emerging as alternatives to traditional surgery, and their application to patient needs and their role in transforming heart valve therapies is worth noting. The objective of this article is to review these innovative technologies in relevance to the technological need they address, improvements in clinical practice they enable, and the overall patient benefit they achieve.

Aortic Valve Technologies

Mechanical Aortic Valves

Stenosis of the aortic valve, due to aging in older people[6] and congenital abnormalities,[7] is the single most prevalent disease requiring valve replacement. Replacement of the calcified leaflets with a prosthetic aortic valve, either mechanical or bioprosthetic, remains the current standard of care. Mechanical heart valves have evolved significantly in their design,[8,9] with better fluid mechanics, reduced transvalvular gradient and improved durability. Bileaflet mechanical heart valves have emerged to be the standard of care with their improved hemodynamic performance and reduced cavitation.[10,11] Yet significant blood damage induced by the hinge recess and B-datum regurgitant jets imposes the need for life long anticoagulation therapy. Experimental and computational fluid dynamic studies on flow in different mechanical valve designs led to various hinge designs, shown in **Figure 1**. Clinical outcomes with these different valve designs at 10-year follow up are comparable, with occurrence of thromboembolism between 7–11%.[12–15] Mitigation of high shear in the diastolic regurgitant jets was recently addressed by Dasi et al using passive flow controllers (shown in **Figure 2**) mounted on the aortic surface of the leaflets, which reduced Reynold's shear stress in the regurgitant jets[16] and reduced overall blood damage.[17] Unique in its design, this technology is yet to be tested in animal models under chronic implantation conditions. In the interest of exploring alternatives to warfarin, dual anti-platelet therapy has been suggested as the anti-coagulant method for mechanical aortic valves. In a swine model using heterotopic implantation of a modified bileaflet mechanical valved conduit model, McKellar and colleagues demonstrated significant reduction in thrombus at 30 days in the dual-anti-platelet groups compared with warfarin, and two orders of magnitude less platelet deposition with dual therapy.[18]

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Valve Name	Valve Type	Hinge Design
Medtronic Advantage®	Bileaflet	Butterfly with outflow recess 
Medtronic Parallel®	Bileaflet	Relief Peg Model 
ATS Open Pivot®	Bileaflet	Open Pivot 
Sorin CM®	Bileaflet	Chamfered Butterfly Recess 
On-X Valve	Bileaflet	Larger inlet smaller outlet butterfly 
SJM Regent®	Bileaflet	Butterfly Recess
SJM Masters®	Bileaflet	
SM Masters HP®	Bileaflet	

Figure 1. Evolution of hinge design in various bileaflet mechanical heart valve designs since their introduction into clinical practice. [Figures reproduced from respective valve manufacturer documentation or website.]

Bioprosthetic Aortic Valves

Native decellularized and glutaraldehyde-fixed homografts or xenografts were introduced by Dr. Alain Carpentier as better alternatives to mechanical heart valves.[19,20] Decellularization eliminated the risk of immune rejection of the graft, while glutaraldehyde fixation stabilized collagen linkage. In the last decade, use of bioprosthetic valves has significantly increased with better stent designs and improved valve hemodynamics. However, structural deterioration of graft material resulting in valve failure, and calcification of the matrix fibers in the pretreated graft materials remains an issue. Specifically, in pediatric and younger patients, up to 10% failure within 4 years of implantation is reported.[21] Although the mechanisms of calcification and age-related accelerated failure are not completely understood, higher metabolic activity and the presence of higher amounts of extracellular calcium in younger patients are indicated. Currently, several methods to increase inhibit calcification are in use: (1) use of bisphosphonates that inhibit the growth of calcium crystals and stabilize bone mineral;[22] (2) treatment with trivalent metal ions that form a complex with phosphate ions and inhibit the formation of calcium phosphate;[23] (3) treatment with 2-α-amino oleic acid that covalently links with aldehyde functions and inhibits calcium flux through the tissue;[24] (4) incubation with surfactants such as sodium dodecyl sulfate, which removes the phospholipids in the graft tissue and eliminates cell membrane contributors to calcification;[25] and (5) incubation with ethanol before glutaraldehyde pretreatment that removes all

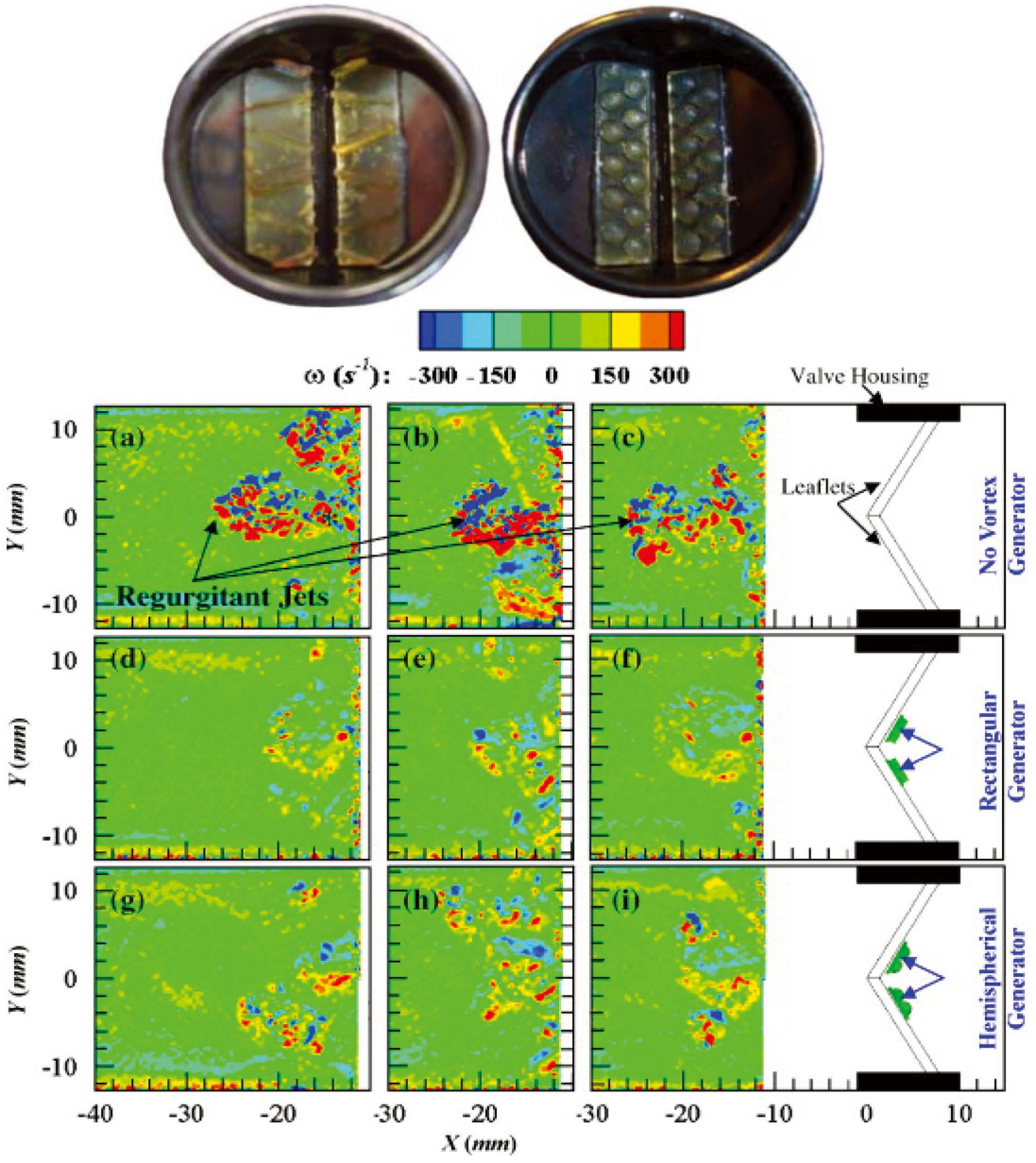

Figure 2. (**Top**) Passive leaflet flow controllers mounted on bileaflet valve leaflets. (**Bottom**) Vorticity measured in a bileaflet mechanical heart valve with and without the passive flow controllers.[16,17]

phospholipids and cholesterol from the tissue, which affects tissue interaction with water and lipids and permanently alters the collagen structure, inhibiting reaction with collagenase to avoid degeneration.[26] Some of these methods are already in commercial use after successful subcutaneous studies in small animals and large animal explant studies. Experimental and computational stress analysis studies of bioprosthetic valves demonstrated specific regions of higher stress magnitude in the leaflets (**Figure 3**), which correlate with the regions of high structural damage and accumulation of calcific deposits.[27] This evidence has fueled the recent developments in stentless and sutureless valve designs that intend to mimic physiological motion of the aortic root and potentially reduce the mechanical loading on the valve leaflets and reduce the chances of failure.

Stentless Aortic Bioprostheses As a solution to the limitations imposed by stented aortic valves, researchers, beginning with David et al in Toronto in 1988, have created stentless aortic valves as shown in **Figure 3**.[28] David et al's operating theory was that without the presence of rigid struts and a sewing ring, transvalvular gradients should be negligible. Additionally, given the inherent mobility of stentless valves, coronary sinus motion should be maintained, thus potentially reducing long-term stress on the bioprosthetic leaflets. Initial experience with subcoronary implantation of the Toronto SPV (St Jude Medical, Inc, St Paul, MN, USA) aortic valve was published in 1990.[3] As expected, the Toronto valve exhibited superior hemodynamics including increased effec-

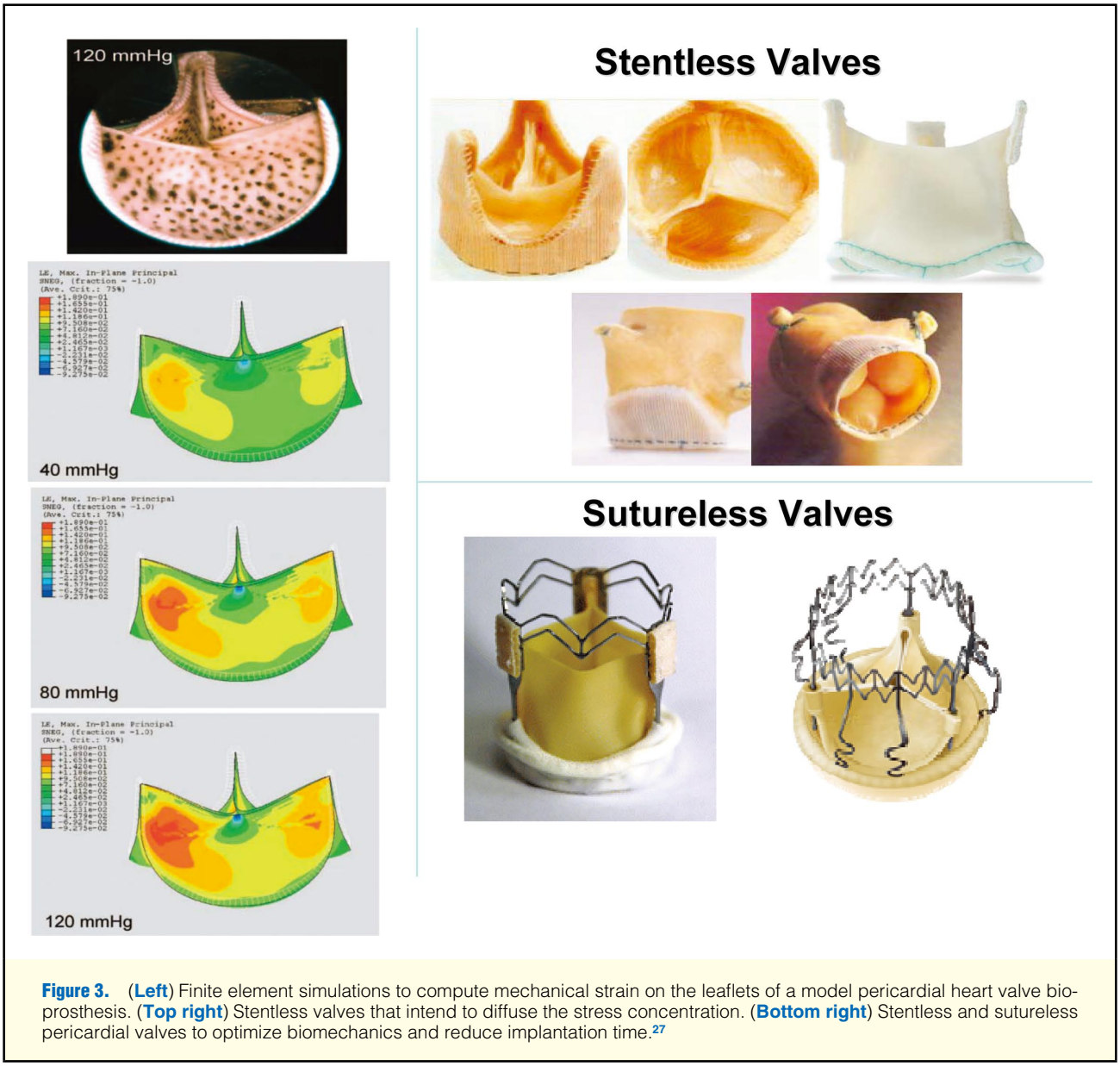

Figure 3. (**Left**) Finite element simulations to compute mechanical strain on the leaflets of a model pericardial heart valve bioprosthesis. (**Top right**) Stentless valves that intend to diffuse the stress concentration. (**Bottom right**) Stentless and sutureless pericardial valves to optimize biomechanics and reduce implantation time.[27]

tive orifice area and lower transvalvular gradients when compared with the available stented bioprosthetic valves. A further advantage of stentless valve technology was illustrated when Walther and colleagues detailed their experience with stentless bioprostheses in patients with small-diameter aortic roots.[29] They noted that significant upsizing was possible when utilizing stentless valves secondary to the increased mobility afforded by the lack of rigid material within the structure of the valve. A multitude of stentless aortic valves have since been invented, marketed, and implanted. While there have been some durability concerns associated with some valves, others have shown excellent long-term follow up with a small incidence of degeneration.[30–33] Newer stentless valves seek to maintain the conformity of the native coronary sinuses or utilize glutaraldehyde-treated autologous pericardium in order to construct a new stentless valve.[34,35]

Sutureless Aortic Valves Traditionally, prosthetic aortic valve replacement has been accomplished by placing a series of sutures circumferentially around the aortic annulus, seating the valve, and tying the sutures securely in place. All of these steps occur during a period of cardiac ischemia with the aortic cross-clamp in place. In order to decrease ischemic time, newer devices have been developed to facilitate sutureless valve implantation. A variety of sutureless valve systems have been developed, which use distinct technologies to anchor the implanted valve to the native annulus or sino-tubular junction as shown in **Figure 3**. The 3f Enable sutureless aortic valve (ATS Medical, now Medtronic, Inc, Minneapolis, MN, USA) is a pericardial valve mounted on a Nitinol frame with a polyester flange to assist in preventing paravalvular leaks. In order to insert the valve, it must first be washed in cool saline and mounted on a guide that prevents expansion. Once the native valve has been debrided, the guide is inserted into the native annulus and the valve is deployed from the guide. The valve is then irrigated with warm water in order to complete expansion and affix it in place. If re-positioning is required, the valve can be irrigated with cool saline and moved. A recent publication detailed implantation of this

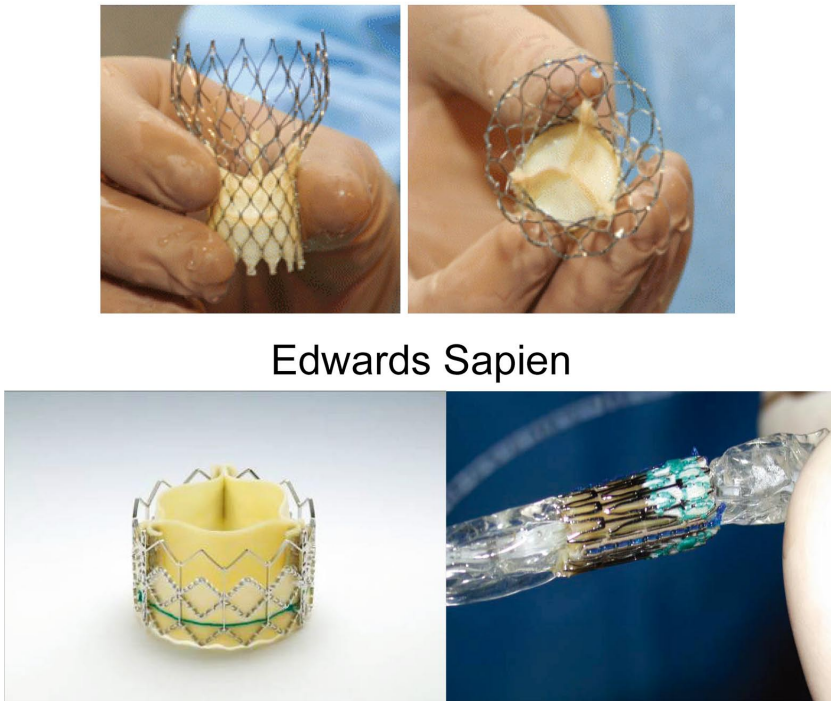

Figure 4. Photographs of the 2 most commonly used transcatheter heart valve technologies.

valve in 32 patients in which two patients were converted intraoperatively, but in the remaining 30 patients no lasting paravalvular leaks were detected with a mean transvalvular gradients at discharge were 9 mmHg.[36] Another sutureless valve, the Perceval S aortic valve (Sorin Group, Arvada, CO, USA), has been implanted in Europe since 2007 with good preliminary results.[37] Unlike the Enable valve, the Perceval S is balloon expandable, but it lacks a prosthetic flange. In a series of 30 patients, all underwent successful valve implantation with a mean ischemic time of 34 min. Of these patients, 23 were available for 1-year echocardiographic follow up, in which 2 patients presented with mild paravalvular leaks and 2 with mild transvalvular leaks. The Edwards LifeSciences Odyssey sutureless valve (formerly the Enable valve system) is currently in animal trials. The most noted advantage for sutureless valves includes the reduction in cardiopulmonary and aortic cross-clamp times and the ease of implantation with minimally invasive upper sternotomy or anterolateral thoracotomy. An expected advantage includes the reduction of paravalvular leaks secondary to partial resection of the stenotic valve leaflets and direct visualization of bioprosthetic valve implantation.

Transcatheter Aortic Valves

As an alternative to surgical implantation of an aortic valve in patients with aortic stenosis using cardiopulmonary bypass (CPB),[38] Cribier et al implanted a catheter-delivered aortic valve starting in 2002.[39] Since then, transcatheter aortic valve implantation (TAVI) under fluoroscopy has increasingly been used for patients at high surgical risk of mortality. While initially performed via a transfemoral (TF) approach, newer techniques including transapical (TA) and transaxillary approaches have been used for patients with unfavorable lower extremity vasculature.

TAVI was first performed in humans via a TF approach, and there has been a large European experience with TF-TAVI.[40] Currently, two devices are used in Europe for TF-TAVI: the SAPIEN valve (Edwards Lifesciences, Irvine, CA, USA) and the CoreValve System (Medtronic, Inc, Minneapolis, MN, USA), both shown in **Figure 4**. The SAPIEN valve is a pericardial bioprosthetic valve mounted on a stainless steel frame within a 22 or 24 (ID) French delivery system. The valve is balloon expandable and is currently available in 23 or 26 mm sizes. The CoreValve is a porcine pericardial valve, but it is mounted on a Nitinol frame. The valve is self-expanding and is mounted in an 18 or 21 French delivery system.[41] Both valves have been extensively implanted and tested in Europe and Canada and await approval in the USA, Japan, and other countries.

Many of the publications regarding TAVI to date involve mixed TF and TA populations. The SOURCE registry is a large, multi-center European collaborative designed to detail outcomes of both TF and TA SAPIEN implantations.[40] Nearly 500 patients in the registry underwent TF-TAVI, and short-term procedural success was greater than 95%. The incidence of postoperative aortic regurgitation was low at 1.5% following TF-TAVI with the SAPIEN valve. Overall 30-day mortality was 6.3% in a population of patients with a mean EuroScore of 25.7. One study that solely looked at TF-TAVI patients who were considered inoperable was the Edwards LifeSciences PARTNER 1 trial published in 2010.[42] The 30-day mortality for this cohort of patients was 5.0%, and the stroke rate was 6.7%. Notably, the rate of vascular complications was 30%, and 3.4% of patients required a permanent pacemaker. Experience with the CoreValve has been limited to European centers, and the CoreValve is also only approved currently for TF insertion. A large, multi-center registry detailing results of CoreValve implantations demonstrated a

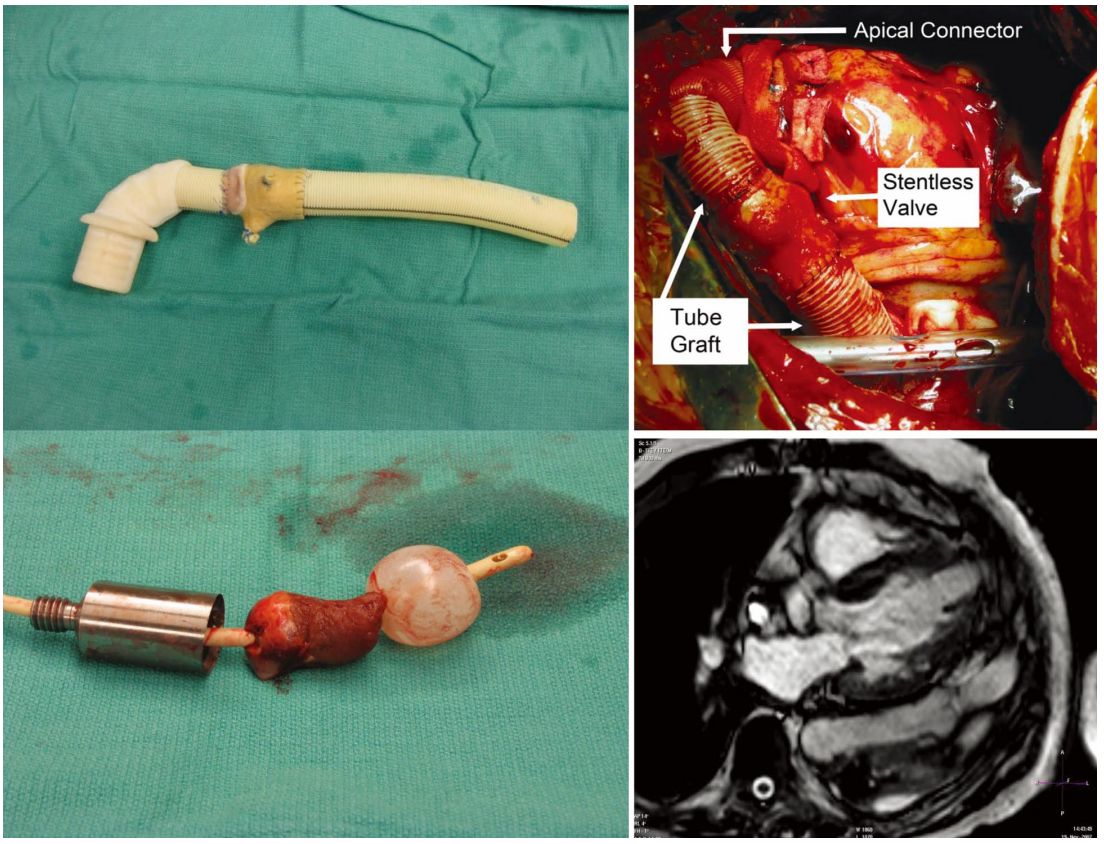

Figure 5. Photograph of an apical aortic conduit for use in patients with severe aortic calcification. (**Top left**) A Medronic freestyle valved conduit prepared for insertion into a patient's left ventricular apex. (**Bottom left**) A left ventricular coring device with an inflatable balloon. (**Top right**) The apical aortic conduit upon implantation in a patient. (**Bottom right**) Magnetic resonance angiography images demonstrating establishment of flow through the graft.

procedural success rate of 97% and a 30-day mortality of 8.0%.[43]

For patients with unsuitable lower extremity vasculature, TA aortic valve implantation offers an alternative route. TA-TAVI was first attempted in animals as a direct consequence of the large delivery systems necessary for first generation TF-TAVI devices.[44] Since that time, large series of TA implantations have been published detailing excellent results. The SOURCE registry data contained over 500 patients who underwent TA-TAVI.[40] TA patients had a higher logistic EuroScore and a higher incidence of a number of preoperative comorbidities than their TF counterparts. Interestingly, TA patients suffered a stroke rate of 2.6% and a 30-day mortality of 10.3% despite their increased preoperative comorbidities. While little long-term data exist regarding TA-TAVI, mid-term data suggest that the hemodynamic and clinical benefits of the procedure are durable out to 3 years.[45] In patients who survived longer than 30 days, the 2-year and 3-year survival in one series was 79.8% and 69.8%, respectively. Mean New York Heart Association classification decreased from 3.3 preoperatively to 1.8 postoperatively, and the mean transvalvular gradient on echocardiography at 3 years was 10.3 mmHg. While long-term data regarding TA-TAVI are not yet available, mid-term data for high-risk patients remain favorable.

While the vast majority of TAVI's have been performed by either the TA or TF methods of implantation, the subclavian artery has also been used as a site of catheter delivery. As only the SAPIEN valve can be implanted transapically, the published series to date involving subclavian or axillary access have involved the CoreValve bioprosthesis. A series of 17 patients undergoing transaxillary insertion of the CoreValve demonstrated excellent procedural success using this approach.[46] Importantly, all patients in this series underwent open vascular repair following sheath withdrawal without major vascular complications. However, there were 2 patients who suffered transient brachial plexus injuries and subsequent arm numbness following the supraclavicular approach. All patients exhibited excellent valve function at the short-term follow up, thereby validating the transaxillary approach as a safe and effective route of insertion for TAVI.

Aortic Valve Bypass

Aortic Valve Bypass (AVB), an old procedure for aortic stenosis, has recently gained momentum in the USA as an alternative to transcatheter techniques for patients who either do not have access or are ineligible for TAVI. First described in the 1950s, this procedure was largely abandoned in adults and used almost exclusively in children with congenital aortic stenosis. As a greater number of older patients are surviving multiple cardiac procedures via sternotomy, this procedure has been revisited as an alternative to avoiding hostile medi-

Table. Summary of Polymeric Materials Used for the Development of Artificial Heart Valves[51]

Material	Advantages	Drawbacks
Silicone	Flexible and biocompatible	Not durable; thrombogenic
PTFE	Good hemodynamic properties	Low resistance to thromboembolism and calcification; free edge inversion and leaflet stiffening
PU-Polyester urethane/-PEU/-PCU	Good viscoelasticity; resistant to hydrolysis; low resistance to oxidation and prone to calcification	Biodegradation and calcification are the main issues
PVA	Good mechanical properties	Not suitable for dip casting
SIBS	Enhanced resistance to hydrolysis and oxidation	Causes platelet activation and thrombogenic
PDMS–PHMO/PU	Biostability and mechanical properties	Difficult to manufacture
POSS-PCU nanocomposite	Excellent resistance to oxidation, hydrolysis and calcification; biocompatible and antithrombogenecity	Not reported yet

PTFE, polytetrafluoroethylene; PU, polyurethane; PEU, polyether urethane; PCU, polycarbonate urethane; PVA, polyvinyl alcohol; SIBS, poly (styrene-block isobutylene-block-styrene); PDMS, polydimethyl siloxane; PHMO, polyhexamethylene oxide; POSS, polyhedral oligomeric silsesquioxane.

astinum, patent grafts following coronary revascularization, porcelain aorta, or a combination of these risk factors.

AVB is performed via a left thoracotomy with single lung ventilation, thus obviating patients with poor preoperative pulmonary function determined by pulmonary function testing. The conduit is constructed on the back table prior to incision using a stentless porcine aortic valve sewn in series with an apical connector device, as shown in Figure 5. After systemic heparinization, the distal anastomosis to the descending aorta is completed using a running polypropylene suture, and the proximal anastomosis to the ventricular apex is performed using a stab incision under rapid ventricular pacing and a urinary catheter to avoid blood loss, as shown in Figure 5. While this procedure has not been widely used, results at certain centers have been encouraging. We and others have published single-center series on the use of an AVB with and without the assistance of CPB.[47–49] Perioperative mortality in this cohort ranges from 10–13%, and one patient suffered a postoperative stroke. Renal function was unchanged in these patients following bypass insertion. Notably, echocardiographic flow across the conduit represented greater than two-thirds of cardiac output. It is possible that avoidance of CPB might be important for some patients, including those with bleeding diathesis or cirrhosis who cannot tolerate even short periods of CPB. AVB performed either with or without CPB is a viable alternative for high-risk patients who are currently ineligible for TAVI.

Polymeric Aortic Valves

Polymeric materials that can be mechanically, structurally and biologically tuned for heart valve implants are gaining attention. Recent advances in material science have produced durable polymers that allow endothelialization and are hemocompatible, thus bringing polymeric heart valves into the limelight after their initial failure in animal models due to poor durability.[50–54] Table summarizes the different polymeric materials used for heart valve design, and their advantages and negative attributes. With advances in material sciences and a growing need for small profile transcatheter heart valves, polymeric valves might define future technological developments in the aortic position.

Innovations in Mitral Valve Technologies

While much innovation and interest in recent years has focused on aortic valve therapies, many new surgical and transcatheter mitral valve innovations are being tested for clinical use. Developments in annuloplasty ring designs have focused on lesion-specific geometries of annuloplasty rings, novel flexible materials to preserve native annular dynamics, and adjustable ring designs. Few transcatheter mitral technologies are currently in clinical trials, all of which mimic surgical procedures. Most of these surgical and transcatheter innovations address mitral regurgitation due to organic mitral valve disease, in which the primary cause of regurgitation is either leaflet distension or chordal rupture. Attempts to translate these technologies to the more challenging lesion of functional mitral regurgitation in a dilated and dysfunctional left ventricle have met with very limited success.

Innovations in Surgical Mitral Annuloplasty Rings

Ring Shape Among the gamut of novel ring shapes, four annuloplasty rings (Medtronic® Profile 3D, Minneapolis, MN, USA; Sorin Biomedical Memo3D, Torino, Italy; Edwards Lifesciences® Physio II, Irvine, CA, USA; SJM Rigid Saddle Ring, Minneapolis, MN, USA) with a 3D saddle shape were introduced, as shown in Figure 6, based on experimental evidence on the mechanical advantage of the saddle shape.[55–59] The long-term benefit of these rings in the true clinical setting of a diseased mitral valve is yet to be assessed. Two annuloplasty rings (Edwards Lifesciences® ET-logix IMR, Irvine, CA, USA and Edwards Lifesciences Geoform, Irvine, CA, USA, Figure 6) with specific geometric features that propose to augment the posterior leaflet mobility in the setting of Type IIIb functional mitral regurgitation were introduced. The ET-logix IMR ring has a reduced septal-lateral dimension at the A1-P1 commissural section of the ring, which specifically addresses functional mitral regurgitation induced by posteromedial papillary muscle displacement, whereas the Geoform® ring has a basal hunch at the P2 annular segment, which provides a basal force to relocate the displaced papillary muscle and improve the posterior leaflet mobility during systole.

Adjustable Annuloplasty Rings Optimal ring sizing to establish sufficient leaflet coaptation and eliminate mitral regurgitation remains challenging to perform on a flaccid heart. To overcome this challenge, several dynamic annuloplasty rings whose size can be adjusted postoperatively under echocardiographic guidance are currently in development and are shown in Figure 6. SJM Attune® and ATS Simulus ADJ® are the only Food and Drug Administration (FDA)-approved adjustable ring designs that are based on a drawstring mechanism for postoperative size tuning. MitralSolutions®

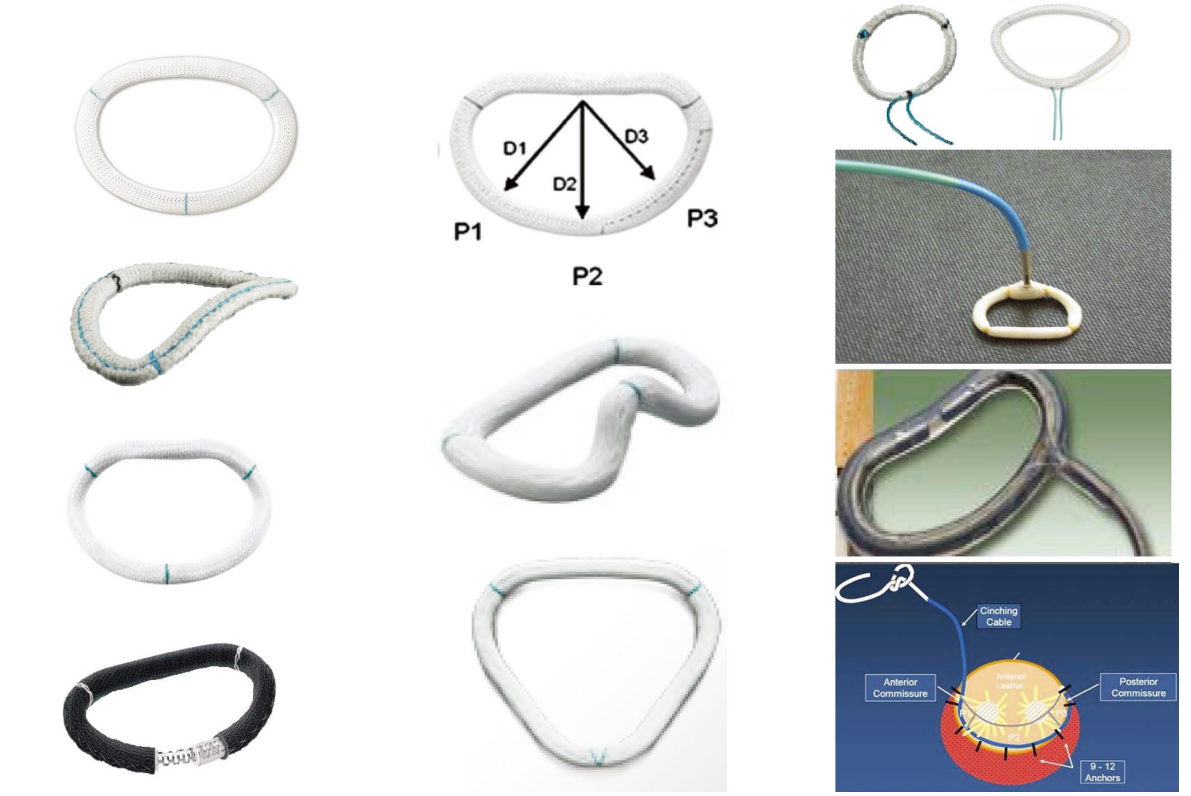

Figure 6. Summary of the most recent advancements in mitral annuloplasty ring development. [Figures reproduced from respective manufacturer website or promotional material.]

(Ft Lauderdale, FL, USA) has reported successful clinical results with a novel gear-based adjustability system, whose size can be adjusted using a catheter system under echocardiographic guidance on a beating heart several months after surgery. Based on a similar concept, MiCardia® (MiCardia Inc, Irvine, CA, USA) has developed a dynaplasty system using an energy absorbing material, which reduces in size upon application of energy to the ring via a remote catheter. The Accucinch® annuloplasty system from Guided Delivery Systems® (Santa Clara, CA, USA) uses a multi-link chain deployed percutaneously into the muscle surrounding the mitral annulus, which can be adjusted in length to cinch the posterior segment of the mitral valve. The MitralSolutions® and MiCardia® annuloplasty systems were tested in a European clinical trial, and the results from these studies are awaited.

Transcatheter Mitral Annuloplasty

Coronary Sinus Devices The coronary sinus approach to mitral annuloplasty is one of the earliest percutaneous mitral valve technologies, designed to achieve reduction in septal lateral dimension of the mitral annulus by exerting force on the poster annulus using an adjustable device implanted into the coronary sinus, as shown in **Figure 7**.[60] Commercial development of this technology was pioneered by Edwards Lifesciences® (Irvine, CA, USA) with the Monarc® system that consists of two self-expandable stents and a bridge spanning the length between the stents consisting of biodegradable chord.[61] Upon implantation, the chord gradually degrades inducing compression of the spring elements, thus inducing annular compression and reduction in the septal lateral dimension. This device was subsequently followed by the Carillon® system from Cardiac Dimensions Inc (Kirkland, WA, USA), which consists of two adjustable proximal and distal anchors and a Nitinol® bridge, which can be progressively shortened during implantation to assess the optimal size for effective reduction of mitral regurgitation. This device is introduced through the jugular vein and implanted into the coronary sinus using the two anchors that compress against the coronary sinus wall, thus providing traction for the device. The third device that has generated much enthusiasm is the PTMA coronary sinus device from Viacor Inc, which consists of a flexible hollow catheter inserted into the coronary sinus, into which up to three Nitinol rods of different stiffness can be inserted to reshape the coronary sinus. Few other technologies such as the NIH-Cerclage device and the Ample PS3 device are in the early stage of development in animal models.

Initial clinical experience with these devices is encouraging from a device implantation and safety standpoint, but has been suboptimal and highly variable in relevance to the functional outcomes.[62] The EVOLUTION-I trial demonstrated the feasibility and safety of the Monarc® device implantation in 82% of patients enrolled in the trial, with significant reduction in mitral regurgitation in the majority of them. However, at the 30-day follow up coronary compression was observed

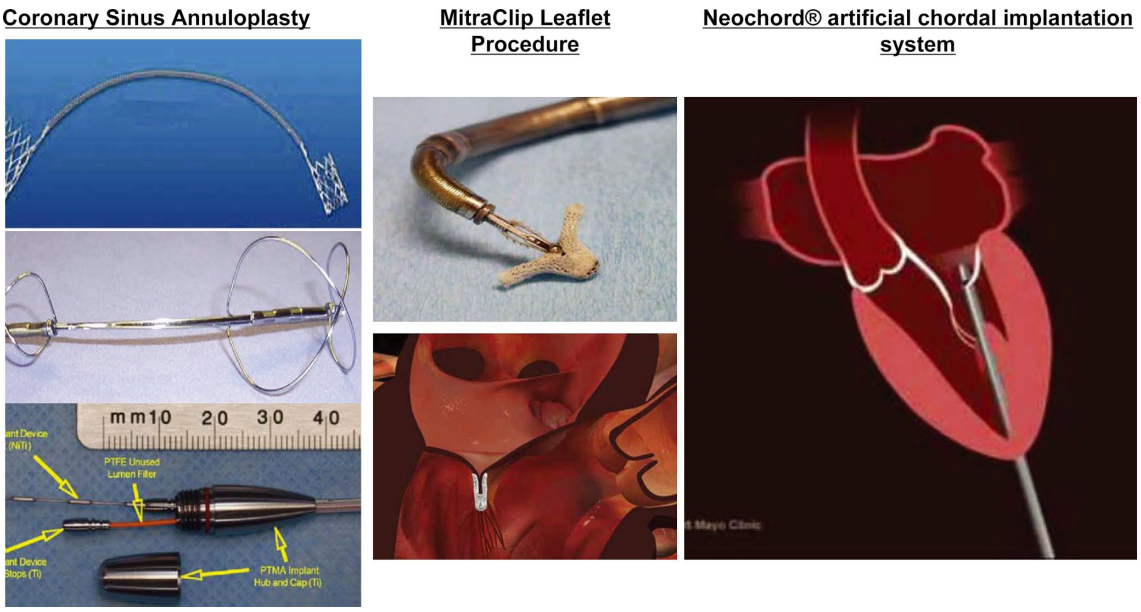

Figure 7. Transcatheter advances in mitral valve repair at the annular, leaflet and chordal levels. [Figures reproduced from respective manufacturer website or promotional material.]

in more than 25% of patients, and major cardiovascular complications and death were reported in 9% of patients. The AMADEUS trail using the Carillon® device demonstrated successful implantation in 60% of patients, with over 30% of the total patients requiring recapturing of the device due to various complications, which included coronary compromise, insufficient reduction in regurgitation and device fracture. The overall rate of major adverse coronary events was 14.6% at 30 days, which questions the safety and efficacy of this device. The PTOLEMY I trial using the Percutaneous Transvenous Mitral Annuloplasty system (PTMA) recently reported results in 27 patients, of which only 9 patients underwent permanent implantation due to device instability, unsuccessful acute reduction in mitral regurgitation, or technical difficulties in implantation. Of these patients, 1 patient required device removal at 1 week due to device fracture, 1 patient died at 3 months due to progressive congestive heart failure, and 3 underwent surgical annuloplasty due to progressive worsening of the severity of regurgitation. Only 4 patients (17%) remained with successful implantation of the device at 17 months after implantation, and comprehensive clinical understanding of the device efficacy remains to be reported.

These preclinical and clinical studies have demonstrated the feasibility of implanting a device in the coronary sinus and their short-term safety, but their suboptimal functional efficacy might be attributed to several anatomical factors. In an anatomical study of normal cadaveric hearts, Maselli et al reported that the coronary sinus was not in proximity of the mitral annulus in most humans, but was vertically away from it, running along the left atrial surface.[63–65] In a more recent study, Plass et al also reported high variability in the angle between the coronary sinus and the mitral annulus, with a significant proportion of patients presenting with an oblique orientation of the sinus.[66] This oblique orientation of the coronary sinus not only reduces the ability of the inserted device to induce reduction in the septal lateral dimension of the mitral annulus, but also causes compression of the circumflex artery.[65] Additionally, the mitral annulus is a dynamic structure with a sphincteric motion involving complex translational and rotational components, and interaction of the mitral annulus with the coronary sinus through the cardiac cycle might govern the efficiency of these devices that are designed for a more static environment. These anatomical constraints will not only induce high variability in patient outcomes using the same device, but might also fail in a variety of ways due to complexity in the mechanical loading in each patient, complicating the design specifications and safety testing protocols for such devices.

Certainly, it is too early to assess this technology on the short-term fallouts and the long-term benefits, but this technology might act as a bridge in those patients diagnosed with mild levels of mitral regurgitation who are thus too early for surgery, or might work additively with other percutaneous techniques to reduce mitral regurgitation in patients who are high-risk candidates for conventional surgical repair.

MitraClip The MitraClip System (Evalve Inc, Menlo Park, CA, USA) shown in **Figure 7** is a transcatheter clip that seeks to recapitulate the edge-to-edge leaflet repair technique popularized by Alfieri.[67,68] This device features a stainless steel clip that captures the anterior and posterior leaflets and affixes them together, effectively creating a double-barreled mitral valve outlet. It is loaded into a 24 French catheter and requires a trans-septal puncture in order to gain access to the left atrium. The initial experience with the MitraClip, named the EVEREST trial, involved 27 patients with mostly degenerative mitral disease, 22 of whom underwent successful clip deployment. There were no peri-procedural deaths, and only one patient suffered a post-procedure stroke. However, at 1 month only 14 patients maintained a mitral regurgitation grade of 2+ or less.

Mid-term results of the EVEREST trial were published in 2009, and the results were somewhat encouraging.[68] This

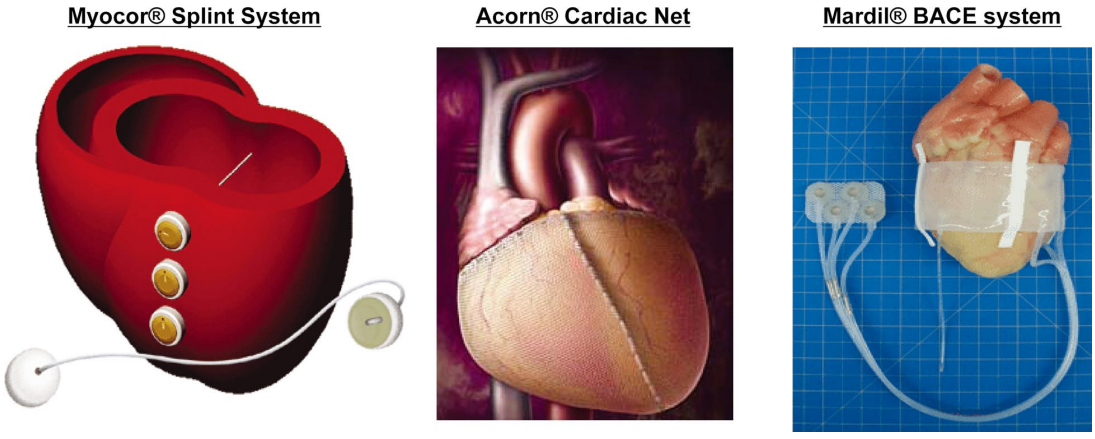

Figure 8. Ventricular restraint or reshaping devices currently in development or clinical testing to address patients with mitral regurgitation due to remodeled and dilated left ventricles. [Figures reproduced from respective manufacturer website or promotional material.]

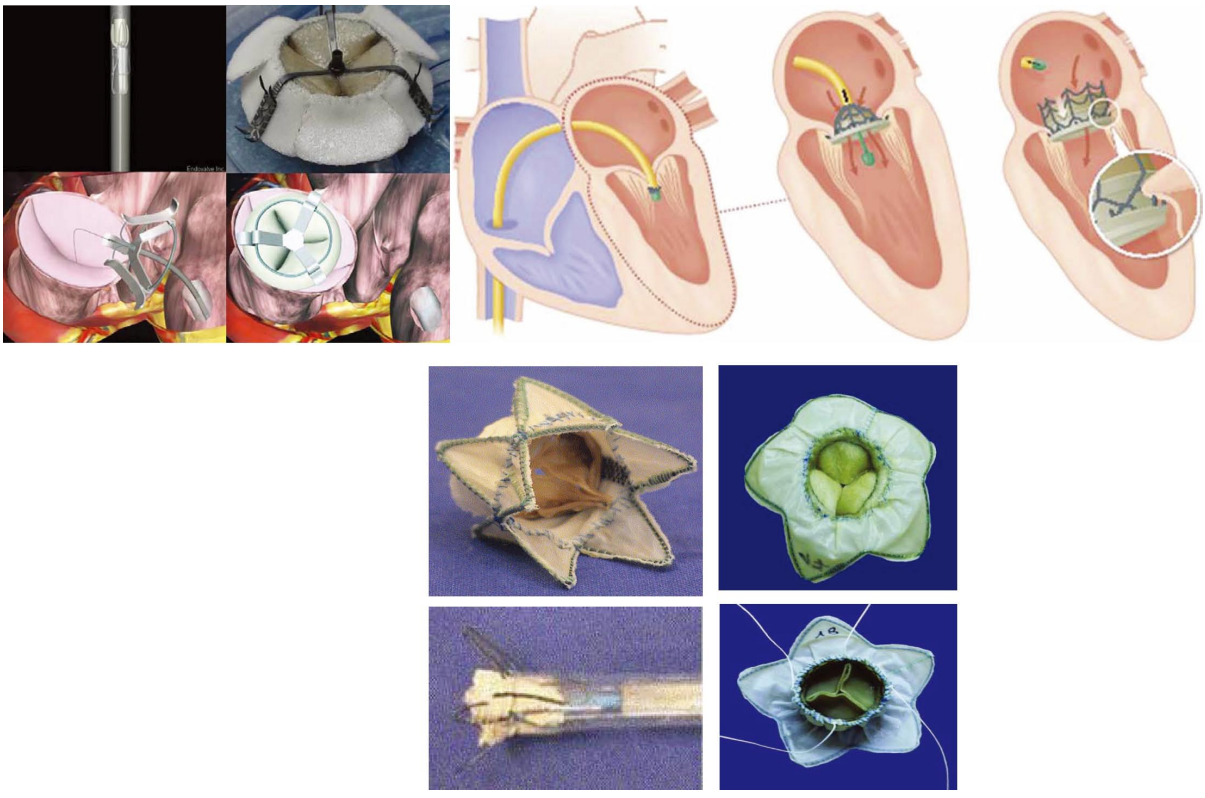

Figure 9. Transcatheter mitral valve replacement technologies that are currently in development.[80–82]

cohort included 107 patients with a planned follow up of 12 months. A greater number of patients with functional mitral regurgitation were included in this study (21%), but the preponderance of patients had degenerative or combined degenerative and functional mitral disease (79%). Procedural success in this trial was similar to previous reports at 74%, and 64% of patients undergoing successful clip placement were discharged from hospital with a mitral regurgitation grade of 1 or less. Importantly, two-thirds of patients who were successfully implanted were free from death, mitral valve surgery, or mitral regurgitation of 2 or more at 12 months. These results prompted the EVEREST investigators to launch a trial comparing the MitraClip device to conventional mitral valve repair.[69] The trial called for 2:1 randomization of a device to

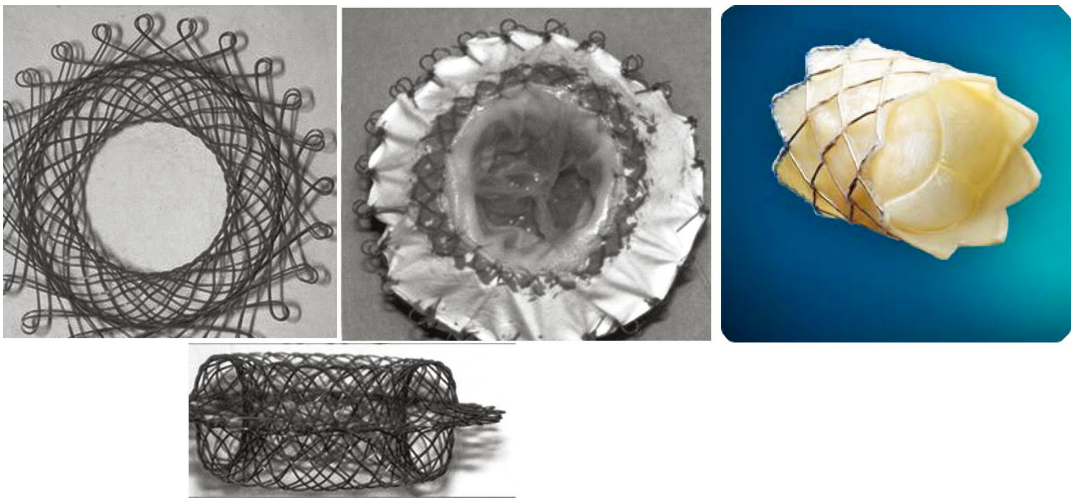

Figure 10. Transcatheter technologies for right heart valve replacement that are currently in development or already in clinical use under humanitarian approval from US Federal Drug Administration mandate.[83,85]

traditional therapy, and close to 280 patients are to be enrolled.

With successful surgical implantation of neochordae for rupture chordae tendineae, and improved valve hemodynamics demonstrated from bioengineering[70] and clinical studies,[71,72] there is now interest in developing transcatheter chordal replacement devices. Neochord (Minnetonka, MN, USA) were the first to license and develop a technology to implant a single neochord via a TA access site (**Figure 7**), and preliminary clinical studies on the efficacy of the device are currently underway. Other such devices are currently in development, but minimal data on the efficacy of these devices is currently available.

Ventricular Restraint Devices

In an effort to mechanically affect ventricular remodeling acutely for patients with functional mitral regurgitation, several ventricular restraint devices were developed, as shown in **Figure 8**. The Coapsys device (Myocor, Inc, Maple Grove, MN, USA) is one of the earlier innovations with clinical data, with other global reshaping devices such as Acorn® Pericardial net and Mardil BACE® device. The Coapsys® device has an adjustable subvalvular cord with pads that anchored to the epicardium, which sought to decrease the septal lateral dimension of the left ventricle to improve mitral leaflet coaptation. This device held promise as it served to improve mitral coaptation without utilizing the coronary sinus. Additionally, leaflet integrity was preserved, as was the native conformation of the mitral annulus. Early work involving animal models and the Coapsys device were promising. In an animal model of acute mitral regurgitation (MR) via rapid ventricular pacing, 10 canines experienced a mean reduction in MR grade from 2.9 to 0.6.[73–76] After 8 weeks, the reduction in MR was durable, and MR recurred when the subvalvular cord was cut.[77]

Initial success in animal models led to human implants. A report from investigators in India detailed the 1-year outcomes of 34 patients who underwent Coapsys implantation.[78] Reduction in mean MR grade for this cohort was from 2.9 to 1.1, and mean New York Heart Association heart failure classification decreased from 2.5 at baseline to 1.2 at follow up. Importantly, no patient required repeat operation for worsening mitral regurgitation, and no patients were admitted to hospital for heart failure. A larger randomized trial was undertaken with corporate underwriting to compare the Coapsys device against traditional mitral repair techniques.[79] Although the trial did not reach full enrollment due to financial constraints, the results were notable nonetheless. Patients with functional MR were randomized to either CABG plus mitral repair or CABG alone at the discretion of the treating surgeon. Within each experimental arm, half of the patients underwent CABG plus Coapsys implantation. After a 2-year follow up, patients undergoing Coapsys implantation showed a survival advantage compared with patients undergoing CABG plus mitral valve repair or CABG alone. In the stratum of patients undergoing mitral valve repair plus CABG, patients undergoing mitral valve repair had a greater decrease in MR than patients who underwent CABG plus Coapsys implantation. While this technology held promise for patients with functional MR, the future of this device is unknown after its sale to Edwards Lifesciences®.

Transcatheter Mitral Valves

Due to the success of transcatheter aortic valve replacement and transcatheter mitral repair techniques, recent research has focused on transcatheter mitral bioprostheses. Chinese researchers first used a double-crowned fixation system on a Nitinol stent constructed around a homograft as shown in **Figure 9**.[80,81] These valves were inserted in a trans-atrial fashion in 8 swine with resultant mild paravalvular leaks in 3. One pig died unexpectedly prior to termination of the experiment due to obstruction of the left ventricular outflow tract by the stent. A group of German investigators constructed a Nitinol frame-supported pericardial tricuspid valve, and a star-shaped atrial fixation system covered with polytetrafluoroethylene for implantation in the mitral position, as shown in **Figure 9**.[82] Seven swine initially underwent implantation, of which 6 survived without paravalvular leaks or device migration after 60 min of implantation. The same group recently published a survival series in an animal model where swine survived on average of 7 days.[83] However, the animals who died early after implantation were found to have stent mal-

position at necropsy. In the USA, EndoValve® and CardiAQ technologies have reported acute animal studies using novel fixation systems, as shown in **Figure 9**, but the stability or chronic outcomes of the devices are currently unknown. Transcatheter mitral valve replacement represents an area of ongoing research but is limited by challenges posed by the anatomy of the mitral valve apparatus and difficulty with valve fixation.

Other Valve Technologies

Although the bulk of novel device technologies have centered on treating aortic and mitral valve disease, investigators have also sought to apply similar technologies to right-sided heart valve disease as well. French researchers developed a transcatheter tricuspid valve constructed on a Nitinol frame with two fixation disks using valved bovine jugular vein segments, as shown in **Figure 10**.[84] It was deployed via an 18F delivery system in 8 sheep, who endured varying lengths of implantation according to experimental design. At deployment, one animal suffered malposition of the valve and a subsequent severe paravalvular leak. For animals surviving 1 month, there was no increase in transvalvular gradients by echocardiography.

The pulmonic valve provides a unique opportunity for novel device therapies given its similarities in anatomy with the aortic valve. Additionally, multiple reoperations on adults and older children with congenital heart disease following right ventricular outflow tract (RVOT) reconstruction with or without a valved conduit provide a perfect setting for transcatheter intervention. The Melody Valve (Medtronic, Inc, Minneapolis, MN, USA) shown in **Figure 10** is a transcatheter pulmonary valve approved in the USA for insertion into degenerated RVOT conduits. It is deployed via a 22F delivery system and is designed for conduits greater than 16 mm in original diameter.

An initial animal model involving transcatheter pulmonary valves was published in 2000 with excellent early results.[85] After a series of successful animal experiments, a series of successful human transcatheter pulmonary valve implantations (PVI) began to appear. Researchers in the United Kingdom reported on a series of 155 patients who underwent tanscatheter PVI using the Melody Valve.[86] The majority of these patients had some form of congenital heart disease with Tetralogy of Fallot the most common,[87] and 92% had a previously placed right ventricle to pulmonary artery conduit. Mean peri-procedural reduction in RVOT gradient was 20 mmHg, and freedom from reoperation in this cohort was 70% at 70 months. In addition to the Melody Valve, the Sapien Valve has been used in an off-label fashion in the pulmonary position.[88] Peri-procedural RVOT gradient following implantation was similar to that seen after Melody implantation in other studies. At a maximum follow up of 3.5 years, no structural valve degeneration was seen in patients undergoing Sapien implantation in the pulmonic position.

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