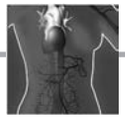
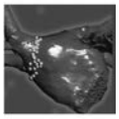
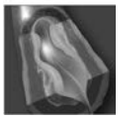

Transcatheter aortic and mitral valve interventions: update 2010

In recent years, the cardiovascular community has witnessed the advent of new, transcatheter-based beating-heart approaches to valvular heart disease. Since the mid-1980s, when balloon valvuloplasty of stenosed aortic valves and percutaneous commissurotomy in mitral stenosis were introduced into clinical practice, interventional valve therapy has seen a tremendous upsurge. Today, transcatheter aortic valve implantation has become a viable treatment alternative for selective cases at specialized centers. While transcatheter aortic valve implantation is currently restricted to high-risk patients and surgical aortic valve replacement remains the reference treatment, broader clinical application can be anticipated for the future. Nonsurgical intervention for treatment of mitral regurgitation is a second field of intense investigation. The growing incidence of congestive heart failure in western societies has created an unmet clinical need for less invasive treatment strategies for patients with functional or organic mitral regurgitation. This article summarizes the current state of transcatheter aortic and mitral valve interventions and discusses future perspectives.

KEYWORDS: aortic stenosis ■ aortic valve replacement ■ mitral regurgitation ■ mitral valve repair ■ percutaneous ■ transcatheter

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Interventional catheter-based approaches to valvular heart disease have been clinically employed at a relevant scale since the mid-1980s. At that time, balloon aortic valvuloplasty (BAV) of stenosed aortic valves (AVs) and percutaneous commissurotomy in cases of mitral stenosis (MS), mainly secondary to rheumatic valve disease, held the promise of being new, less invasive and equally effective treatment modalities compared with open heart surgery [1,2]. As for BAV, initial enthusiasm was curbed by high rates of recurring stenosis in the majority of patients [3]. If there is any indication for BAV in adults today, it may be as an emergency measure for patients in cardiogenic shock, as a palliative treatment for end-stage patients or as a bridging technique until definitive AV implantation [4].

By contrast, the catheter-based approach to MS has yielded good outcomes, both acutely and in the long-term, and has established itself as the treatment of choice [5]. However, rheumatic heart disease has become a rare occurrence in western communities. Currently, mitral regurgitation (MR) is by far the leading mitral valvular defect with which clinicians are confronted. The complex pathophysiological nature and different underlying etiologies of MR have slowed the development of interventional techniques.

Transcatheter aortic valve implantation: background & patient selection

The overwhelming majority of AV interventions is performed for degenerative disease, notably calcified aortic stenosis (AS). For this entity, surgical AV replacement (AVR) is currently the treatment of choice, with well-defined indications [6] and low perioperative morbidity and mortality [7]. Even in an elderly population with relevant comorbidities, surgical AVR can be carried out with good patient outcomes [8–10].

However, it is a clinical reality that a substantial share of patients meeting the formal criteria for AVR are deemed inoperable owing to real or presumed contraindications to surgery. A recent analysis of the Euro Heart Survey found that a third of all patients with severe symptomatic AS were not referred for surgery, most commonly owing to advanced age or left ventricular (LV) dysfunction [11]. By contrast, the dismal prognosis of medically treated AS has triggered the development of less invasive, beating-heart, transcatheter-based techniques for AV implantation (AVI). In 2002, the first successful implantation of an interventional AV prosthesis was accomplished by Alain Cribier in a 57 year-old man with severe AS and cardiogenic shock as a last resort treatment [12]. Since then, multiple technical and procedural

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refinements have led to the clinical introduction of different devices, two of which – the Edwards Sapien™ valve (Edwards Lifesciences, Inc., CA, USA) and the CoreValve™ system (Medtronic, Inc., MN, USA) – have received commercial approval in Europe (CE mark) (Figure 1).

Today, most clinicians involved agree that transcatheter AVI (TAVI) should be restricted to patients with high or prohibitive operative risk due to comorbidities. This point of view has recently been expressed in a joint position statement by the European Association of Cardiothoracic Surgery (EACTS), the European Society of Cardiology (ESC) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) [13]. Although most patients receiving TAVI are well over 75 years of age, age alone should not determine treatment strategies in view of the good results of surgical AVR in otherwise healthy octogenarians [14]. Relevant comorbidities include severe calcifications of the ascending aorta ('porcelain aorta'), end-stage organ failure of lung, liver or kidneys, history of coronary surgery with patent grafts or history of chest radiation. Risk stratification tools such as the logistic EuroSCORE (>20%) or the Society of Thoracic Surgeons (STS) score (>10%) may also be helpful in determining the individual treatment strategy. Both transfemoral approach (TF)- and transapical approach (TA)-AVI can only be executed successfully if performed with an interdisciplinary team approach involving cardiologists, cardiac surgeons, anesthesiologists and radiologists with their respective specialized expertise.

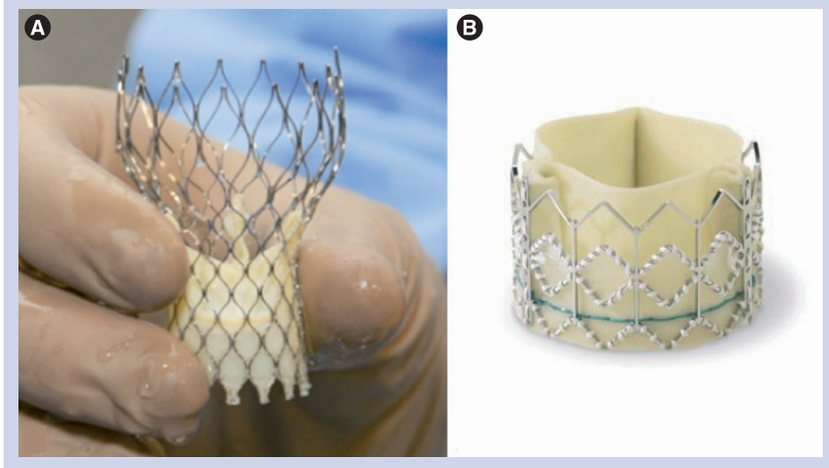

Figure 1. Transcatheter aortic valves with CE mark. (A) The CoreValve™ (Medtronic Inc., MN, USA) self-expanding valve is made of porcine pericardium inside a nitinol mesh frame. **(B)** The Edwards Sapien™ (Edwards Lifesciences, Inc., CA, USA) valve is a balloon-expandable, bovine pericardial interventional aortic valve.

Transcatheter AV implantation: current & future devices

■ The Edwards Sapien™ valve

The Edwards Sapien valve consists of a balloon-expandable stent of stainless steel surrounded by a polyester fabric sealing cuff in which a trileaflet valve made from bovine pericardium is mounted. The pericardial leaflets undergo ThermaFix™ (Edwards Lifesciences, Inc.) treatment to prevent valve calcification. Currently, the valve is available in 23- and 26-mm sizes, which require 22- and 24-Fr introducer sheaths, respectively, for the TF. For the TA, a 26-Fr sheath is commonly used. For firm seating of the valve inside the native aortic annulus and to reduce the risk of paravalvular leakage, moderate oversizing of approximately 2–3 mm is essential. The valve is crimped onto a balloon delivery catheter prior to implantation and is deployed by balloon expansion under rapid ventricular pacing. For TF valve delivery, the latest-generation device has been equipped with the RetroFlex™ 3 (Edwards Lifesciences, Inc.), a deflectable steering catheter with a nose cone that facilitates passage of tortuous access vessels, aortic arch and the stenotic AV. In order to extend patient inclusion, a 29-mm valve is under development.

■ The CoreValve™ prosthesis

In contrast to the Edwards Sapien valve, the CoreValve prosthesis is of a self-expanding design. The leaflets are constructed from porcine pericardium and are mounted inside a tubular nitinol mesh frame, which allows for compression at low temperatures and resumes its original form when released at body temperature. Along its longitudinal axis (53 mm in length for the 26-mm valve, 55 mm for the 29-mm valve), mechanical properties of the stent material vary: the lower inflow segment of the stent exhibits high radial force to displace calcified leaflets of the native AV and to withstand compression. The middle segment carrying the valve is constrained to avoid compromise of coronary flow. Finally, the upper part is cup-shaped to provide longitudinal stability and to facilitate annular orientation. Two device sizes are currently available: 26 and 29 mm. Owing to the implant being self-expandable and allowing for blood flow until complete deployment, repeated rapid pacing is not necessary for valve deployment. With the third-generation device, both devices can now be implanted through a delivery sheath measuring only 18 Fr, which facilitates a purely percutaneous procedure without the need for surgical cutdown of the access vessel, especially since percutaneous

closure systems (e.g., Prostar XL™, Abbott Laboratories, IL, USA) have become available. Although successful transapical deployment has been reported using the CoreValve device [15], it is primarily designed for transarterial TAVI owing to its relative bulkiness (stent length: ~5 cm).

■ The Direct Flow valve

Persistent problems of the aforementioned devices in terms of paravalvular leakage and the inability to reposition or even retrieve valves after final deployment have led to the development of the Direct Flow device (Direct Flow Medical, Inc., CA, USA). The Direct Flow prosthesis is a stentless valve type consisting of bovine pericardium, which is suspended in a conformable polyester fabric cuff and designed for transfemoral implantation. Two inflatable and deflatable ring balloons are used for subcoronary seating (Figure 2). The ventricular and the aortic ring balloons are successively inflated using a mix of saline and contrast agent. Since the rings can be deflated, repositioning or even complete retrieval of the prosthesis is possible until definite device deployment. After correct positioning has been confirmed, the saline contrast mix is replaced by a solidifying polymer. The first-in-man application was performed by our group with encouraging results both acutely and at 6-month follow-up [16,17].

■ Further investigational devices

Among the many other devices currently under development, some have been tested in preclinical or early clinical trials (Figure 3). The Ventor™ valve (Medtronic, Inc., MN, USA) is a self-expanding, nitinol-stented pericardial valve equipped with three arched support arms fitting the aortic sinuses and allowing for a self-centering mechanism upon valve deployment [18]. The JenaValve™ (JenaValve Technology, Germany), the Lotus™ Valve (Sadra Medical, Inc., CA, USA) and the AorTx™ system (AorTx, Inc., CA, USA) have also been investigated in a limited number of patients.

Techniques of transcatheter AV implantation

The initially chosen transvenous, antegrade, trans-septal access route has been abandoned due to the complexity of the procedure and to complications associated with passage of the interatrial septum and the mitral valve (MV). Today, two approaches for TAVI are being routinely used: a transfemoral retrograde approach via puncture or surgical cutdown of the femoral artery [19] or a transapical antegrade approach via a left anterolateral minithoracotomy (Figure 4) [20,21]. At present, there is no scientific proof of the superiority of one technique over the other. Outcomes in single-center studies are influenced by many factors, such as the experience of the implanting physicians or by patient selection. Therefore, it is difficult to attribute outcomes to the respective technical approach. Many groups consider the least invasive, completely closed-chest TF approach as

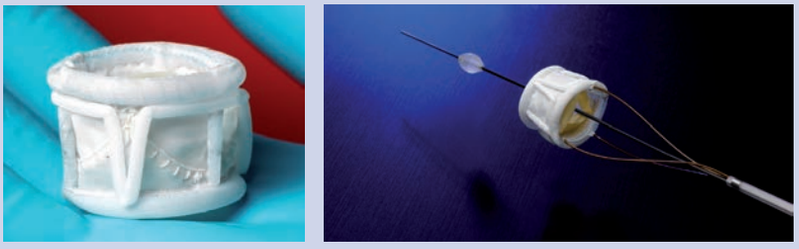

Figure 2. The stentless Direct Flow (Direct Flow Medical, Inc., CA, USA) valve. A trileaflet valve made from bovine pericardium is suspended between two inflatable and deflatable ring balloons allowing for device repositioning and retrieval.

Figure 3. Investigational aortic valves. (A) Ventor™ (Medtronic, Inc., MN, USA) interventional heart valve, **(B)** the JenaValve™ (JenaValve Technology, Muenich, Germany), **(C)** the Lotus™ valve (Sadra Medical, Inc., CA, USA) and **(D)** the AorTx™ system (AorTx, Inc., CA, USA) are being tested in preclinical or early clinical trials.

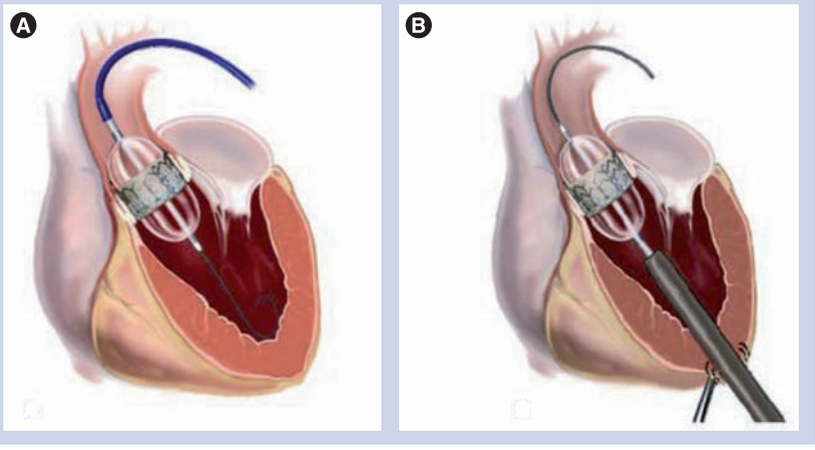

Figure 4. The Edwards Sapien™ transcatheter aortic valve. (A) Transfemoral retrograde approach and **(B)** transapical antegrade approach for transcatheter aortic valve implantation.

the technique of first choice (allowing for TAVI under local anesthesia and sedation) and resort to the TA approach only in case of contraindications. Severe peripheral artery disease may make femoral vascular access impossible. Severe tortuosity of the abdominal aorta (passage) or a heavily calcified aortic arch (stroke risk) must also be taken into account. Furthermore, TF-AVI is a highly complex procedure and may be more technically demanding than the more direct TA approach. The presumed disadvantage of performing a small thoracotomy is clinically relevant only in cases of contraindications to the associated general anesthesia in patients with severely impaired pulmonary function.

Many groups have reported a tendency towards more adverse events and higher mortality rates in patients treated by TA-AVI as opposed to TF-AVI. However, detailed analysis of the respective patient populations has revealed patient risk factors to be responsible for this effect, rather than procedural determinants [22,23]. Since the patients' vascular status, (i.e., the presence and extent of peripheral vascular disease) is one important determinant for feasibility of TF-AVI, patients with significant aorto-iliac, peripheral vessel and cerebrovascular disease, or with previous coronary artery bypass grafting, are more likely to undergo TA-AVI. In short, a transfemoral-first approach to TAVI, as advocated by most groups, will lead to sicker patients with more severe comorbidities in the TA groups. This holds true even for randomized trials such as the Placement of Aortic Transcatheter Valve Trial (PARTNER; ClinicalTrials.gov Identifier: NCT00530894), when trial design precludes a TA approach when TF-AVI is feasible.

In clinical practice, the optimal strategy has to be carefully planned according to the individual patient's characteristics. Both types of procedures are ideally performed in a specially equipped hybrid operating suite, providing the implanting staff with adequate technical equipment should emergency conversion to surgery with cardiopulmonary bypass become necessary. Modern imaging techniques are essential to guide the implantation process. The combination of transesophageal echocardiography (TEE), fluoroscopy and aortic angiography guarantees optimal conditions for TAVI. In particular, precise measurements of the native aortic annulus by TEE (e.g., long axis view) are of paramount importance to determining suitable valve size, although a tendency towards underestimation of true annulus dimensions has been reported and 3D imaging modalities may be more accurate. In the future, DynaCT technology (Axiom Artis, Siemens Inc., Germany) is expected to further enhance visualization and decrease the amount of contrast agent that is necessary during TAVI procedures [24].

■ Transfemoral transcatheter AV implantation

Adequate vascular access is the major determinant and limitation for TF-AVI. Current generation prostheses of the Edwards Sapien system require a 22 and 24-Fr-sheath for the 23- and 26-mm valve, respectively. This limits the TF approach to femoral artery luminal diameters of at least 7 mm. Severely calcified, rigid and tortuous femoral and iliac vessels are not uncommon in the typical patient population, implying a significant risk of vascular injury. The third-generation CoreValve system allows for the introduction of both 26- and 29-mm systems through an 18-Fr sheath, which makes even a subclavian access feasible [25]. Usually, TF-AVI is performed under general anesthesia although, especially with the CoreValve system, the use of local anesthesia and moderate sedation has been advocated at certain sites.

A detailed account of the procedural technique of TF-AVI has recently been published in an excellent review by Cribier and colleagues [26]. Briefly, the procedure is as follows: after placement and testing of a transvenous pacemaker lead in the right ventricular apex and a pigtail catheter in the aortic root, a superstiff guidewire with a flexible, atraumatic tip is introduced via a sheath in the contralateral femoral artery and placed in the LV. Immediately prior to BAV, rapid ventricular pacing is initiated at a

rate of 180–220 bpm to decrease mean arterial pressure to less than 50 mmHg and to minimize cardiac output in order to prevent displacement of the valvuloplasty balloon. After successful dilatation of the native AV, the valve prosthesis is advanced to the aortic annulus and deployed. When using the balloon-expandable Edward Sapien valve, a second phase of rapid ventricular pacing is necessary. Adequate valve positioning and function is constantly assessed by echocardiography, fluoroscopy and aortic angiography. In cases of severe paravalvular regurgitation, postdilation of deployed valves is possible but not always helpful.

■ Transapical transcatheter AV implantation

Surgical access to the LV apex is gained via a 5–6-cm minithoracotomy through the fifth or sixth intercostal space. After opening of the pericardium and placement of pericardial stay sutures, a pacemaker lead and Teflon-pledget reinforced purse-string sutures are placed (Figure 5). Then, the LV apex is directly punctured, allowing for insertion of a guidewire and introducer sheaths in Seldinger's technique (14 Fr for the valvuloplasty catheter, then 26 Fr for the valve delivery catheter). As in the TF approach, rapid ventricular pacing is performed for BAV and repeated for valve deployment. After adequate valve function has been confirmed by TEE and angiography, the apical sheath is removed and the access site closed using the purse-string sutures. For greater detail of the TA procedure, we recommend a recently published step-by-step description by Walther and colleagues [27].

Results after transcatheter AV implantation

When reporting results after TAVI, the pronounced risk profile of the treated patient population has to be taken into account. Generally, patients are in their eighties and are afflicted with severe comorbidities, making them unfit as surgical candidates. Logistic EuroSCORE (even though it is known to overestimate procedural risk) usually ranges between 20 and 30%. Furthermore, TAVI is a relatively young technique with a steep learning curve.

A recent review on the safety of TF- and TA-AVI procedures summarizes patient outcomes excluding early series, where a procedural learning curve is expected to have had an impact [28]. The authors found 30-day mortality rates of 6.4–7.4% and 11.6–18.6% in the TF and TA series, respectively. However, since data from industry-sponsored registries (summarized in [29]) such as the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry were incorporated in their results, outcomes as reported from large-volume centers or from multicenter trials may be more representative in reflecting real-world data. Table 1 provides an overview of the most recent series at leading heart centers [23,30–35].

Regarding periprocedural complication rates, technical advances have led to lower rates in most of the more recent TAVI series. Downsizing of sheaths and introduction of percutaneous suture-based closure systems has reduced the incidence of serious vascular injury, which was common in the early TF-AVI series [29,36]. Since both the CoreValve and the Edwards Sapien devices have limited repositioning abilities and cannot be retrieved after final deployment, optimal imaging modalities such as 3D echo or CT imaging are of paramount importance for safe TAVI. With both devices, malpositioning continues to be a problem, and may result in coronary obstruction or valve embolization if valves are deployed too high or in significant paravalvular leakage or compromise of MV function if they are deployed too low.

Conduction abnormalities are a known complication following surgical AVR and are frequently reported after TAVI, with permanent pacemaker implantation rates ranging from 5.7 to 18% [29]. Permanent conduction disturbances are more common in series using the CoreValve device, presumably related to its deeper implantation with radial forces affecting the left ventricular outflow tract [37,38].

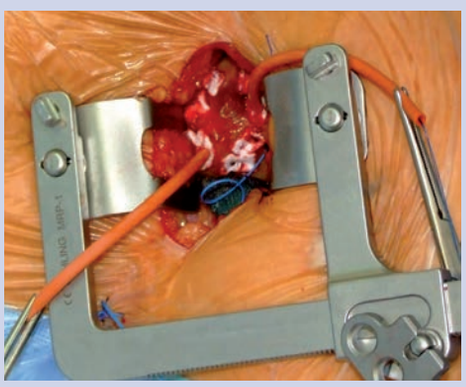

Figure 5. Transapical transcatheter aortic valve implantation. For transapical transcatheter aortic valve implantation, the left ventricular apex is accessed via a left anterolateral minithoracotomy (5–6 cm) and the access site is secured by Teflon-felt reinforced purse-string sutures.

Table 1. Results after transfemoral and transapical aortic valve implantation at selected leading heart centers.

Institution	Study	Valve type	TF/TA approach	Number of patients (n)	Logistic EuroSCORE (%)	30-day mortality (%)	Stroke (%)	Ref.
Siegburg	Grube *et al.* (2007)	CV	TF	86	21.5	12	10	[30]
Vancouver	Webb *et al.* (2007)	ES	TF	50	28	12	4	[31]
Leipzig	Walther *et al.* (2010)	ES	TA	240	32.0	9.5	0.8	[32]
Munich	Bleiziffer *et al.* (2009)	CV/ES	TA/TF	137	24.3	12.4	5.1	[33]
Hamburg	Seiffert *et al.* (2010)	ES	TA/TF	116	27.1	12.9	5.2	[23]
Canadian TAVI program (multicenter)	Rodés-Cabau *et al.* (2010)	ES	TA/TF	339	NR	10.4	0.6	[34]
Rotterdam (multicenter)	Piazza *et al.* (2008)	CV	TF	646	23.1	8.0	1.9	[35]

CV: CoreValve; ES: Edwards Sapien; NR: Not reported; TA: Transapical; TAVI: Transcatheter aortic valve implantation; TF: Transfemoral.

In a recent comprehensive review article, Masson and coworkers from the Vancouver group summarized the current evidence on periprocedural complication rates associated with TAVI [39].

Transcatheter mitral valve repair: background

Surgical MV repair (MVR) strategies have evolved with constant technical refinements ever since the underlying mechanisms were classified in the landmark paper 'The French Correction' by Alain Carpentier in 1983 [40]. Differentiation of the complex pathophysiology of MR is beyond the scope of this article. However, in addressing modern therapy for MR it is most important to distinguish between primary (i.e., organic) and secondary (i.e., functional) MR. In primary MR, dysfunction of the valve itself leads to regurgitation and subsequent volume overload of the LV. If this condition persists for long enough, it will lead to LV remodeling and dysfunction, pulmonary hypertension, heart failure and eventually death. Since there is a definite causal relation between primary MR and its effects on the LV, surgical correction of the defect, preferably by repair of the defective valve, is usually curative if performed in a timely fashion prior to advanced ventricular remodeling. The beneficial effect of MVR and its superiority to prosthetic valve replacement has been well documented in many studies [41,42] and has been incorporated into international guidelines [6].

By contrast, secondary MR is the consequence of a ventricular dysfunction caused by coronary artery disease or other causes of dilated cardiomyopathy. Therefore, the benefit of restoring MV function is less certain in secondary MR. Surgical correction of secondary MR by the use of restrictive annuloplasty has been proven to induce reverse remodeling and a modest increase in LV function [43]. However, as of yet there is no proof that such interventions lead to improved patient survival [44,45]. It is for this growing patient population that nonsurgical means for the treatment of secondary MR, which often occurs in the wake of congestive heart failure, seem most promising.

In recent years, a multitude of transcatheter approaches for the treatment of MR have been developed, many of which mimic established surgical techniques. Transcatheter techniques of MVR include coronary sinus (CS) annuloplasty, direct annuloplasty, leaflet repair strategies and LV chamber remodeling devices. This article will focus on the CS annuloplasty and leaflet repair techniques, since it is with these devices that most clinical experience has been gathered to date.

Transcatheter mitral valve repair: coronary sinus annuloplasty devices

The proposed anatomical vincinity of the CS and the posterior aspect of the mitral annulus (MA) has spurred the development of numerous new technologies for transcatheter mitral repair strategies. However, even supporters of the CS approach admit that the relationship between the CS and the MA is somewhat variable from patient to patient.

One of the cornerstones of modern surgical MVR is the use of annuloplasty rings either alone or in addition to valvuloplasty techniques. In order to downsize MA dimensions or stabilize additional repair procedures, the ring has to be firmly anchored in the MA, especially at the two fibrous trigones. Anatomical studies have revealed the distance between the CS and the fibrous trigones to reach up to several centimeters, allowing for a commissure-to-commissure annuloplasty at best [46]. In addition, the

anterior aspect of the MA is not addressed and may be subject to further dilatation in heart failure patients. Another issue is the fact that in healthy hearts, the CS courses at a distance of 5.8–14 mm from the MA [47]. This distance has been shown to increase even further in patients with dilatation of the LV and MA [48]. Finally, concern has been expressed regarding a possible interposition of the left circumflex artery between the CS and the MA, which has been reported to be present in up to 80% of the hearts investigated [47]. It may be for these reasons that results from CS approaches to MR have been widely disappointing.

Relevant clinical experience has been reported for three CS devices (Figure 6). The Carillon™ device (Cardiac Dimensions, WA, USA) is a double-anchor nitinol device that is introduced via the jugular vein and advanced to the CS. During deployment, the central segment is progressively shortened and the immediate effect on the posterior MA is monitored. Results of the prospective multicenter Carillon Mitral Annuloplasty Device European Union Study (AMADEUS) have recently been published [49]. Successful device implantation was achieved in 30 out of 48 patients (60%). In over 30% of patients, the device had to be recaptured owing to various reasons (e.g., coronary compromise, insufficient reduction of MR and device failure). The overall rate of major adverse coronary events was 14.6% at 30 days and included death, myocardial infarction and CS perforation and/or dissection.

The Monarc™ device (Edwards Lifesciences) consists of a distal and a proximal self-expanding anchor segment interconnected by a spring element that is constrained by a bioabsorbable chord. After deployment in the CS, tension develops progressively as the spring shortens during the following weeks. The EVOLUTION-I feasibility and safety trial reported successful device implantation in 82% of patients (59 out of 72 patients) and a significant reduction in MR in the majority of patients. However, the 30-day rate of major adverse coronary events (comprising death, myocardial infarction and cardiac tamponade) was 9% and there was evidence of coronary compression in more than 25% (15 out of 59 patients) of all cases [50]. Currently, further clinical experience is being gathered in the EVOLUTION-II trial.

A third device, the Percutaneous Transvenous Mitral Annuloplasty system (Viacor Inc., MA, USA) uses a multilumen polytetrafluoroethylene (Teflon®; Dupont™, DE, USA) catheter that is placed in the CS. Subsequently, up to three nitinol rods with variable stiffness can be inserted into the catheter in order to affect CS conformation. The safety of the device was assessed in a preliminary study, the Percutaneous Transvenous Mitral Annuloplasty

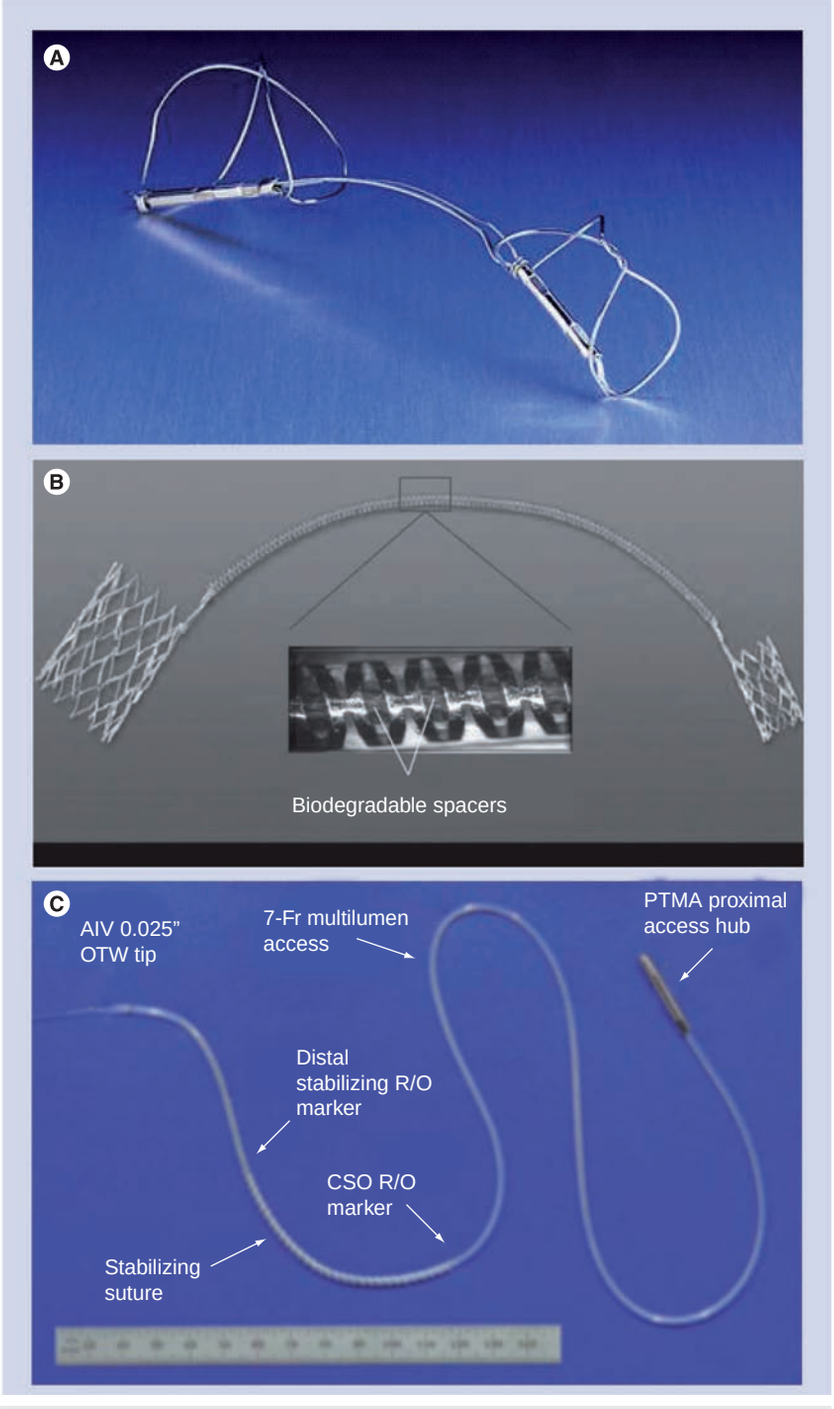

Figure 6. Coronary sinus devices for transcatheter mitral valve annuloplasty. (A) The Carillon™ device (Cardiac Dimensions, Inc., MA, USA), **(B)** the Monarc™ device (Edwards Lifesciences, CA, USA) and **(C)** the PTMA device (Viacor Inc., MA, USA).
OTW: Over-the-wire; PTMA: Percutaneous transvenous mitral annuloplasty.

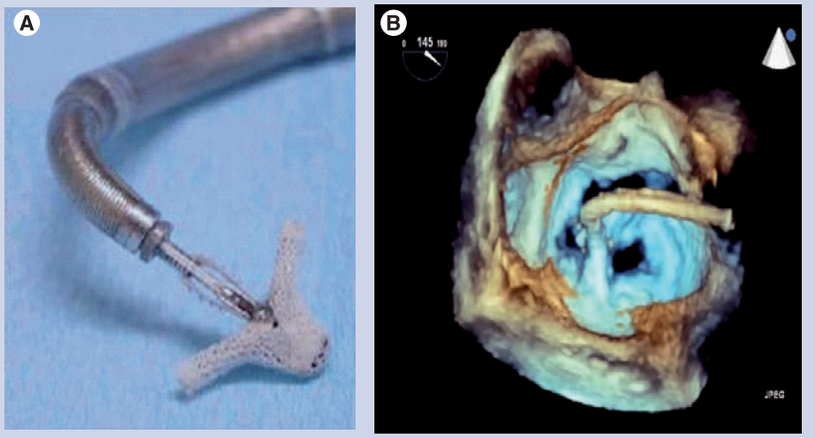

Figure 7. The MitraClip™ device for percutaneous leaflet repair. (A) The MitraClip attached to the delivery catheter in the opened position immediately prior to grasping of the mitral valve leaflets. **(B)** 3D echo of the delivery catheter advanced through the interatrial septum, with clip still attached after grasping the mitral valve leaflets.

trial (PTOLEMY I; ClinicalTrials.gov Identifier NCT00571610) [51], while proof of functional benefit regarding reduction of MR is still awaited (PTOLEMY II trial; ClincalTrials.gov Identifier NCT00815386).

Transcatheter mitral valve repair: percutaneous leaflet repair

In the surgical literature, an edge-to-edge MVR technique was described by Alfieri and colleagues in 2001, whereby the edges of the anterior mitral leaflet (AML) and the posterior mitral leaflet (PML) are sewn together at the coaptation line, producing a double-orifice valve [52]. Today the Alfieri technique is primarily indicated in organic MR due to AML prolapse or in selected cases of bileaflet prolapse. Attempts to emulate this surgical maneuver by catheter-based techniques have been pursued.

The Mobius™ II leaflet repair system (Edwards Lifesciences) has been evaluated in a safety and feasibility trial, but further investigation has been halted owing to technical difficulties and disappointing preliminary results.

By contrast, the MitraClip™ device (Abbott Vascular, CA, USA) has achieved considerable early clinical success. It consists of a polyester-covered metal clip, which engages and approximates the edges of the AML and PML (Figures 7 & 8). It is introduced via the femoral vein and delivered to the MV via puncture of the interatrial septum. Guided by TEE and fluoroscopy, the clip is advanced into the LV, opened and then pulled back, grasping the leaflet margins. Before the clip is detached from the deployment catheter, it can be repositioned or retrieved. One or more additional clips can be applied if adequate reduction of MR is not achieved. In case of persistent or recurring MR, surgery remains an option for most patients, with reports of successful MVR up to 5 years after the procedure [53].

The device has been evaluated for safety in a Phase I clinical trial (A Study of the Evalve Cardiovascular Valve Repair System Endovascular Valve Edge-to-Edge Repair Study [EVEREST I]; ClinicalTrials.gov Identifier NCT00209339) in 55 patients [54]. In the EVEREST II trial (ClinicalTrials.gov Identifier NCT00209274), 279 patients were randomized in a 2:1 ratio to receive treatment with the MitraClip system or surgical MVR. The 12-month results were recently presented at the American College of Cardiology (ACC) Annual Meeting 2010 [55]. Both the superiority hypothesis regarding safety as well as the noninferiority hypothesis regarding clinical success rate were formally met according to prespecified margins. However, trial design, especially the definition of clinical end points, remains a controversial subject.

At present, our group has gathered the largest single-center experience with the MitraClip system worldwide, with over 150 patients treated. In contrast to the EVEREST trials, the device is exclusively being applied in patients with severe comorbidities and a prohibitively high surgical risk as evaluated by an interdisciplinary team of cardiologists and cardiac surgeons. Usually, these patients present with functional MR or mixed MV disease (MR grade 3 or 4 in all patients) in combination with cardiomyopathy. In an interim analysis, acute outcome after treatment of 51 patients was assessed [56]. The mean patient age was 73 ± 10 years; the mean LV ejection fraction was 36 ± 17%. Risk stratification revealed a mean logistic EuroSCORE

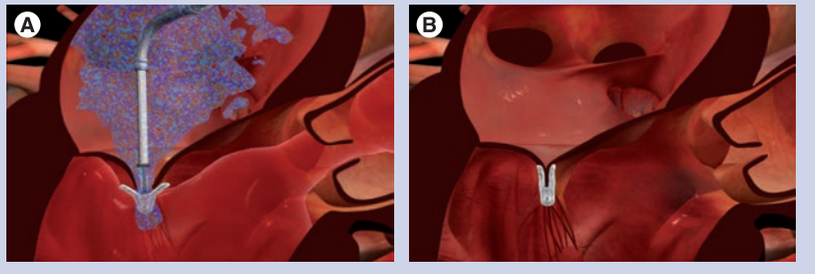

Figure 8. The MitraClip™ device for percutaneous leaflet repair. (A) After trans-septal puncture, the delivery catheter with the MitraClip is advanced into the left ventricle and opened after adequate positioning. **(B)** Retraction and closure of the clip results in approximation of the free leaflet margins.

of 28 ± 22%. Clip implantation was successful in 96.1% (49 out of 51 patients). Most patients were treated by a single clip, while two clips were used in 14 patients (27.5%) and three clips were used in one patient (2.0%). Despite a pronounced risk profile, there were no major periprocedural complications and no in-hospital mortality. At discharge, the severity of MR was reduced by one grade in 16 patients (32.7%), by two grades in 24 patients (48.9%) and by three grades in nine patients (18.4%). Whether these favorable acute results will translate into long-term benefit remains to be determined. However, preliminary experience appears to suggest stable reduction of MR in the majority of patients and marked clinical improvement regarding New York Heart Association (NYHA) functional class in a follow-up of 3 months [Franzen O, Unpublished data].

Future perspective

In view of an aging population in western societies and a rising prevalence of valvular heart disease, transcatheter heart valve therapies will gain increasing prominence in the future. At present, technical deficiencies and unknown long-term performance of current-generation devices limit their clinical application for a broader patient population. Modern valve surgery has evolved over decades to become the standard of care for the vast majority of patients, with excellent clinical outcome.

For TAVI, current technical problems seem resolvable and an extension of the technique to younger and healthier patients appears likely. However, before expanding inclusion criteria, randomized clinical trials are needed to compare TAVI to surgical AVR and to determine the adequate treatment strategy for the individual patient. The currently ongoing North American Placement of Aortic Transcatheter Valve (PARTNER) Trial has randomized high-risk patients to TF- or TA-AVI using the Edwards Sapien valve or to the standard of care (surgical AVR or medical therapy), with interim data expected later in 2010.

At present, we believe evaluation of patients for TAVI or surgery is best accomplished by a dedicated interdisciplinary teams of cardiologists and cardiac surgeons at specialized heart centers.

Executive summary

Transcatheter aortic valve implantation: background & patient selection

- For the vast majority of patients with valvular heart disease, minimally invasive or conventional surgical valve repair or replacement remains the procedure of choice with well-defined indications, low perioperative morbidity and mortality and excellent long-term results.
- Transcatheter aortic valve implantation has been established as an alternative treatment option for patients with severe aortic stenosis presenting with prohibitively high surgical risk or contraindications to surgery.

Transcatheter aortic valve implantation: current & future devices

- To date, most clinical experience has been gathered using the Edwards Sapien™ and the CoreValve™ systems, both of which have received commercial approval in Europe (CE mark).

Techniques of transcatheter aortic valve implantation

- Transcatheter aortic valve implantation via a transfemoral or a transapical approach has become a viable treatment alternative at specialized centers. As of yet, definite proof of the superiority of one technique over the other remains to be demonstrated.
- Complications following transcatheter aortic valve implantation include prosthesis malpositioning with resulting paravalvular leakage, device migration or coronary obstruction, persistent conduction disturbances with the need for subsequent pacemaker implantations or vascular injury after transfemoral aortic valve implant. However, with increasing experience, technical advances and improved imaging modalities, complication rates have decreased substantially in the more recent series.

Transcatheter mitral valve repair: background

- In recent years, different transcatheter approaches for the treatment of mitral regurgitation have been developed, many of which mimic established surgical techniques. These techniques include coronary sinus annuloplasty, direct annuloplasty, leaflet repair strategies and left ventricular chamber remodeling devices.

Transcatheter mitral valve repair: coronary sinus annuloplasty devices

- Coronary sinus techniques for mitral repair have been conducted with disappointing results due to anatomical incongruities, technical difficulties with current-generation devices or inadequate reductions in grade of mitral regurgitation. Reported complications include sinus perforation or thrombosis, cardiac tamponade or compression of coronary arteries.

Transcatheter mitral valve repair: percutaneous leaflet repair

- In our experience, transcatheter mitral leaflet repair using the MitraClip™ device yields good results as an adjunct to medical therapy in patients with end-stage heart failure or in case of prohibitively high surgical risk or contraindications to surgery.

Conclusion

- At present, the use of transcatheter heart valve therapies should remain restricted to high-risk patients with limited surgical options. However, for transcatheter aortic valve implant, extension of the technique to a broader patient population seems likely to occur in the foreseeable future as technical shortcomings of the current-generation devices are being resolved.

Regarding MV disease, the bar for transcatheter therapy may be an even higher one. For degenerative disease, where surgical strategies are highly complex procedures comprising combined valvuloplasty and annuloplasty in most cases, it seems most unlikely that any interventional technique will ever be able to compete. Functional MR on the other hand, may represent a new indication for palliative transcatheter treatment as an adjunct to medical therapy in otherwise inoperable patients.

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