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Multimodality imaging to guide cardiac interventional procedures

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Percutaneous valve procedures: an update

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ABSTRACT

Valvular heart disease is an important cause of morbidity and mortality. Aortic stenosis and mitral regurgitation account for the majority of patients with native valve disease. Although surgical treatment provides satisfactory outcome, a large proportion of patients do not undergo a surgical intervention, because of the high estimated operative risk and multiple co-morbidities.

Recently, new techniques that enable percutaneous treatment of valvular heart disease have been developed and their feasibility has been reported in several studies. All techniques target a minimal invasive procedure with a low risk of procedure related complications. In this manuscript, an overview of the various percutaneous procedures for mitral and aortic valve disease will be provided. In addition, an update on the ongoing trials in percutaneous valve procedures will be presented. Finally, the role of imaging in performing percutaneous valve procedures will be discussed.

INTRODUCTION

Valvular heart disease is an important cause of morbidity and mortality. Aortic stenosis (AS) and mitral regurgitation (MR) account for the majority of native valve disease (1,2). Although surgical treatment has good outcome in most patients, operative risk may be high due to age and co-morbidity. Importantly, a large proportion of patients (in particular with AS) are not referred for surgery. Data from the recent Euro Heart Survey on valvuluar heart disease, revealed that up to 30% of the patients with severe valvular disease did not undergo surgery, although an indication existed (3). The high estimated operative risk, multiple co-morbidities and patient's age are the main reasons for denial of surgery. Therefore, there is a need for alternative procedures, particularly in the elderly.

Over the past few years, techniques for percutaneous valve repair and replacement have been developed and feasibility has been reported in numerous studies, both in animal models and randomized trials in patients (4). All techniques target a minimal invasive procedure with a low risk of complications. This review provides an overview of the various percutaneous procedures for mitral and aortic valve disease and a summary of the ongoing trials. Moreover, the role of imaging in these percutaneous valve procedures is also discussed.

PERCUTANEOUS MITRAL PROCEDURES

Several percutaneous approaches for the treatment of mitral valve (MV) stenosis and MR are available. The field of percutaneous MV repair has many important differences compared to percutaneous aortic valve (AV) replacement. The anatomy or mechanism of MR may involve one or more elements of the MV apparatus. The patient population, depending on the mechanism of regurgitation, can vary in age, co-morbidities and symptomatology. The timing of intervention and the goals (or endpoints) of treatment are also less well defined. The surgical "gold standard" is not as readily identifiable when different mechanisms of MR are critically analyzed. Therefore, the development and evaluation of MV technologies pose unique challenges compared to the percutaneous AV replacement. The different percutaneous MV procedures are summarized in Table 1, and will be discussed in the following paragraphs.

Percutaneous mitral commissurotomy

Balloon commissurotomy is now an accepted therapy for selected patients with rheumatic mitral stenosis (1,2). It has been shown that percutaneous mitral commissurotomy provides excellent early hemodynamic effects, and a lower rate of residual stenosis and restenosis as compared with surgical mitral commissurotomy (5). Currently, percutaneous mitral commissurotomy is typically performed utilizing the Inoue technique with transseptal access to the left atrium and antegrade access to the MV and the use of a self-seating balloon (6). The goal

Table 1. Percutaneous mitral valve procedures reported to date

Approach	Device	Feature	Company	Status
Leaflet repair				
	MitraClip	Edge-to-edge clip	Evalve	Pivotal
	Mobius	Edge-to-edge suture	Edwards Lifesciences	On hold
Coronary sinus annuloplasty				
	MONARC	Delayed effect	Edwards Lifesciences	Clinical data
	PTMA	Late adjustment	Viacor	Clinical data
	Carillon	Adjustable	Cardiac Dimensions	Clinical data
Direct remodeling				
	Coapsys	Transmyocardial cord (minimal invasive)	Myocor	Clinical data
	iCoapsys	Transmyocardial cord	Myocor	Clinical data
	PS^3	Transatrial cord	Ample Medical	Clinical data
Annular plication				
	Mitralign	Left ventricular procedure	Mitralign	Preclinical
	Accucinch	Left ventricular procedure	Guided Delivery Systems	Preclinical
Annular shrinking				
	QuantumCor	Radiofrequency	QuantumCor	Preclinical
Valve replacement				
	Endovalve	Catheter delivered valve	Endovalve	Preclinical

is to produce a controlled tear of the fused MV commisures. Since this is a well-established procedure, and has been studied extensively, percutaneous balloon mitral commissurotomy will not be reviewed in detail here.

Paravalvular leak closure

Paravalvular leaks may occur following surgical valve replacement due to suture dehiscence, endocarditis or technical errors. When regurgitation is hemodynamically significant or results in clinically important hemolysis, percutaneous closure may offer an alternative to re-operation in high risk patients and patients with contraindications for surgery (7). Only selected defects are suitable for percutaneous closure. In general, multiple defects, defects that measure above 8 mm in diameter, or extend over a broad circumference of the valve, cannot be effectively dealt with. A variety of implantable devices have been utilized. At present, coils are favored for very small defects, patent ductus devices for medium defects and atrial septal occluders for larger defects. However, more experience is needed to fully understand the best strategy and optimal approach for patients with paravalvular leakage (7).

Leaflet repair (Edge-to-edge)

The most advanced percutaneous mitral repair procedure is the edge-to-edge repair procedure with the Evalve Percutaneous Mitral Repair System or MitraClip® device (Evalve Inc., Menlo

Park, CA) modeled after a surgical procedure which has been shown to be effective in selected patients (8). Alfieri surgical repair involves suturing a small segment of the anterior mitral leaflet to the posterior leaflet. The result is a double-orifice MV with improved leaflet coaptation. The percutaneous procedure using the MitraClip device (Figure 1) involves transseptal cannulation of the left atrium, and positioning of the delivery catheter perpendicular to the MV. During echocardiographic guidance, a clip is placed to appose the anterior and posterior MV leaflets, creating a double-orifice valve (9). An example of the percutaneous edge-to-edge repair with the use of the MitraClip is shown in Figure 2.

A similar procedure utilizing percutaneously placed sutures (Mobius™, Edwards Lifesciences Inc., Irvine, CA) has been reported (10). However clinical trials have been put on hold due to the technical difficulty of suture placement and poor durability.

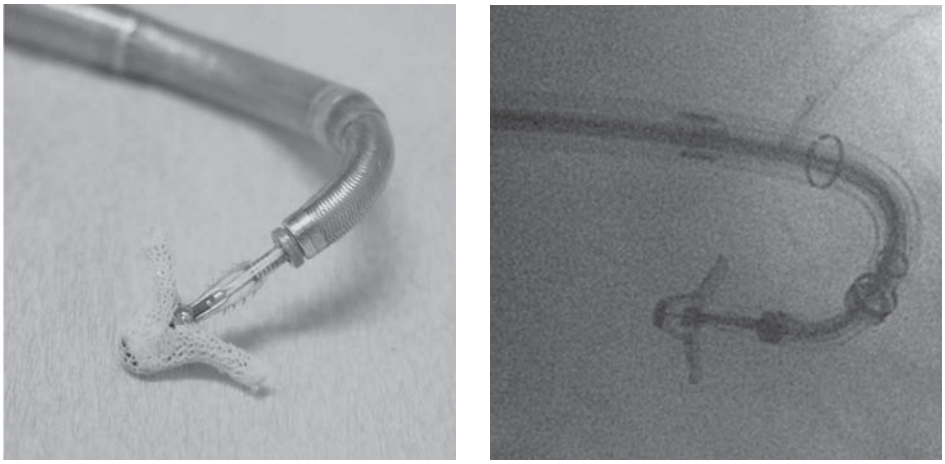

Figure 1. The MitraClip device is a 2-armed, polyester-covered, soft tissue–fixation device (left panel). The outside dimension when closed is 4 mm; in the grasping position, the 2 "arms" span about 20 mm. In the open position, it is used to grasp and immobilize the central mitral leaflet scallops by retraction of the delivery catheter. Each arm has an opposing "gripper" that aids in securing the leaflets in the clip by means of small, multipronged friction elements. All these elements are clearly visible on fluoroscopy (right panel).

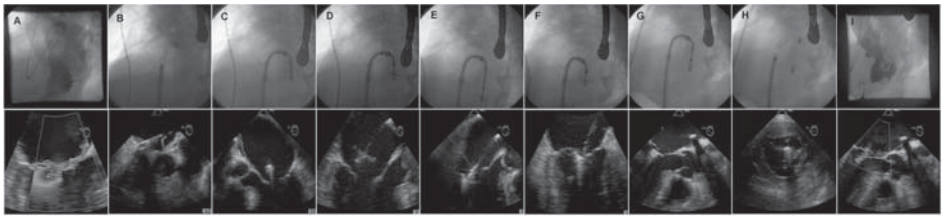

Figure 2. Outline of the percutaneous MV repair procedure (MitraClip) using fluoroscopic and echo guidance. Severe MR is seen by transthoracic and transesophageal echocardiography (panel A). The device sheath is placed in the left atrium after transseptal puncture (panel B). The clip is advanced just above the MV in the closed configuration (panel C). The MitraClip is then opened in the left atrium (panel D) and advanced into the left ventricle (panel E). Subsequently, the clip is pulled back in systole to stabilize the MV leaflets (panel F), the grippers are quickly lowered and the clip is closed (panel G). After confirming that the leaflets are adequately captured between an arm on the ventricular side and a gripper on the atrial side, the clip is closed in a locked position. Once a functioning double-orifice mitral valve is confirmed with echocardiography, the clip is detached (panel H). There is minimal MR after the procedure with excellent procedural outcome.

Coronary sinus annuloplasty

This approach is based on the close anatomical relation of the mitral annulus with the coronary sinus. Several devices for this approach exist. The MONARC^{TM} device (Edwards Lifesciences Inc.) consists of a nickel titanium alloy (nitinol) implant (11). The implant itself is comprised of three sections; a distal self-expanding anchor, a spring-like 'bridge', and a proximal self-expanding anchor (Figure 3). The distal anchor is deployed in the great cardiac vein and the proximal anchor is deployed in the proximal coronary sinus. The bridge has shape memory properties that result in shortening forces at body temperature. Biodegradable suture is interwoven in the spring like bridge section, initially preventing shortening. Following implantation the suture degrades allowing the bridge section to shorten. The anchors draw the proximal coronary sinus and distal great cardiac vein together while the bridge section tenses and straightens indirectly displacing the posterior annulus anteriorly and reducing mitral annulus diameter and septal-lateral distance.

The Percutaneous Transvenous Mitral Annuloplasty system (PTMA^{TM}, Viacor Inc., Wilmington, MA) utilizes an indwelling catheter placed within the coronary sinus (12). Wire-like implants can be placed into the coronary sinus via the catheter system. A potential advantage of the system is the ability to add or remove rods to vary the effect of the device. Late adjustment is possible by surgically accessing the closed system from a subclavicular pocket.

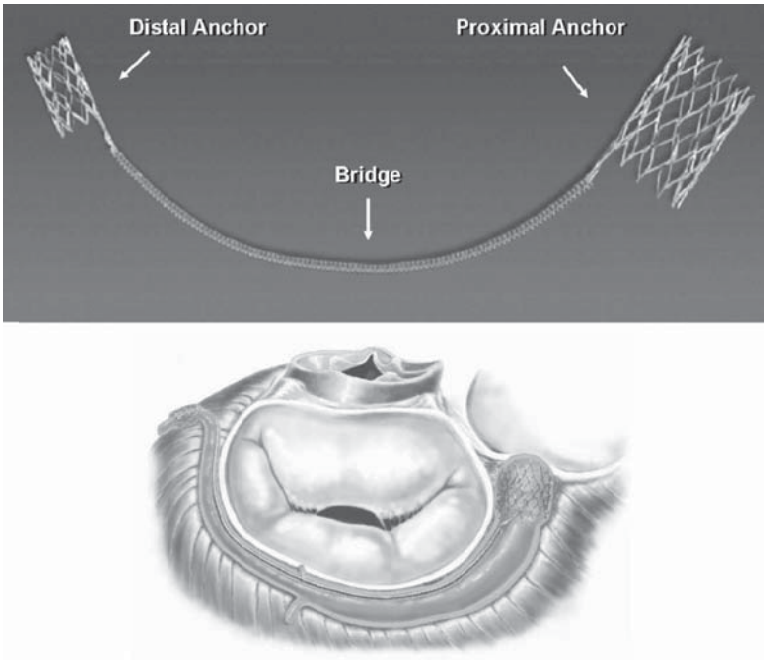

Figure 3. The MONARC device consists of two self-expanding stent-like anchors which are implanted in the coronary sinus (upper panel). The anchors are joined by a longer bridge segment which is designed to gradually shorten after implantation. As this occurs the anchors are drawn together shortening the coronary sinus and the adjacent posterior mitral annulus. The lower panel demonstrates the position of the MONARC device in the coronary sinus.

The CARILLON™ Mitral Contour System (Cardiac Dimensions Inc., Kirkland, WA) consists of a steel wire shaped with distal and proximal stent like anchors (13). The length of the central connector segment can be varied at the time of implantation to adapt the degree of shortening of the coronary sinus. Advantages of the device include the ability to adjust or remove the device at the time of implantation.

Direct remodeling

Several percutaneous techniques for direct remodeling of the left ventricle and the MV for the treatment of MR are in early testing stages. The Coapsys® and iCoapsys™ devices (Myocor® Inc., Maple Grove, MN) target remodeling of the left ventricle as well as the mitral annulus and subvalvular apparatus by implantation of a transventricular cord. The Coapsys device (Figure 4) consists of three epicardial pads implanted on the exterior surface of the heart at the level of the mitral annulus using a surgical approach (14,15). A tether connecting the three anchors can be

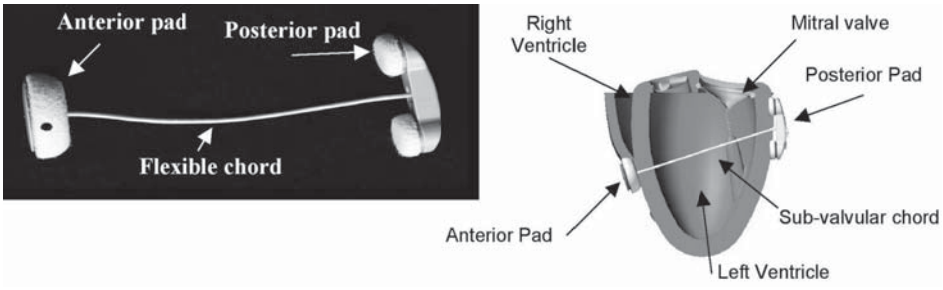

Figure 4. The Coapsys device consists of three epicardial pads and a flexible chord connecting them (left panel). The right panel schematically shows the implantation of the Coapsys device and the final position of the epicardial pads.

shortened to cause a conformational change in the left ventricle and mitral annulus. Recently, a truly percutaneous implanted version of the device entitled iCoapsys has been introduced (16). For implantation of the iCoapsys device, a specifically designed needle, guidewire and sheath are used to obtain controlled access in to the pericardial space. The posterior target zone is between the papillary muscle and the P2 segment of the mitral annulus, about two centimeters apical to the atrioventricular groove. Once proper alignment is achieved, a needle is passed from each catheter into the ventricle. A flexible wire introduced through the posterior catheter is captured by a snare from the anterior catheter. The flexible wire is used to place the transventricular cord, which is exteriorized through the delivery sheath. Then, the permanent implant device is placed over the cord, posterior pad first. Finally, the cord is tightened to achieve the desired effect, trimmed and the catheters are removed.

The Percutaneous Septal Shortening System PS^3 (Ample Medical Inc., Foster City, CA) delivers an implant into the posterior annulus with a tether attached to an atrial septal closure device. Both produce anterior movement of the posterior annulus, thereby restoring the line of coaptation (17,18). The PS^3 system differs from the Coapsys system in that it creates a transatrial

bridge as opposed to a transventricular bridge. The advantages of the PS^3 system when compared to the transventricular cinching devices include the relative ease of placement and avoidance of left circumflex coronary artery impingement. However, this transatrial approach may not result in additional advantages, such as left ventricular remodeling, as compared with the transventricular devices.

Other percutaneous mitral procedures

Several other percutaneous procedures in the treatment of MR are being evaluated in pre-clinical studies (Table 1). Percutaneous procedures that replicate surgical suture plication of the posterior mitral annulus have been developed. The Mitralign Direct Annuloplasty System™ (Mitralign Inc., Salem, NH) and the Accucinch Annuloplasty System™ (Guided Delivery Systems Inc., Santa Clara, CA) involve catheter access through the AV in order to place various types of anchors into the left ventricular aspect of the posterior mitral annulus. These anchors are attached by sutures which can then be pulled tight drawing the anchors together and plicating the mitral annulus.

The QuantumCor catheter device (QuantumCor Inc., Lake Forest, CA) targets remodeling of the MV annulus by delivery of radiofrequency energy directly to the tissue.

The Endovalve Mitral Valve Replacement System (Endovalve Inc., Princeton, NJ) is a prosthetic valve folded in into a catheter and delivered antegrade through transseptal access. The first animal study has shown the feasibility of the device, and more results are eagerly awaited.

PERCUTANEOUS AORTIC PROCEDURES

The different percutaneous AV procedures will be discussed in the following paragraphs and are summarized in Table 2.

Aortic valvuloplasty

Current guidelines indicate that aortic valvuloplasty might be useful as a bridge to surgery or as palliation in non-surgical candidates (1,2). The procedure is generally performed utilizing retrograde access from the femoral artery, although some operators prefer an antegrade, transseptal approach. Since the first reports of this procedure more than 20 years ago (19), various procedural enhancements such as lower profile balloons and sheaths, more appropriate

Table 2. Percutaneous aortic valve procedures reported to date

Approach	Device	Feature	Company	Status
Valve implantation				
	Cribier-Edwards valve	Balloon expandable	Edwards Lifesciences	Clinical data
	SAPIEN valve	Balloon expandable	Edwards Lifesciences	Clinical data
	CoreValve	Self-expanding	CoreValve	Clinical data

balloon sizing in relation to annulus diameter, and burst pacing to reduce balloon and cardiac movement during balloon inflation, may have improved outcome beyond that encountered in the early reported experience (6). Nonetheless, no survival benefit after balloon valvuloplasty has been shown (20). Therefore, at present AV balloon valvuloplasty plays a limited role in the management of degenerative AS.

Aortic valve implantation

The balloon expandable percutaneous AV was first tested in 1992 by Andersen et al. in an animal model (21). The subsequent initial human implantation was performed by Cribier et al. in 2002, via an antegrade approach, in a 57-year old man with calcific AS and cardiogenic shock (22). Immediately after valve implantation, the patient's hemodynamic conditions improved markedly with good valve function. The valve performed well over the next four months, although the patient died from complications unrelated to the procedure or the prosthetic valve. At present, two types of catheter delivered aortic prosthetic valves are available and have seen extensive clinical use.

The first is the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences Inc.), successor of the initially used Cribier-Edwards valve (Figure 5). It incorporates a balloon-expandable stainless steel stent, fabric sealing cuff and bovine pericardial leaflets. Current prosthesis sizes include 23 and 26 mm expanded size for aortic annulus diameters between 18 to 22 mm and 21 to 25 mm, respectively. Typically, a balloon valvuloplasty is performed first, and subsequently the prosthesis is deployed; both processes are performed during rapid right ventricular pacing (23). Initial procedures were performed utilizing femoral venous puncture, transseptal access to the left atrium and passage through the MV to reach the AV (22,24). However, the antegrade delivery of the AV has a potential drawback of damaging the anterior mitral leaflet as the valve traverses through the left atrium to the aorta. Currently, a retrograde approach from the femoral artery is preferred (25,26). Recently an alternative, transapical approach has been proposed

Figure 5. The Edwards balloon expandable prosthetic valve is constructed of a stainless steel stent, bovine pericardial leaflets and a fabric sealing cuff.

in patients with extensive femoral artery disease. After an intercostal incision, direct puncture of the apical portion of the left ventricular free wall is performed to gain catheter access to the left ventricle and AV (27).

The other type of catheter delivered aortic prosthetic valve is the CoreValve ReValving system™ (CoreValve Inc, Irvine, CA), consisting of a self-expanding nitinol alloy stent with a pericardial sealing cuff and leaflets (Figure 6). The device is constrained within a delivery sheath, expanding to its predetermined shape when the sheath is withdrawn (28). The CoreValve total length is 50 mm, and it has a specific design features with a waist in the middle part. The lower part of the valve is designed to expand using high radial forces; the middle part includes the pericardial tissue valve and is constrained to avoid coronary occlusion. The

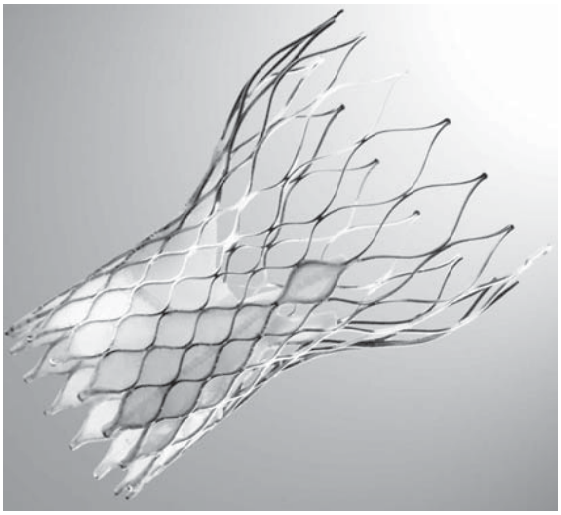

Figure 6. The CoreValve self expanding prosthetic valve is constructed of a nitinol stent and pericardial leaflets and sealing cuff.

upper part of the prosthesis enables fixation in the ascending aorta. While the first-generation device used bovine pericardial tissue and was constrained within a 24F delivery sheath, the second-generation device incorporated a porcine pericardial tissue valve within a 21F sheath. The first generation CoreValve was limited to an ascending aorta diameter of 30 mm, whereas the broader upper section of the second-generation device allowed for its deployment in an ascending aorta up to 45 mm diameter. Currently, third-generation (18F) prostheses are available with an inner valve diameter of 21 mm. The CoreValve is typically implanted retrograde from the femoral artery under fluoroscopic guidance, and a cardiac assist device, extracorporal membrane oxygenation or a full-bypass support was used in the first series (29). However, at present, the CoreValve is implanted without cardiac assist or full-bypass support. In May 2007, the CoreValve became the first percutaneous valve to receive CE mark approval in Europe.

Finally, many new percutaneous valves such as Lotus™ Valve System (Sadra Medical Inc., Campbell, CA), and the percutaneous AV from Direct Flow Inc. (Santa Rosa, CA), AorTx Inc. (Palo

Alto, CA) and Heart Leaflet Inc. (Maple Grove, MN) are also entering early human studies. The hope is that these newer valve technologies will improve on first-generation devices by using collapsible, inflatable valve frames for repositioning before final deployment and hopefully a smaller size for easy deliverability.

(PRE)CLINICAL STUDIES AND TRIALS ON PERCUTANEOUS VALVE PROCEDURES

The introduction of new technology typically involves preclinical developmental studies, phase I and phase II clinical trials. In general, it should be noted that only limited numbers of patients have been treated with percutaneous valve procedures, and that a clear learning curve for performing these procedures is present. In the following paragraphs, the reported studies and ongoing clinical trials for both percutaneous MV and AV procedures will be discussed.

Percutaneous mitral valve procedures

Leaflet repair (Edge-to-edge) For this percutaneous MV repair approach, the MitraClip is the most commonly used device. Preclinical data from a porcine model was first published in 2003 (9). Complete endothelialization and encapsulation of the clip was seen with no clip embolization or thromboembolism. The phase I prospective, multi-center safety and feasibility trial entitled EVEREST (Endovascular Valve Edge-to-Edge Repair Study) has been reported in 2005, with short-term and six-month results in the first 27 patients (30). All patients enrolled were candidates for MV surgery and had MR that was centered between A2 and P2, meeting prespecified parameters for flail dimensions or leaflet tethering to ensure device capture of the leaflets. Most patients had degenerative MV disease (n = 25, 93%). Successful deployment of the clips was achieved in 24 of the 27 patients (89%). Partial clip detachment (n = 3), severe residual MR (n = 2) and device malfunction (n = 1), required MV surgery after initial successful percutaneous clip implantation. Now that the capability to place two clips has been introduced, residual MR may become less common. Of the 27 initial patients in the EVEREST trial, 13 patients (48%) remained with MR grade 2+ or less at six months follow-up. One year follow-up on these patients shows a durable reduction in MR if initial procedural success is achieved (Figure 7) (31). The primary safety endpoint of EVEREST I was freedom from death, myocardial infarction, cardiac tamponade, cardiac surgery for failed clip, clip detachment, stroke or septicemia. A prespecified event rate of 34.4% was expected based on comparison to surgical event rates, however only 15% of patients had a major adverse event (clip detachment n = 3; stroke n = 1). The pivotal phase II trial has been initiated (EVEREST II) comparing percutaneous MV repair approach to standard cardiac surgery. The study design is a prospective, multicenter, randomized, controlled trial with a 2:1 randomization to study and control arms, respectively (Table 3).

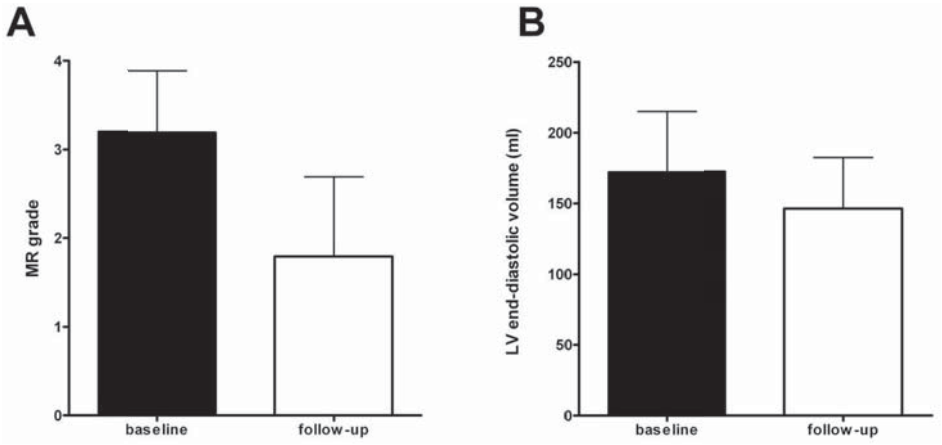

Figure 7. After 12 months follow-up, a significant improvement in MR grade (panel A) and left ventricular (LV) end-diastolic volume (panel B) was observed in 46 patients with severe MR treated with percutaneous edge-to-edge repair (MitraClip). Mitral regurgitation grade decreased from 3.2 ± 0.7 to 1.8 ± 0.9 ($p<0.001$), and LV end-diastolic volume decreased from 172 ± 43 to 146 ± 36 ($p<0.001$) indicating a sustained benefit of successful percutaneous MV repair at long-term follow-up.

Coronary sinus annuloplasty As discussed in previous paragraphs, several devices are available, each with specific features. The MONARC system has recently been implanted in patients with chronic ischemic MR. Initial results in humans showed successful implantation in four of five patients, with one failure leading to coronary sinus perforation. However, separation of the nitinol bridge segment was observed in three of four patients, and no significant changes in MR grade or mitral annulus diameter were found at follow-up (11). With additional animal experience showing improved results with the new device design, a trial using the MONARC device has started enrolling functional MR patients. The EVOLUTION trial, a multi-center feasibility and safety study in Europe and Canada, has begun with a primary safety objective of procedural success and 30-day safety, and a 90-day efficacy endpoint of reduction in MR by one grade (Table 3). Preliminary results were recently presented, showing successful implantation in 32 of 36 patients (89%). Preliminary efficacy data indicate the efficacy endpoint (MR reduction by 1 grade at 90 days) was met in 9 of 17 patients analyzed (53%) (32).

The PTMA system has also been reported to effectively reduce severe MR. In a sheep model of ischemic MR a single rod resulted in immediate reduction of MR from grade 3+ or 4+ to grade 0 or 1+ in all animals. A reduction of the mitral annulus diameter was observed (pre-insertion 30 ± 2 mm vs. post-insertion 24 ± 2 mm, $p<0.03$), without any sign of mitral stenosis (12). Human implantation has been performed in patients undergoing open heart surgery for ischemic MR (33). In four patients who had attempted implantation of the multi-lumen device, there was successful delivery in only three patients. The mitral annulus anterior-posterior diameter decreased from 41 ± 4 mm to 35 ± 2 mm, resulting in a reduction in MR from grade 2 or 3+ to 1+. Unfortunately, the PTMA device could not be implanted permanently (33). Further short- and long-term human data, including the PTOLEMY trial (Table 3), are pending.

Table 3. Ongoing trials on percutaneous valve procedures

Name	Device	Type	Design	Sample Size	Primary Endpoint	Comment
Percutaneous mitral valve procedures						
EVEREST II	MitraClip device	Randomized	Percutaneous Edge-to-Edge repair vs. surgical MV repair / replacement	390	Safety: Freedom from MAE (30 days) Efficacy: Freedom from surgery for valve dysfunction, death, and 3+ or 4+ MR	Up to 42 US and Canadian sites
EVEREST – High Risk Registry	MitraClip device	Single arm Non-randomized	Percutaneous Edge-to-Edge repair	70	Safety: Freedom from MAE (30 days) Efficacy: Freedom from surgery for valve dysfunction, death, and 3+ or 4+ MR	May continue enrollment beyond initial allocation
EVOLUTION	MONARC system	Single arm Uncontrolled	Safety and feasibility	120	Clinical Endpoints and quality of life indicators	19 sites in Europe and Canada
PTOLEMY	PTMA system	Single arm Uncontrolled	Safety and feasibility	20	Device related MAE (30 days)	Feasibility study
AMADEUS	CARILLON system	Single arm Non-randomized	Safety and feasibility	n/a	n/a	European study
COMPETENT	CARILLON system	Single arm Non-randomized	Safety and feasibility	n/a	n/a	US study
RESTOR-MV	Coapsys device	Randomized	Coapsys device vs. surgical MV repair	250	Safety: Freedom from MAE (12 months) Efficacy: Mean change in MR grade	Concomitant coronary artery bypass graft surgery
VIVID	i-Coapsys device	Single arm Uncontrolled	Safety and feasibility	30	Intra- and peri-procedural safety Intra-procedural efficacy	Enrollment not yet started
Percutaneous aortic valve procedures						
PARTNER	Edwards SAPIEN Valve	Randomized	Percutaneous AVR vs. surgical AVR	350	1-year mortality	Group A: High risk surgical patients
	Edwards SAPIEN Valve	Randomized	Percutaneous AVR vs. no AVR	250	1-year mortality	Group B: Inoperable patients

AMADEUS = cArillon Mitral Annuloplasty Device European Union Study; AVR = aortic valve replacement; EVEREST = Endovascular Valve Edge-to-Edge REpair STudy; MAE = major adverse events; MR = mitral regurgitation; PARTNER = Placement of AoRTic TraNscathetER Valve trial; RESTOR-MV = Randomized Evaluation of a Surgical Treatment for Off-pump Repair of the Mitral Valve; VIVID = Valvular and Ventricular Improvement Via iCoapsys Delivery.

The initial preclinical testing of the CARILLON system indicated that there were anatomical, design and safety issues with this coronary sinus device, as three of twelve dogs had left circumflex coronary artery ischemia, causing fatality in two dogs (13). Nonetheless, in the seven dogs with successful implantation, a reduction in mitral annular size at four weeks follow-up was observed compared to those with unsuccessful implantation (33.7 ± 2.3 mm vs. 37.3 ± 1.1 mm, $p<0.05$) (13). Subsequent experiments were done in an ovine model, demonstrating favorable acute hemodynamic effects and no mortality (34). A multi-center human safety and feasibility study is currently underway in Europe entitled AMADEUS (cArillon Mitral Annuloplasty Device European Union Study), enrolling patients with grade 2+ to 4+ functional MR and NYHA class II to IV. A Phase I investigational device exemption study entitled COMPETENT targets a similar patient population in the United States and is designed to assess hemodynamics, quality of life, and exercise tolerance (Table 3).

Direct remodeling There are several other approaches to percutaneous treatment of MR that are being evaluated (Table 1). The Coapsys, iCoapsys and PS^3 system have both proven feasible in animal and human studies and therefore are discussed at some length in the following paragraphs.

The Coapsys system involves surgical placement of pericardial implants off-pump. These implants are placed on each side of the heart, with a tethering subvalvular cord that crosses the ventricle directly. This cord is then cinched up to decrease the septal-to-lateral diameter and eliminate MR. In initial animal studies using a canine tachycardia-model of functional MR ($n = 10$), this device reduced the mean MR grade from 2.9 ± 0.7 to 0.6 ± 0.7 ($p<0.001$), without adverse consequence on ventricular function (14). The safety and efficacy of the Coapsys device has also been demonstrated in humans. In 11 patients a sustained benefit after 12 months follow-up on the severity of MR (from grade 2.9 ± 0.5 to 1.1 ± 0.6, $p<0.05$) and NYHA functional class (from 2.5 ± 0.5 to 1.2 ± 0.4, $p<0.05$) has been shown (15). The Randomized Evaluation of a Surgical Treatment for Off-pump Repair of the Mitral Valve trial (RESTOR-MV) is enrolling patients with coronary artery disease and ischemic MR, who undergo coronary artery bypass grafting combined with either traditional MV repair or Coapsys device placement (Table 3). Intra-operative results from this trial have been reported in the first 19 patients receiving the implant, showing a reduction in MR after implantation from grade 2.7 ± 0.8 to 0.4 ± 0.7 ($p<0.001$). All implants were performed successfully without cardiopulmonary bypass and no hemodynamic compromise or structural damage to the mitral apparatus was experienced (35). A similar system is currently under development for percutaneous use (iCoapsys). The device is implanted percutaneously through a pericardial access sheath, as previously described. The device was initially tested in a canine model ($n = 8$), achieving a reduction in MR grade from 3.2 to 0.7 (16). However, in the first animal studies, device placement was complicated and it has been redesigned to more closely mimic the surgically-placed device. The iCoapsys system allows for the ability to intervene in non-surgical candidates and those undergoing

percutaneous coronary intervention. This device theoretically provides a more comprehensive mechanism of action, preserving normal valve dynamics, and addressing the mitral annulus as well as the subvalvular space and abnormal left ventricular geometry. This geometric reshaping of the ventricle may be advantageous to ventricular function and remodeling and is unique to this device. The Valvular and Ventricular Improvement Via iCoapsys Delivery (VIVID) Feasibility Study will assess the safety and efficacy of the iCoapsys device in humans and is expected to be launched soon (Table 3).

The PS^3 system utilizes the coronary sinus and a septal closure device to place a cord across the atrium, create tension on the annulus, and subsequently reduce the septal-to-lateral dimension. This device has been applied to an ovine model of tachycardia-induced cardiomyopathy created by rapid right ventricular pacing (17). The degree of reduction in functional MR, and in the septal-lateral systolic distance, was the primary efficacy measure of this study. Sheep underwent short-term (n = 19) and long-term (n = 4) evaluation after implantation. The PS^3 system was successfully implanted in all animals with no evidence of left circumflex coronary artery impingement and maintenance of coronary sinus patency. The short-term results indicated a significant reduction in septal-lateral diameter from 32.5 ± 3.5 mm to 24.6 ± 2.4 mm post-procedure ($p<0.001$). This was maintained at 30-days in the long-term animals (septal-lateral diameter 25.3 ± 0.8 mm after 30 days). The results for reduction in MR in the short-term animals were similar, with an MR grade of 2.1 ± 0.6 pre-procedure versus 0.4 ± 0.4 post-procedure ($p<0.001$). This result was maintained at 30-days follow-up (mean MR grade 0.2 ± 0.1). Additional hemodynamic and laboratory data were consistent with improved cardiac function (17).

Recently, the results of the first-in-human feasibility study of the PS^3 system have been reported. In two patients with MR referred for surgical MV repair, the percutaneous PS^3 system was implanted successfully before the conventional surgical procedure. Both MR severity and septal-to-lateral diameter decreased after device implantation. No coronary impingement was noted and surgery confirmed good device position, without complications (18). Larger studies are needed to fully appreciate the strengths and limitations of the PS^3 system.

Percutaneous aortic valve procedures

Balloon-expanding valve: Cribier-Edwards Valve After extensive testing in animal models (21) and a successful first-in-man experience (22), a single center Phase 1 project was started in 2003 for compassionate use of the Cribier-Edwards valve in patients with end-stage AS (24,36). These patients had been formally evaluated by two cardiothoracic surgeons and deemed to be unsuitable for surgical AV replacement. Thirty-six patients were enrolled in the Initial Registry of EndoVascular Implantation of Valves in Europe (I-REVIVE) trial which was followed by the Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST) trial (36). Twenty seven of these patients underwent successful percutaneous AV implantation without coronary

occlusion or disruption of MV architecture. Of these, antegrade approach was successful in 85% (23 of 26 patients) and retrograde approach in 57% (4 of 7 patients). The noteworthy procedural limitations were prosthesis migration/embolization, failure to cross the stenotic AV and para-valvular aortic regurgitation. Anatomic and functional success was obtained as evidenced by an improvement in aortic valve area (AVA) from 0.60 ± 0.11 cm^2 to 1.70 ± 0.10 cm^2 ($p<0.001$), an increase in left ventricular ejection fraction (from 45 ± 18% to 53 ± 14%, $p<0.05$), and an improved NHYA functional class (from IV to I-II in over 90% of patients). Importantly, the improvement in AVA and mean aortic gradient was maintained at 24 months and the maximum improvement in left ventricular ejection fraction was observed in patients with depressed systolic function at baseline. The 30-day mortality was 22% (6 of 27 patients). Eleven patients were alive at nine months follow-up, and no device related deaths occurred up to 26 months after implantation (36).

In their first cohort, Webb et al. successfully implanted the Cribier-Edwards valve in 14 of 18 patients who had previously been deemed unsuitable for surgical valve replacement (25). The AVA increased from 0.6 ± 0.2 to 1.6 ± 0.4 cm^2 ($p<0.001$), and remained stable at one month follow-up. The early mortality was 11% (2 of 18) and short-term survival was 89% (16 of 18) at a mean of 75 days follow-up (25). The same group subsequently reported both short- and mid-term outcomes in an extended cohort of 50 patients who underwent percutaneous Cribier-Edwards valve implantation via a retrograde approach (26). Valve implantation was successful in 43 patients (86%) and the reasons for procedural failure were similar to those previously reported (36). The main difference was in the frequency of the vascular complications with the retrograde approach. In 43 patients who had successful implant, the 30-day mortality was 12% (5 of 43 patients) compared to expected mortality of 28% according to the logistic EuroScore. Of interest, there was a clear dichotomy in both procedural success and 30-day mortality, representing the learning curve. Procedural success increased from 76% in the first 25 patients to 96% in the second 25, and 30-day mortality fell from 16% to 8%. Importantly, no patients needed open heart surgery in the first 30 days. There were no subsequent deaths and at median follow-up of 359 days, 81% of the patients who underwent successful transcatheter AV replacement were alive. Additionally, there was a significant improvement in AVA and NYHA functional class (Figure 8) with durability of these parameters at one-year follow-up (26).

In addition, the feasibility of transapical implantation of the Cribier-Edwards valve has been shown. Lichtenstein et al. successfully implanted the valve in seven patients unsuitable for open heart surgery and for percutaneous transfemoral AV implantation, secondary to severe aorto-iliac disease (27). This was a very high-risk elderly population (mean age 77 ± 9 years) with poor functional class (mean NYHA III) and high logistic EuroScore (mean 35 ± 26%). After implantation, the AVA increased from 0.7 ± 0.1 cm^2 to 1.8 ± 0.8 cm^2 and the mean AV gradient decreased from 31 ± 10 to 9 ± 6 mmHg. These parameters remained stable up to six months after implantation and four of the seven patients were alive after six months (27).

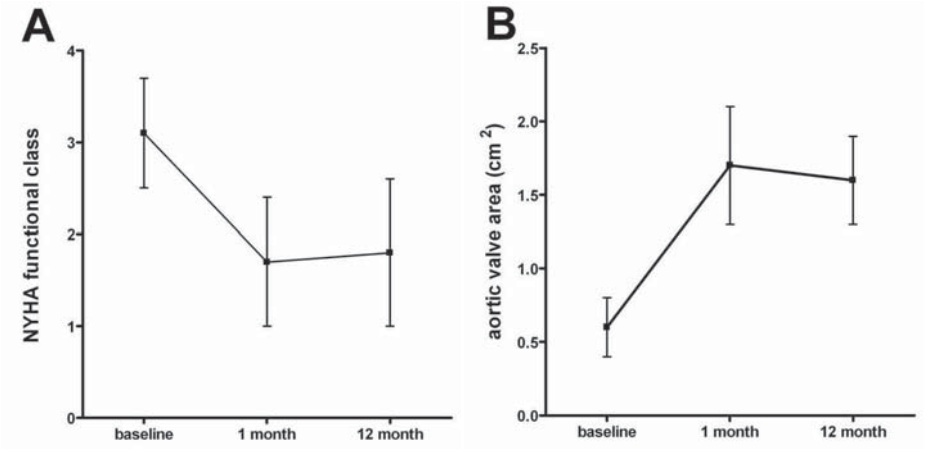

Figure 8. In 50 patients undergoing percutaneous AV replacement, a significant improvement in NYHA functional class was observed after 1 month (from 3.1 ± 0.6 to 1.7 ± 0.7, p<0.001). This improvement was maintained after 12 months follow-up (panel A). Similarly, aortic valve area significantly improved after 1 month (from 0.6 ± 0.2 to 1.7 ± 0.4, p<0.001) and 12 months follow-up (panel B).

In another recent study, Walther et al. successfully used the transapical approach for implantation of the prosthesis in 55 of 59 (93.2%) elderly patients (mean age 81 ± 6 years) with a poor functional class (NYHA III-IV), high mean logistic EuroScore (27 ± 14%), and severe calcified AS (mean AVA 0.5 ± 0.2 cm^2) (37). After successful implantation, echocardiography revealed good valve function (mean AV gradient 9 ± 6 mmHg) with minor paravalvular leakage in 17 patients. At a mean follow-up of 110 ± 77 days (range 1 - 255 days) 78% of the patients were alive. It is evident from these series that device and technique related shortcomings can be readily addressed and to date over 500 Edwards percutaneous valves have been deployed worldwide, with high technical success. Importantly, use of the larger valve (26 mm) seems to be related to less para-valvular aortic regurgitation.

Balloon-expanding valve: Edwards SAPIEN valve Initial results of the feasibility trial in the United States were presented at the 2007 TCT meeting (38). In this series, retrograde delivery was successful in 47 of 54 patients (87%). The intent-to-treat analysis of all 54 patients showed a 30-day mortality of 7.4% with a 30-day major adverse cardiac events rate of 16.7%. After this initial feasibility trial, a pivotal randomized multi-center trial, entitled PARTNER (Placement of AoRTic traNscathetER valves) has been started in North America and Europe and is projected to complete enrollment by the end of 2008 (Table 3). This prospective randomized clinical trial will enroll 600 patients in 2 separate treatment arms. The surgical arm of the trial is comparing the SAPIEN valve to standard surgical AV replacement in 350 patients, with the objective of demonstrating non-inferiority. The medical management arm of the trial will compare the SAPIEN valve to appropriate medical therapy (including balloon valvuloplasty) in 250 patients who are considered too high risk for conventional open heart surgery, with the objective of demonstrating superiority of the SAPIEN valve. The primary endpoint in both arms of the trial is

mortality at one year with secondary endpoints that focus on long-term adverse cardiovascular events composite, valve performance and quality-of-life indicators.

Self-expanding valve: CoreValve In 2005, the CoreValve aortic prosthesis was first implanted in a patient. The subject was a 73-year old woman with severe calcified AS, NYHA class IV heart failure and reduced left ventricular systolic function who was declined surgical AV replacement because of extensive co-morbidity (39). At two weeks follow-up her initial hemodynamic improvement persisted and she improved to NYHA class II.

Subsequently, Grube et al. have reported significant advancement in the CoreValve ReValving system from first-generation to third-generation (28,29). In the pilot study, 25 patients underwent CoreValve implantation under general anesthesia with extracorporeal support (extracorporeal percutaneous femoro-femoral bypass) using the retrograde approach via a surgical arterial cut-down (28). These patients had been deemed unsuitable for open heart surgery by a cardiologist and cardiovascular surgeon. Only first- and second-generation devices were used in the pilot study. The patient cohort was elderly (mean age 80 ± 5 years) with NYHA class III-IV (96%), a mean AVA of 0.72 ± 0.13 cm^2, and a median logistic EuroScore of 11%. Acute procedural success was achieved in 21 of 25 patients (84%) with a reduction in mean AV gradient, and a functional improvement in NYHA class at 30-days follow-up (Figure 9). Interestingly at 30-days follow-up, 17 of 18 patients (94%) had none or only mild aortic regurgitation. Procedural limitations and complications were similar to the Cribier-Edwards valve. Major in-hospital cardiovascular and cerebral events occurred in 8 patients (32%) whereas major bleeding occurred in 5 of 10 patients (50%) treated with the first-generation device and in 1 of 15 patients (7%) treated with the second-generation prosthesis. Among 18 patients with device success (82%), no further adverse events occurred within 30 days after hospital discharge (28).

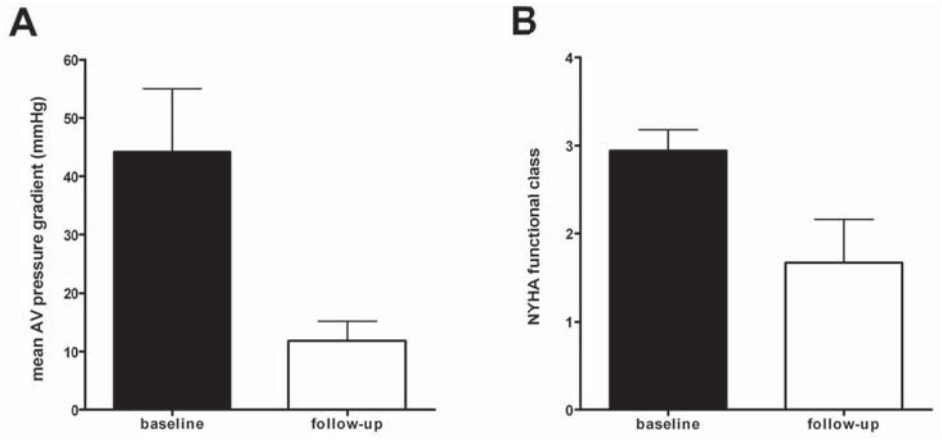

Figure 9. After percutaneous implantation of the CoreValve prosthesis, a significant improvement of mean AV pressure gradient (panel A) and NYHA class (panel B) was observed. Mean AV pressure gradient decreased from 44.2 ± 10.8 to 11.8 ± 3.4 mmHg ($p<0.001$) and NYHA class decreased from 2.9 ± 0.2 to 1.7 ± 0.5 ($p<0.001$) after 30 days of follow-up.

In the second series, the CoreValve was implanted in 50 and 36 patients using second- and third-generation devices, respectively (29). The study population included elderly patients (mean age 82 ± 6 years) with a poor functional class (83% NYHA class III-IV), high logistic EuroScore (22%), and severe calcified AS. Acute device success, which was similar in both groups, was achieved in 76 of 86 (88%) patients. After implantation the mean AVA increased significantly (from 0.60 ± 0.16 cm^2 to 1.67 ± 0.41 cm^2, $p<0.05$) along with an improvement in NYHA functional class (from 2.85 ± 0.73 to 1.85 ± 0.60, $p<0.001$). Peri-procedural rate of death, stroke, and myocardial infarction was 14%. Overall 30-day mortality rate was 12%, while the combined rate of death, stroke, and myocardial infarction was 22%. Impressively, in patients with device and procedural success, the mortality was 9% and 5%, respectively.

Valve-in-valve concept While the experience with percutaneous AV procedures increases rapidly, a new concept has emerged also. Recently, the feasibility of a 'valve-in-valve' model has been reported for replacement of a aortic and mitral valve xenograft (40). Walther et al. implanted conventional aortic and mitral valve prostheses (23 or 25-mm Carpentier Edwards) in seven pigs. Subsequently, a transapical puncture was performed for positioning of the repeat 23 mm transcatheter valve (Edwards SAPIEN). All transcatheter 'valve-in-valve' implantations were performed successfully and good valve function was demonstrated after the procedure.

Recently, Grube and coworkers reported the first use of the CoreValve to treat severe aortic regurgitation of a degenerated aortic bioprosthesis in an 80-year old man with extensive co-morbidity and a logistic EuroScore of 36% (41). The insertion of the percutaneous AV using the CoreValve resulted in a complete resolution of severe, symptomatic aortic regurgitation of the seven-year old aortic bio-prosthesis placed by open heart surgery for severe calcified AS. After one year follow-up, the patient is still free of symptoms with good 'valve-in-valve' prosthesis function (no aortic regurgitation, mean gradient 12 mmHg) (41).

The 'valve-in-valve' concept is of particular interest since re-operation for degenerated xenografts may be challenging. The mortality risk for re-operation is significantly higher than for first isolated aortic valve replacement (42). Performing a percutaneous procedure when the initial AV xenograft has failed does not require re-sternotomy, cardiopulmonary bypass or cardioplegic arrest and thus has the potential for a lower morbidity and mortality rate. The initial results of the 'valve-in-valve concept' in animal models and in humans are promising.

PERFORMING PERCUTANEOUS VALVE PROCEDURES

In percutaneous valve therapy, both careful selection of potential candidates and thorough follow-up after the procedure are of critical importance. In the following paragraphs, the selection of patients, procedural issues and strategies for follow-up are discussed.

Selection of patients

The success of percutaneous valve procedures depends heavily upon appropriate selection of patients for a particular device. Both for percutaneous MV and AV procedures, a comprehensive assessment of valve pathology, vascular access and co-morbidity are critical for patient selection.

Percutaneous mitral procedures Mitral regurgitation can result from many different anatomical and functional aberrations of the MV, mainly related to annulus dilatation, leaflet prolapse or restricted leaflet motion. While percutaneous leaflet edge-to-edge repair is appropriate for patients with MR related to leaflet prolapse, the percutaneous coronary sinus mitral annuloplasty is more suitable for patients with mitral annulus dilatation (43). Therefore, anatomical selection of patients for percutaneous MV procedures is directly dependent on the echocardiographic analysis including the mechanism of MR, leaflet size, coaptation height, annular dimension and severity of prolapse (44). In addition, for percutaneous coronary sinus annuloplasty, proper imaging to define the proximity of the coronary sinus to the mitral annulus and the left circumflex coronary artery is mandatory (13).

Percutaneous aortic valve procedures In general, the selection of patients for percutaneous aortic valve procedures includes several issues. The severity and prognosis of the AS should be assessed first. Afterwards, the presence of co-morbidity and surgical risk should be thoroughly investigated. If the patient is no surgical candidate, the feasibility of a percutaneous AV procedure should be evaluated, including assessment of vascular access.

A comprehensive assessment of the patient's surgical risk with input from cardiologists, cardiac surgeons and cardiac anesthesiologists is crucial in the selection of potential candidates. The initial feasibility experience of percutaneous AV replacement was appropriately restricted to patients that were deemed not to be candidates for surgical AV replacement (22,25). However, in the ongoing PARTNER trial (Table 3) patients with STS score >10 are randomized between surgical or percutaneous AV replacement (group A). Most of these patients have a high estimated surgical risk based on age, previous cardiac surgery, renal failure, cerebrovascular disease and pulmonary disease. On the other hand, patients with estimated surgical mortality of more than 15% that are deemed inoperable by two surgeons with experience in performing high risk AV replacement are randomized between percutaneous AV replacement or no AV replacement in Group B (Table 3). Many of these patients have co-morbidities including severe chronic obstructive pulmonary disease or anatomical challenges to surgery such as porcelain aorta, cardiac chambers or grafts adherent to the sternum. Careful selection and a thorough clinical evaluation for the assessment of the surgical risk are therefore essential in these patients.

Extensive calcifications and tortuosity of the femoral artery and aorta may hamper positioning of the AV prosthesis. In patients with limited vascular access, a transapical approach should

be considered (27). Careful screening of vascular access is therefore important in patients referred for percutaneous AV replacement.

Procedure-related issues

The majority of the technical issues are related to vascular access, transseptal puncture, device positioning and deployment.

Vascular access The vascular access for percutaneous valve procedures may be challenging since catheters are often large: mitral balloon valvuloplasty or implantation of a coronary sinus device typically requires a 12F venous sheath (external diameter ~5 mm) (11). In contrast, percutaneous AV implantation may require a sheath as large as 24F (external diameter ~9 mm) (26). Insertion of such a large sheath is associated with a significant potential for vascular injury including bleeding, dissection, occlusion and perforation. In 50 high-risk patients undergoing percutaneous AV replacement through the femoral artery, vascular injury occurred in 4 patients (8%) (26). However, vascular access techniques, equipment and pre-procedural screening may reduce this number.

Transseptal puncture Many percutaneous valve procedures, including mitral valvuloplasty, paravalvular leak closure and antegrade aortic valvuloplasty or valve implantation, require a transseptal puncture to access the left atrium. Puncture of the interatrial septum is associated with a risk of pericardial bleeding and tamponade and may result in residual interatrial shunts. By visualizing the interatrial septum and the transseptal puncture needle, intracardiac echocardiography is helpful in performing transseptal punctures safely and at precisely the desired locations (45).

Device positioning and deployment In general, a clear learning curve for performing percutaneous valve procedures is present (26,30). During the procedure, various problems can be encountered while positioning and deploying the device. For all procedures, passage of bulky therapeutic catheters through the cardiac chambers, particularly in compromised patients can result in cardiac perforation or provoke arrhythmias, ranging from atrial to ventricular fibrillation.

In percutaneous edge-to-edge leaflet repair, inappropriate device positioning may result in partial clip detachment (30) and should be monitored carefully. In case of unsuccessful percutaneous mitral edge-to-edge repair, surgical repair may be needed (30). During percutaneous mitral annuloplasty, acute ischemia due to left circumflex coronary artery impingement can be encountered (13). A paravalvular plug may interfere with mechanical valve leaflets or may become dislodged and embolize requiring a complex percutaneous snaring procedure or even unplanned surgery (7).

In percutaneous AV replacement, technical errors can result in a percutaneous AV being implanted within the ventricle or aorta (36). In addition, percutaneous aortic valvuloplasty or

AV replacement may cause injury to adjacent conducting tissue and transient or sustained atrioventricular heart block requiring ventricular pacing. Finally, coronary occlusion may occur if a bulky native leaflet is displaced over a coronary ostium (25).

Follow-up

With the exception of valvuloplasty, little is known on late implications of percutaneous valve procedures. A careful follow-up of patients after percutaneous valve procedures is mandatory to assess prosthesis function and the presence of residual regurgitation or paravalvular leakage.

Prosthesis function should be monitored since device fatigue may result in late stent fracture, as has been common with first-generation pulmonary valve implants (46). In the initial feasibility study using the coronary sinus annuloplasty for MR, separation of the nitinol bridge segment occurred without any adverse clinical events (11). Regular follow-up on prosthesis function is therefore mandatory.

Furthermore, residual regurgitation, paravalvular leakage or failure of the bioprosthetic valve may require additional interventions. In a large cohort of 86 patients treated with the CoreValve for AS, two patients required an implantation of a second prosthesis (valve-in-valve) due to severe residual regurgitation (29).

Finally, percutaneous implants may have unexpected implications, such as thromboembolism and infection. In addition, the durability of percutaneous valves is currently unknown. Therefore, close follow-up of patients after a percutaneous valve procedure is warranted. In the reported and the ongoing trials on percutaneous valves, an extensive echocardiogram is typically performed for the assessment of prosthesis function and presence of residual regurgitation or paravalvular leakage.

THE ROLE OF IMAGING IN PERCUTANEOUS VALVE PROCEDURES

Accurate visualization of the native valve, the prosthesis or device and their relationship is crucial before, during and after the percutaneous valve procedure. An overview on the role of various imaging modalities in percutaneous valve procedures is provided in Table 4. Several imaging modalities are available including echocardiography (transthoracic, transesophageal and intracardiac), multi-slice computed tomography (MSCT), magnetic resonance imaging (MRI) and fluoroscopy. Whereas transthoracic echocardiography, MSCT and MRI are valuable imaging techniques before and after the procedure, transesophageal and intracardiac echocardiography are mainly used during the percutaneous valve procedure.

Before percutaneous valve procedures

Selection of potential candidates and procedural risk assessment are crucial issues before percutaneous valve procedures. The various imaging modalities are important for the assessment

Table 4. The role of imaging modalities in percutaneous valve procedures

Imaging modality	Before percutaneous valve procedure	During percutaneous valve procedure	Follow-up	General comment
Echocardiography, transthoracic (TTE)	Assessment of valve morphology Quantification of severity of valve disease	---	Assessment of prosthesis function Detection of complications	
Echocardiography, transesophageal (TEE)	Assessment of valve morphology* Quantification of severity of valve disease*	Facilitating transseptal puncture Prosthesis sizing Prosthesis positioning Detection of complications	Assessment of prosthesis function* Detection of complications*	Mainly used peri-operatively
Echocardiography, intracardiac (ICE)	---	Facilitating transseptal puncture Prosthesis positioning Detection of complications	---	Only used peri-operatively
Fluoroscopy	Assessment of vascular access †	Prosthesis sizing Prosthesis positioning Detection of complications	---	Mainly used peri-operatively
Multi-slice Computed Tomography	Assessment of vascular access † Assessment of valve morphology Assessment of surrounding structures ‡	---	Assessment of prosthesis position/ morphology	Mainly used pre-operatively
Magnetic Resonance Imaging	Assessment of vascular access † Assessment of valve morphology Assessment of surrounding structures ‡	---	---	Mainly used pre-operatively

* Recommended if TTE quality is not sufficient. † In particular for retrograde aortic valve implantation. ‡ For example, relation between coronary sinus and circumflex coronary artery/ mitral annulus in percutaneous mitral annuloplasty.

of valve morphology, quantification of the severity of valvular disease and assessment of vascular access and surrounding structures.

For the assessment of both mitral and aortic valve morphology and the quantification of the severity of valve disease, a routine transthoracic echocardiogram (Figure 10) is typically performed (1,2). However in case of suboptimal image quality of transthoracic echocardiography, transesophageal echocardiography may be needed. In addition, recent studies have demonstrated that MSCT and MRI can also provide detailed information on valve morphology and function. Good correlations between MSCT and echocardiography for the assessment of

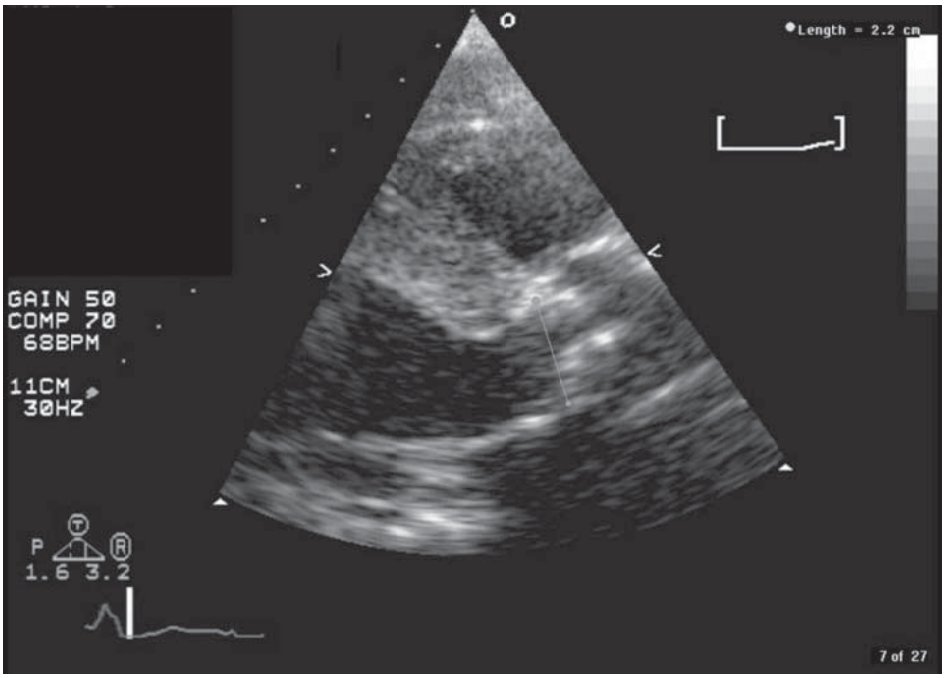

Figure 10. Transcatheter aortic valve implantation requires non-invasive estimation of the size of the annulus. One method is to estimate the diameter of the aortic annulus from a transthoracic long axis echocardiogram. Typically the measurement is made at the ventricular aspect of the leaflet insertion.

valve morphology and valve area have been reported (47). Finally, assessment of specific surrounding structures, such as coronary arteries, is important before percutaneous MV and AV procedures.

Percutaneous mitral valve procedures For coronary sinus annuloplasty in patients with MR, assessment of coronary sinus anatomy is of critical importance (Figure 11). Particularly, the relation with the MV annulus and the left circumflex coronary artery should be explored. The close relationship between the coronary sinus and the circumflex coronary artery (48) may explain the impingement of the coronary artery described in the first animal studies (13). With the use of MSCT, this relation can be assessed non-invasively before the mitral annuloplasty procedure (49,50). In a recent study, the relation between the coronary sinus and the circumflex coronary artery was assessed in 105 patients, including 34 patients with heart failure and/or severe MR. It was noted that the circumflex artery coursed between the coronary sinus and the MV annulus in almost 70% of the patients, with a minimal distance of 1.3 ± 1.0 mm between the two structures (49). In addition, a broad variation in minimal distance between the coronary sinus and the mitral annulus was noted (Figure 12). Performing a percutaneous mitral annuloplasty may not be feasible if the coronary sinus courses along the left atrial posterior wall rather than along

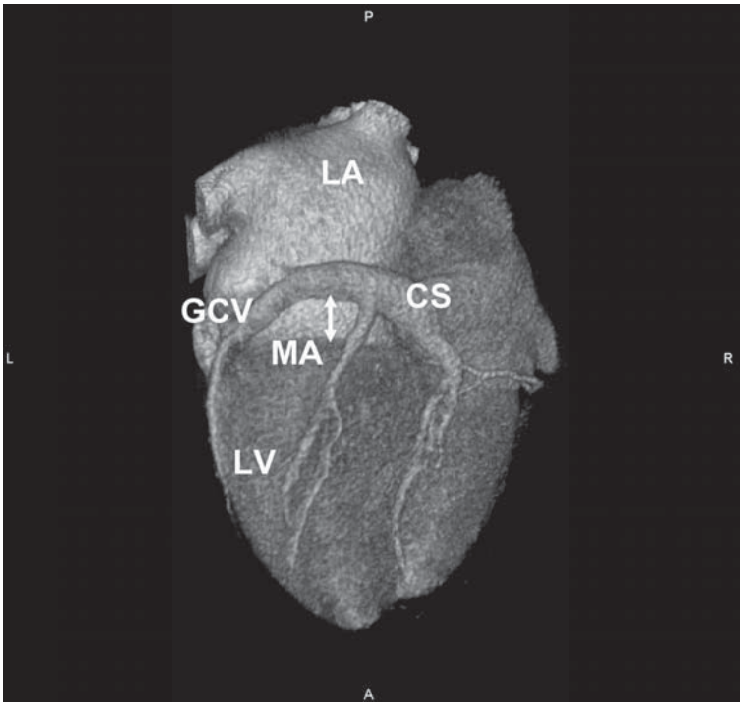

Figure 11. Three-dimensional volume-rendered reconstruction of a 64-slice MSCT scan demonstrating the relationship between the coronary sinus (CS) and the mitral annulus (MA). In this patient, the CS coursed along the left atrial (LA) posterior wall, rather than along the MA, as indicated by the white arrow. Percutaneous mitral valve annuloplasty via the coronary sinus may not be feasible in these patients. GCV = great cardiac vein; LV = left ventricle.

the mitral annulus. By visualizing the coronary sinus and other relevant structures, MSCT may help in the selection of patients for percutaneous mitral annuloplasty.

Percutaneous aortic valve procedures Before percutaneous AV procedures, vascular access should be screened. The calcifications and tortuosity of the aorta and femoral arteries should be evaluated, since this has important implications for the delivery of the prosthesis (transarterial vs. transapical). Conventional angiography, MSCT and MRI are available for the assessment of vascular access.

In addition, the extent and location of AV calcifications can be accurately assessed with MSCT. An example of a heavily calcified AV is shown in Figure 13. In addition, MSCT enables accurate assessment of the diameter of the aortic annulus, necessary for correct prosthesis sizing. Finally, the relation between the aortic annulus and the ostium of the left coronary leaflet can be visualized with MSCT (51). This may be important since occlusion of the coronary ostium has been reported as a serious complication of percutaneous AV replacement (25).

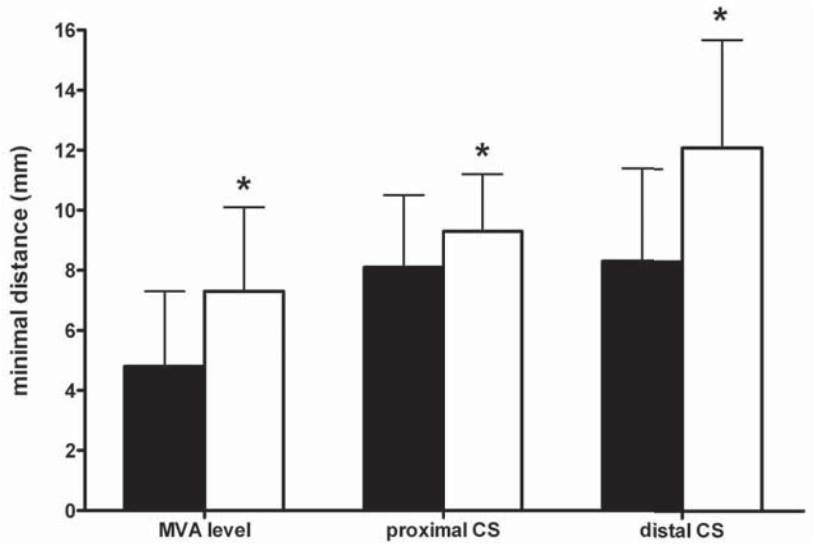

Figure 12. With the use of MSCT, the minimal distance between the coronary sinus (CS) and the mitral valve annulus (MVA) was assessed. In 90 patients without severe MR (black bars) and in 15 patients with severe MR (white bars), the distance was assessed at three different levels (MVA level, proximal CS, distal CS). In the patients with severe MR, the distance between the CS and the MVA was significantly greater compared to the patients without severe MR at all levels. The greater distance between the CS and MVA may hamper the use of percutaneous mitral annuloplasty. * = $p<0.05$.

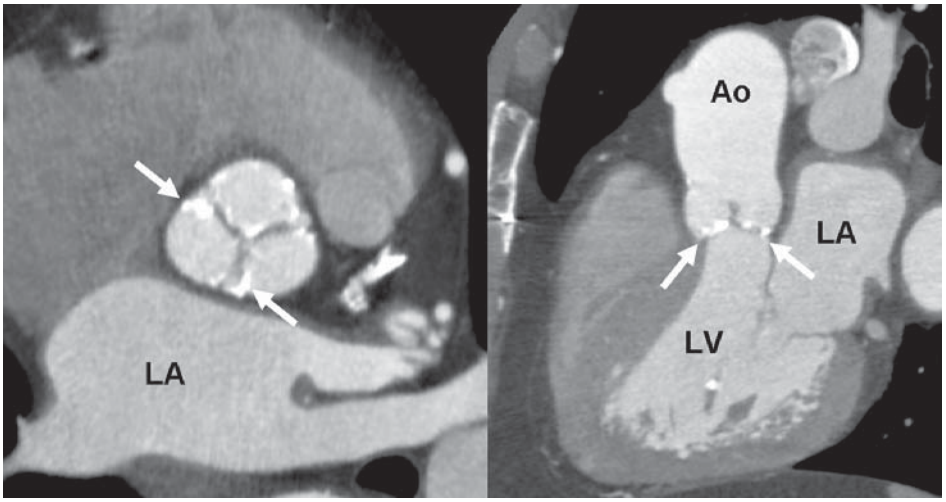

Figure 13. Multi-slice computed tomography images demonstrating a heavily calcified AV in a patient referred for percutaneous AV implantation. The left panel shows a short-axis reconstruction of the AV, indicating the calcifications on all leaflets (white arrows). In the right panel, the reconstructed sagittal view (similar to a parasternal long-axis view on transthoracic echocardiography) clearly demonstrates the extent and location of the calcifications. Ao = aorta; LA = left atrium; LV = left ventricle.

Procedure-related issues

During percutaneous valve procedures, performing a transseptal puncture, positioning and deployment of the device are all critical processes and can be guided by various imaging modalities. Fluoroscopy remains the technique of choice, although it does not permit visualization of cardiac soft-tissue structures and for patient and physician safety the radiation burden should be kept to a minimum. Therefore, both transesophageal and intracardiac echocardiography have been used during AV (25,26,28,37) and MV (17,18,33,35) procedures in addition to fluoroscopy.

Transesophageal and intracardiac echocardiography are valuable techniques for performing transseptal procedures (45). Accurate real-time visualization of the interatrial septum and the transseptal puncture needle may greatly facilitate safe and accurate transseptal punctures.

The positioning and deployment of the prosthesis are the most important processes during percutaneous valve procedures. Using fluoroscopy (and contrast agents if needed) the relationship between the native valve and the prosthesis can be well visualized. An example of coronary sinus assessment with the use of fluoroscopy during a percutaneous MV procedure is shown in Figure 14. In addition to fluoroscopy, transesophageal and intracardiac echocardiography can facilitate percutaneous valve procedures. In an animal model of percutaneous edge-to-edge repair, Naqvi et al. demonstrated that intracardiac echocardiography can accurately visualize

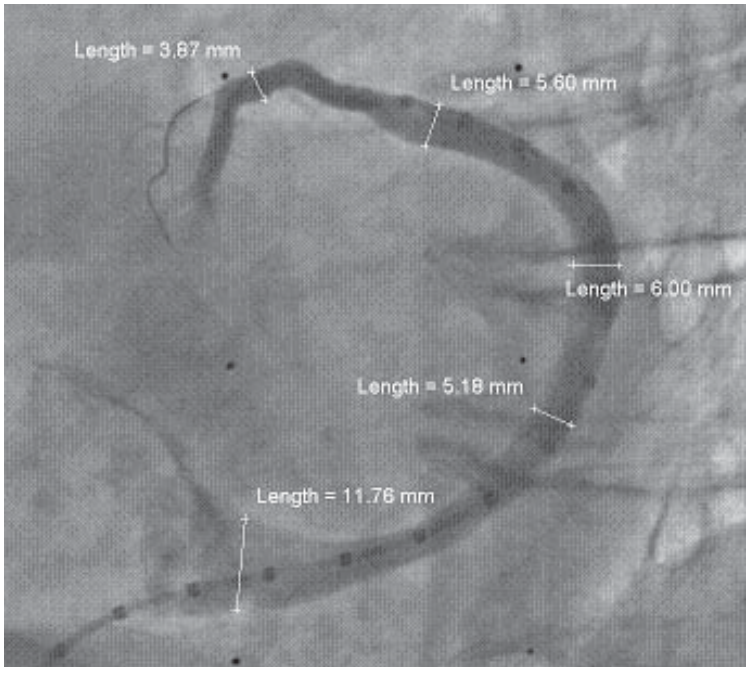

Figure 14. Assessment of the coronary sinus prior to MV annuloplasty in a patient with severe MR. The coronary sinus has been cannulated from the femoral vein with a calibrated angiographic catheter. Contrast injection allows visualization of the coronary sinus and calibration using the radiopaque 1 cm markers on the catheter allow estimation of diameter and length of the coronary veins.

the MV apparatus, guide the deployment of the leaflet suture and confirm a double orifice mitral valve (52).

Furthermore, transesophageal echocardiography is useful for the positioning of the percutaneous valve devices (Figure 2). In the EVEREST-I trial, a standardized protocol for transesophageal echocardiography was implemented during the course of the trial (53). It was noted that the use of a standardized imaging protocol reduced the median 'device time' (defined as the time from the initial insertion of the guiding catheter to the final removal of the clip delivery system) from 198 to 132 minutes. It was concluded that transesophageal echocardiography is essential for guiding percutaneous edge-to-edge repair (53). Recently, real-time three-dimensional transesophageal echocardiography has been introduced. The three-dimensional aspect of this technique may further facilitate percutaneous valve procedures. However, experience is currently limited and more studies are needed to assess the relative merit of this new technique.

Follow-up

After a percutaneous valve procedure careful follow-up of the patient is essential. In particular, assessment of prosthesis function and position, and the presence of residual regurgitation or paravalvular leakage are important during follow-up. Transthoracic echocardiography is the primary imaging modality for all these issues. An example of transthoracic echocardiography in a patient with severe MR undergoing percutaneous edge-to-edge repair with the use of MitraClip is shown in Figure 15. Transthoracic echocardiography allows serial and quantitative assessment of prosthesis function and the presence of residual regurgitation or paravalvular leakage (54). In the EVEREST-I trial it has been demonstrated that it is feasible to use quantitative parameters systematically for the follow-up of MR in patients undergoing percutaneous edge-to-edge repair using transthoracic echocardiography (55).

For exact assessment of the position of the prosthesis, and its relation with surrounding structures, MSCT may be preferred over transthoracic echocardiography. Due to the high spatial resolution, MSCT enables a detailed evaluation of the prosthesis position in relation to the native valve and surrounding structures (11). An example of a patient with a percutaneous

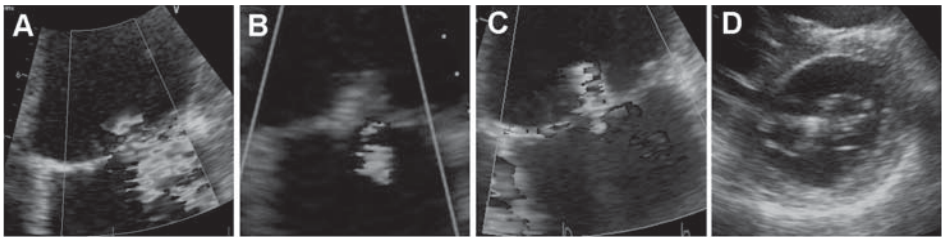

Figure 15. Transthoracic echocardiograms from a patient undergoing percutaneous edge-to-edge repair with the use of a MitraClip device. Severe MR is present at baseline (panel A). After placement of the MitraClip device there is immediate reduction in MR (panel B) with continued success on 2-year follow-up (panel C). Double barrel mitral orifice is seen on the short axis view (panel D).

AV, assessed with MSCT is shown in Figure 16. Although the radiation exposure of MSCT is significant and should always be considered, it may be the best imaging modality to visualize the exact prosthesis morphology and location.

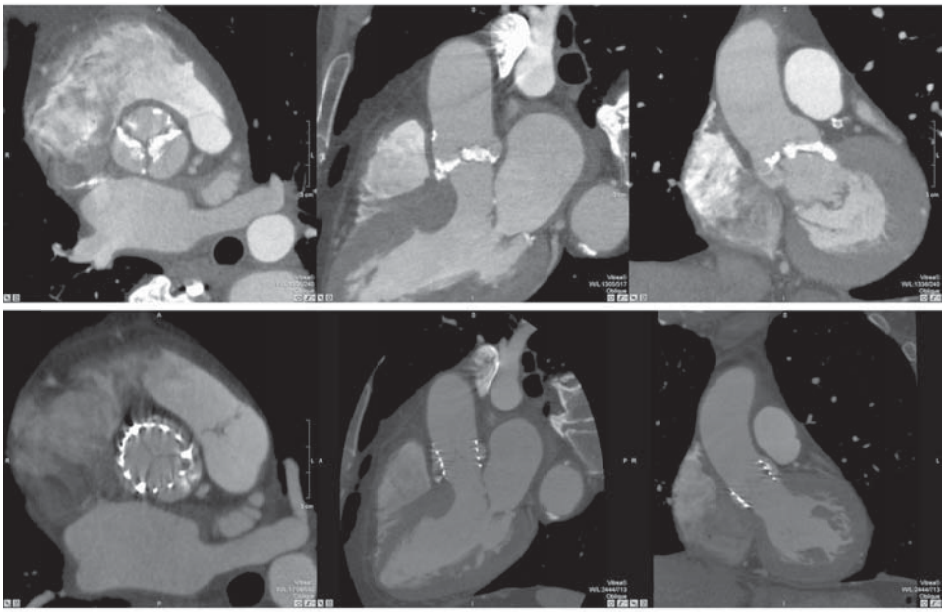

Figure 16. Multi-slice computed tomography of the aortic valve (AV) in a patient referred for percutaneous AV replacement, in an axial (left panel), sagittal (middle panel) and coronal view (right panel). In the upper panel the extensive calcifications of the native AV are well visualized. The lower panel clearly demonstrates the location of the AV prosthesis (Edwards SAPIEN valve).

CONCLUSIONS

Percutaneous aortic and mitral valve procedures are promising strategies in the treatment of patients with valvular heart disease. Both for AS and MR, different procedures have demonstrated their feasibility and safety in animal and human studies. Several clinical trials, including randomized trials between surgical and percutaneous treatment, are currently performed. The results of these trials will demonstrate the precise value of percutaneous valve procedures in patients with severe valvular heart disease, unsuitable for surgical treatment. Careful selection and screening of patients is crucial for percutaneous valve procedures. Different imaging modalities are available for the selection of patients for percutaneous valve procedures. In addition, performing the actual procedure may be greatly facilitated by implementation of various imaging techniques. At present, only short-term results are available and therefore a careful follow-up of the patients after percutaneous valve procedures is mandatory.

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