

Transcatheter Aortic and Mitral Valve Update

The progress and promise of valvular interventions.

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The field of valvular intervention is the fastest growing subspecialty of the interventional cardiologist and cardiac surgeon. The predominant experience has been with implantation of the aortic valve, with nearly 20,000 cases performed worldwide. The progress in transcatheter mitral valve repair is also exciting, as seen in the recent presentation of the EVEREST II trial. We summarize the current state of transcatheter aortic and mitral interventions, knowing the limitations of such a review in a field that is evolving so rapidly.

TRANSCATHETER AORTIC VALVE IMPLANTATION

Since the first transcatheter aortic valve implantation (TAVI) 8 years ago,¹ physicians and industry have worked together to greatly improve procedural techniques and device design, expanding the applicability of TAVI technology. Currently, there are three transcatheter heart valves (THV) undergoing human implantation: the Edwards Sapien valve (Edwards Lifesciences, Irvine, CA), the CoreValve (Medtronic, Inc., Minneapolis, MN), and the Direct Flow valve (Direct Flow Medical, Santa Rosa, CA).

THE EDWARDS SAPIEN VALVE

The Edwards Sapien valve (Figure 1) is a tricuspid, bovine pericardial valve mounted in a balloon-expandable stainless steel (23- or 26-mm diameter) stent. The expanded stent displaces the native valve into the sinuses of Valsalva and anchors within the aortic annulus in the subcoronary position. The 23-mm valve is intended for an aortic annulus of 18 to 21 mm; the 26-mm valve is intended for a 22- to 24.5-mm annulus.^{2,3} Although the original concept was to place the valve through an antegrade transseptal route, at present, the valve is delivered through either a retrograde transarter-



Figure 1. The Edwards Sapien valve.

rial (22- or 24-F sheath in the United States) or a transapical route. The former is limited by the size and extent of atherosclerotic disease in the iliofemoral system of the patient because the actual outer diameters of the delivery sheaths are 8.3 (25 F) and 9.3 mm (28 F) for the respective valve sizes. Most delivery sheaths are placed via a surgical femoral artery cutdown, although some centers use a true percutaneous approach for patients who need the 23-mm valve. In Europe, the new-generation Edwards Sapien XT valve (cobalt chromium stent frame) and NovaFlex delivery system are available, and the 23- and 26-mm valves are implanted through an 18- and 19-F sheath, respectively, expanding the application of the transfemoral approach to patients with a femoral artery size > 6 mm, favoring completely percutaneous procedures under local anesthesia/conscious sedation.

THE COREVALVE

The CoreValve device (Figure 2) is a porcine valve mounted in a self-expanding nitinol stent. The distal end is flared to anchor in the ascending aorta, and the proximal end is designed to be deployed at the left ventricular edge of the aortic annulus. The 26-mm CoreValve (accommodates annuli 20–23 mm) and the 29-mm



Figure 2. The CoreValve device.

CoreValve (accommodates annuli 23–27 mm) can be delivered through an 18-F sheath, and thus the CoreValve is commonly used as a true percutaneous device.⁴ However, it is placed only via a retrograde arterial route from the femoral or subclavian approach; a transapical approach is not available for this valve. Unlike the Sapien valve, the CoreValve does not require rapid pacing during deployment.

THE DIRECT FLOW VALVE

The DirectFlow (Figure 3) valve is a new trileaflet bovine pericardial tissue valve attached to an inflatable framework with a conformable polyester fabric cuff. A hardening polymer is injected into the inflatable frame before final deployment to provide additional radial strength. The DirectFlow valve is limited to an annulus diameter between 19 and 23 mm. In the catheterization laboratory under general anesthesia, a 22-F sheath is placed in the femoral artery, and the THV is guided retrograde across the aorta.⁵ Because the frame is collapsible, the valve has the advantage of being repositioned and retrieved before the injection of the hardening polymer. Furthermore, it does not require rapid ventricular pacing during deployment.

OUTSIDE UNITED STATES REGISTRY DATA European PARTNER Trial

So far, the majority of short- and midterm TAVI data have come from European and Canadian registries. The PARTNER European Registry is one of three major registries of “outside United States” experience using the Edwards Sapien THV. Its primary safety endpoint was freedom from death from the index procedure to 30 days and 6 months. The primary efficacy endpoint was hemodynamic status of the valve, quality of life (QOL), and New York Heart Association (NYHA) improvement at 12 months after implantation. To be included in the registry, patients had to meet strict criteria for high surgical risk: a logistic EuroSCORE of > 20% and/or an STS

score of $\geq 10\%$ if the EuroSCORE was < 20%, and comorbidities such as porcelain aorta or chest deformities that precluded open chest surgery. All patients had senile degenerative aortic valve stenosis with a documented aortic valve area < 0.8cm², a mean valve gradient of > 40 mm Hg, and/or jet velocity by ultrasound > 4 m/s.

Outcomes. The results showed the mean age of the patients was 82 years, and 84% and 85% of the transfemoral and transapical group had NYHA class III and IV heart failure, respectively. The EuroSCORE was 26 and 34 for the transfemoral and transapical groups, respectively. Not surprisingly, the transapical cohort had greater comorbidities.

With placement of the THV, mean aortic gradient decreased to 10 mm Hg and aortic valve area rose to 1.6 cm². These values remained the same at 6-month and 1-year follow-up. Mean left ventricular ejection fraction, reasonably well preserved at 54% before implantation, was unchanged. Patients who survived to 1-year follow-up had a dramatic improvement of NYHA class (60% class I–II). To support this, QOL scores improved at 1 year by 23 points.

At 18-month follow-up, patients in the transfemoral group had a 71% survival rate, whereas those in the transapical group had a 44% survival rate. It must be emphasized that comparisons between the transfemoral and transapical groups are not valid due to the major differences in comorbidities between the two groups and especially the presence of peripheral vascular disease (a marker of more severe atherosclerotic disease and hence poorer outcomes) in the transapical group.⁶

The post-PARTNER registry (SOURCE) has recently reported on the 30-day outcomes and complications

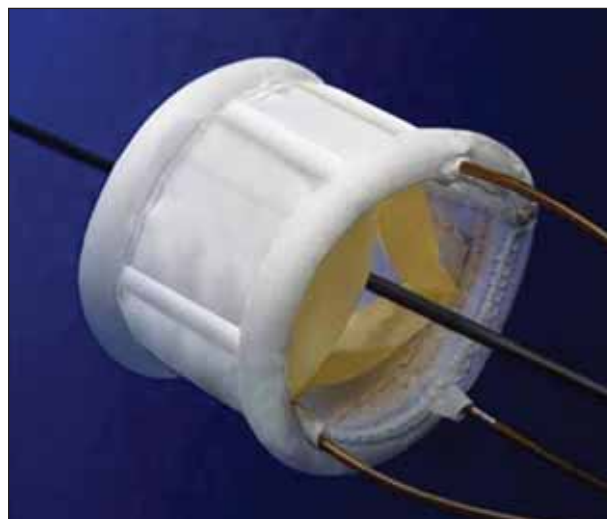


Figure 3. The Direct Flow valve.



Figure 4. The MitraClip device.

of the 1,038 patients (transfemoral, $n = 463$; transapical, $n = 575$) undergoing TAVI between 2007 and 2008. The procedural success rate was 94%, with 22 patients requiring a second valve-in-valve procedure due to malposition or severe aortic insufficiency. The mortality rate at 30 days was 8.5% (transfemoral, 6.3%; transapical, 10.3%). Major vascular complications were the most common problem, occurring in 10.6% of transfemoral patients, accompanied by significant aortic insufficiency (2.3%), stroke (2.5%), valve embolization (0.3%), coronary obstruction (0.6%), pacemaker implantation (7%), and aortic dissection (1.3%).⁷

Canadian Edwards Registry

The Canadian registry of the Edwards Sapien THV from 2005 to 2009 in six centers also had very encouraging results:⁸ there were 339 high-risk patients (STS $9.8\% \pm 6.4\%$) enrolled, with 49.6% transfemoral and 50.4% transapical cases. The procedural success rate was 93.3%, with a 30-day mortality of 10.4%. Mortality was 22% at a mean follow-up of 8 months, with periprocedural sepsis, need for hemodynamic support, chronic kidney disease, and chronic obstructive pulmonary disease as independent predictors of late mortality, regardless of the approach. Patients with porcelain aorta and frailty had acute outcomes similar to the overall cohort, and patients with porcelain aorta had as good or better survival at 1-year follow-up.

FRANCE Registry

In November 2009, the results of the FRANCE Registry were released from 19 sites. Patients in this registry had similar baseline demographics to the European PARTNER Registry, but patients in this registry received either the Edwards Sapien THV or the CoreValve device.⁹ Patients had severe aortic stenosis with valve areas $< 0.6 \text{ cm}^2/\text{m}^2$, NYHA > 2 , high surgical risk with a EuroSCORE $> 20\%$ (STS $> 10\%$), or a contraindication for surgery. The primary endpoint was 30-day mortality, and secondary endpoints were up to 3-year mortality, major adverse cardiac events, hemodynamics, and QOL.

Approaches used. Thirty-nine percent of the patients

in this registry received the Edwards Sapien THV via the transfemoral route, 29% received the Edwards Sapien THV via a transapical approach, 27% received a CoreValve device via the transfemoral approach, and 5% received a CoreValve device via a subclavian approach. Placement of the devices was accomplished in 97% of patients.

Outcomes. Major complications, including death at 30 days, stroke, vascular complications, and transfusions of > 1 unit, occurred in 13%, 4%, 7%, and 21%, respectively. There were few differences in mortality, stroke, or vascular complications among the groups. However, the need for a new permanent pacemaker was considerably higher in the CoreValve group compared to the Edwards Sapien THV group. At 6 months, 76.5% of the registry patients were alive, with mean valvular gradients of approximately 10 mm Hg. Eighty-six percent were NYHA class I and II.

German CoreValve Registry

In Siegburg, three generations of the CoreValve device have been tested between 2005 and 2008.¹⁰ With the latest generation (18 F), the report of 102 consecutive patients is excellent, with 0% procedural death and 91.2% procedural success. Major stroke occurred in 1%, and the 30-day mortality rate was 14.7%. The mean gradient decreased from 41.5 ± 16.7 mm Hg to 8.1 ± 3.8 mm Hg postprocedure, and NYHA class improved from 3.3 ± 0.5 to 1.7 ± 0.7 , with sustained improvement during the 1-year follow-up. The mortality rate at 1 year was 32%, although only half of the patients were followed for more than 30 days. In-hospital pacemaker requirement was 33.3%.

Spanish CoreValve Registry

Midterm results have recently been published from the experience of three Spanish hospitals of 108 patients who underwent TAVI between 2007 and 2009 with the third-generation (18 F) CoreValve device.¹¹ Procedural success was 99%, with one patient requiring a second valve due to a poorly positioned first valve and another experiencing aortic annulus rupture during valvuloplasty before implantation. The mortality rate at 30 days was 7.4% compared to a logistic EuroSCORE of 16%. Mean gradient decreased from 55 mm Hg to 2.4 mm Hg after the procedure. Morbidity was low, but there was a high incidence of permanent pacemaker placement (35%).

Direct Flow Registry

Two centers in Germany placed Direct Flow valves in 31 patients between 2007 and 2008.⁵ Successful implantation was reported in 71% of patients, with a decrease

in the mean gradient from 50 mm Hg to 15 mm Hg and an increase in aortic valve area from 0.55 cm² to 1.39 cm². Six-month follow-up showed a mean transvalvular gradient of 20 mm Hg. Symptomatic improvement at 6 months has been impressive, with 94% of patients experiencing NYHA I/II symptoms compared to only 29% at baseline.

Conclusions From Canadian and European Registry Trials

Some conclusions can be drawn from these registry data. First, THV implantation with the CoreValve and Edwards Sapien bioprostheses in high-risk patients seems to be safe and efficacious. The 30-day mortality rate is 7% to 15% in patients at high or prohibitive risk for surgery. In these multiple registries, patients receiving a THV have 1-year survival rates of approximately 75%. Almost certainly much of the later mortality occurring after 30 days is due to patient comorbidities, although the deaths have not been adjudicated. NYHA class is much improved in patients receiving a THV, as is QOL. Similar results have been seen with the Direct Flow valve, although experience is early, and the follow-up data are limited.

These positive conclusions are accompanied by some limitations. Although mortality at 1 month is reported to be in the low double digits, morbidity can be higher. Patients must be screened carefully for clinical and anatomical factors to maintain a reasonable safety profile before proceeding to TAVI. Pacemaker need, although also present in surgical series of aortic valve replacement, can be much higher when using devices such as the CoreValve. All of the currently available valves have acceptable short- and midterm maintenance of valve area and low residual aortic gradients, but longer-term data are needed before these devices can be recommended to younger patients.

TRANSCATHETER MITRAL VALVE REPAIR

Transcatheter treatment of mitral regurgitation has been focused on mitral valve repair rather than replacement. Several strategies for transcatheter mitral valve repair have been evaluated, but the one with greatest promise appears to be the edge-to-edge repair technique.

Edge-to-Edge Repair

Edge-to-edge repair was initially designed for patients with primary degenerative mitral valve disease and was first demonstrated surgically by Dr. Alfieri in 1991.¹² The MitraClip (Abbott Vascular, Santa Clara, CA) (Figure 4) is a percutaneous device that mimics the Alfieri stitch

by placing a clip on the A2–P2 segments of the mitral valve, thus improving coaptation and decreasing mitral regurgitation (MR). The technique involves the introduction of a 24-F grasper into the left atrium where it is directed toward the central MR jet. The anterior and posterior leaflets are captured, and the clip is released after successful reduction of MR is shown on echocardiography. The majority of patients in the phase I trial had degenerative MR (93%), and a small number (two patients, 7%) had ischemic MR.¹³ The results showed that this approach was feasible (89%, 24 of 27 patients received clips), and the major adverse events rate at 1 month was 15% (three patients had partial clip detachment and one patient had a postprocedural stroke [not related to clip detachment] that resolved by 30 days). Based on these results, a pivotal trial comparing the MitraClip with traditional surgery was performed in the United States (EVEREST II).¹⁴

In the EVEREST II trial, the MitraClip was successfully implanted in 77% of patients. At 12 months, the clinical success rates, defined as freedom from death, > 2+ MR, and mitral valve surgery, were 72% for those undergoing successful implantation versus 88% for those undergoing mitral valve surgery, achieving statistical noninferiority. Reverse remodeling of the ventricle was observed in the MitraClip and surgical patients, although there was greater reduction in MR severity in the surgical cohort. Clinical benefit was observed in both groups, with 98% of successful MitraClip implant patients and 88% of surgical patients experiencing NYHA class I/II symptoms at 12 months.

When patients with degenerative MR were compared to those with functional MR, results were similar. Improvement in MR to ≤ 2+ was achieved in 83% of patients with degenerative MR and in 78% of patients with functional MR. Durability of the MitraClip was excellent, with no difference between the two groups in the need for mitral valve surgery after 1 year. The greatest difference between the MitraClip and surgery was in procedural safety. The rate of major adverse events was 57% in the surgical cohort compared to 10% for MitraClip patients, due largely to the need for transfusion in the surgical group. These results suggest that the MitraClip is clinically equivalent to mitral valve surgery in early follow-up, with the advantage of having significantly less periprocedural morbidity.

Coronary Sinus Devices

Other devices to treat functional MR aim to remodel the annulus, thus decreasing the septal-lateral annular distance of the mitral apparatus, increasing leaflet

coaptation. The majority of the experience in humans has been with devices placed in the coronary sinus, although data are limited to phase I trials. The Carillon mitral contour device (Cardiac Dimensions, Kirkland, WA) consists of a 9-F teflon catheter and a self-expanding, fixed-length nitinol frame with helical anchors at each end that recontours the posterior annulus, bringing it more anterior.¹⁵ The results of the phase I study (AMADEUS) showed that implantation was feasible (30 of 48 patients) and that there was an average reduction in MR of 20% to 30% across a variety of measures of severity. Furthermore, significant improvements in 6-minute walk distance and NYHA symptoms were reported. Based on these results, the Carillon device received CE Mark approval in Europe in January 2009.

The Viacor percutaneous transvenous mitral annuloplasty device (Viacor Inc., Wilmington, MA) uses a 7-F system composed of a multilumen catheter containing internal nitinol rods that can be positioned in the coronary sinus to reduce the anterior-posterior dimensions of the valve.¹⁶ It also allows for adjustment of the rods with real-time assessment of MR reduction before permanent device deployment. Successful implantation was accomplished in nine patients as part of a phase I investigation in Europe and Canada, with most patients having a reduction in regurgitation of at least one grade. Coronary sinus devices can jeopardize the underlying circumflex artery, and careful selection of patients must be made to avoid compression at the time of implantation.

Noncoronary Sinus Devices and Other Strategies

Noncoronary sinus devices have been tested in animals, but human experience has been very limited. These devices include the iCoapsys (Myocor, Maple Grove, MN), PS3 (Ample Medical, Foster City, CA), Mitralign System (Salem, NH), QuantumCor (Lake Forest City, CA), and many others in even earlier stages of development. Implantation of the Edwards Sapien THV within a degenerated surgical valve has been performed successfully for the treatment of MR. Other THV implants are under study.

CONCLUSIONS

Significant progress has been made during the last decade in the field of valvular interventions. The forecast for TAVI is very promising as an alternative to surgery for all high-risk patients. As long-term data are accumulated, this technology may be extended to healthier and younger patients. The MitraClip has shown promise as a reasonable alternative to surgery in

highly selected patients, although longer follow-up is needed to assess the durability of repair. ■

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