Transcatheter Aortic Valve Implantation in High-Risk Patients With Severe Aortic Stenosis

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Although surgery is the gold standard for severe aortic stenosis (AS) treatment, it is considered high risk in elderly patients because of high complication rates, which leads to substantial hesitation in submitting such patients to surgery. With the growing need to treat elderly patients with severe AS, percutaneous transcatheter aortic valve implantation (TAVI) was pioneered in 2001, followed by implantation of a self-expanding percutaneous aortic valve in 2005. As of April 2010, these 2 methods of TAVI have been used in more than 15,000 patients throughout the world. The acute success rate of this procedure is now increasing up to 95.4% by the transfemoral approach and 92.7% by the transapical approach with regard to Edwards SAPIEN® valve implantation. In terms of the CoreValve ReValving® system, it is reported as 98.2% in an expert's hands. This article reviews the methods of TAVI and the devices, not yet been approved in Japan but are expected to be available in a few years. (Circ J 2010; 74: 1513–1517)

Key Words: Aortic stenosis; Elderly; Percutaneous aortic valve replacement; Transcatheter aortic valve implantation

Advent of Transcatheter Aortic Valve Implantation

Aortic stenosis (AS) has increased markedly in developed countries and AS, caused by valve calcification in the elderly, will continue to increase as the aging of society accelerates. 1 With a growing need for treatment of elderly patients with severe AS, Cribier et al from France succeeded in percutaneously implanting a stent-mounted aortic valve in 2001 (Figure 1). 2 In 2003, the European Heart Journal reported that at least 30% of patients who should have surgery for valvular heart disease do not actually undergo surgical treatment, 3 which drew great attention to percutaneous transcatheter implantation of a stent-mounted aortic valve, as done by Cribier et al, for the treatment of severely ill patients via the venous approach under local anesthesia. 4 The fact that surgery is not being performed for 30% or more of patients requiring it represents the reality as it exists for treating valvular heart disease. In 2005, Grube et al implanted a self-expanding percutaneous aortic valve and published their short-term results for 25 patients the following year. 5

The mechanism of AS pathophysiology and the specific methods of recent examination and treatment are well described in the literature. 1,6,7 The prevalence of cases of AS in the elderly is now 5–7% in developed countries and continues to increase. AS is thought to be initiated by arteriosclerosis and inflammation, leading eventually to calcification and restricted opening of the valve with advancing age. Once symptoms of chest pain, syncope, and cardiac failure develop, the prognosis becomes significantly worse. 8 Although AS resulting from a congenital bicuspid valve is usually not considered as suitable for percutaneous treatment, 9 this method has nevertheless been tried in some cases.

Design of the Device

Several hurdles had to be overcome before percutaneous valvular disease treatment became possible via catheter. Requirements for device design, platform, and delivery system had to be met, including valve construction from biocompatible materials and a design that minimized leakage after implantation. Morphology of the landing zone, the annulus and subvalvular area, and other morphologic features mandate tricuspid configuration. Moreover, the system had to be small enough to allow percutaneous access, and could not cause hemodynamic deterioration when implanted. After tolerability studies and implantation experiments in animals, percutaneous therapy was applied to patients.

Cribier-Edwards Valve

This valve was developed and used by Cribier et al in France. 4 The first-generation valve was made of polyurethane and the second-generation one was crafted from bovine pericardium. Initial valves were 21–23 mm in diameter and 14 mm in length. The valves withstood 100 million or more heartbeats during bench tests (equivalent to use for 2.5 years) and were initially implanted in the hearts of 60 sheep. After confir-
ing that this technique was practicable and did not lead to abnormal valve function, clinical application was initiated. Subsequently, devices made from horse pericardium were developed, followed by an increase in the number of implantation procedures. The valves had stainless steel stents and were balloon-expandable. The 23-mm diameter valve was the one first utilised by Cribier et al. Currently, new models known as the Edwards SAPIEN® (Figure 2a) and SAPIEN XT® are used, with several others in development.

**Initial and Midterm Results**

An early pilot study (n=4) was done between 2002 and 2003, followed by I-RIVIVE (n=16) between 2003 and 2004, and RECAST (n=20) between 2004 and 2005. These phase I studies were sequentially performed in Rouen, France. The inclusion criteria were age 70 years or older, unsuitability for surgical aortic valve replacement (as confirmed by different teams of 2 or more surgeons), and the presence of 2 or more complications. These patients were so sick that 27 died preoperatively while waiting for TAVI. In the phase 1 studies, there was neither coronary artery occlusion nor prosthetic

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**Figure 1.** (Left) 23-mm percutaneous aortic valve implantation with balloon dilatation. (Middle) The percutaneous prosthetic valve is placed in the position of the original aortic valve. (Right) Although aortography shows very slight regurgitation (arrow), there are no abnormalities of the right and left coronary ostia. PHV, percutaneous heart valve; LCA, left coronary artery; RCA, right coronary artery. (Cited from Circulation 2002; 106: 3006–3008.)

**Figure 2.** (a) Edwards SAPIEN® valve stent used for percutaneous transcatheter aortic valve implantation. Bovine pericardium is sewn to a stainless steel stent. Diameter: 23 mm and 26 mm (corresponding to 22Fr and 24Fr sheath, respectively). (b) Sheath and flex catheter (RetroFlex3™) dedicated for implantation of Edwards SAPIEN® valves. (Permission from EdwardsLifesciences LLC.)
Advent of Transcatheter Aortic Valve Implantation

valve displacement or dysfunction after successful implantation until 2006. The combined results of I-RIVIVE and RECAST were published in 2006, showing that 33 of the 36 registered patients actually underwent implantation, with success in 27 (82%). With good postoperative valve function, there was an increase of valve area from 0.6 cm$^2$ to 1.7 cm$^2$ and a decrease of the mean aortic valve pressure gradient from 37 mmHg to 9 mmHg. The overall incidence of major adverse cardiac and cerebrovascular events (MACCE) up to 30 days postoperatively was 26%, with 6 deaths (2 because of cardiac tamponade and 1 each of sepsis, post-resuscitation, ventricular arrhythmia, and unknown) and 1 stroke, but no myocardial infarctions and no emergency surgery. The postoperative 30-day mortality rate (predicted by the Personnet score) of this patient group was 25% or higher. The incidence of MACCE at 6 months was high (37%) and many patients died after other surgery or because of renal failure following successful percutaneous treatment of AS (10 deaths: renal failure, 3; postoperative, 3; pulmonary embolism, 1; pneumonia, 1; cancer, 1; multiple organ failure, 1). However, there were no cases of stroke, myocardial infarction or emergency open heart surgery, and there were no adverse events caused by the implanted prosthetic valve in any of the patients. In the patients without MACCE, 2-year follow-up disclosed no problems regarding the aortic valve area and pressure gradient, and significant improvement of symptoms.

Evolution of Implantation Techniques, Devices, and Systems

The technique of Cribier et al was successful via the antegrade approach, but it was cumbersome, suggesting that increased adoption of percutaneous TAVI would require development of the retrograde approach. However, because the risk of arterial complications was known as a limitation of that approach, careful screening of the site was necessary, and it became routine to select the approach site after carefully examining imaging studies for vessels tortuosity and determining whether the arteries at the puncture site and through which the catheter would pass were of sufficient diameter.

Another difficulty with the percutaneous approach is precise localization of the prosthetic valve during implantation. Because the heart is functioning, each heartbeat moves the valve, making precise localization difficult. Therefore, the rapid pacing method (220 beats/min) was initiated with a pacemaker during the actual implant.

Because it was unlikely that a 22–24 Fr sheath could be used via the femoral artery in elderly patients with marked arteriosclerosis and vascular tortuosity, the FLEX catheter series was developed (the current model is RetroFlex3™), which allows the device to pass through even a tortuous aorta (the 18Fr NovaFlex catheter obtained CE mark in March 2010).

Transapical Approach

After adoption of the retrograde approach, screening examination of the lower limb vessels revealed that the system could not be inserted in some patients. In Canada, Webb et al experienced a case of iliac artery rupture when they tried to insert a Cribier-Edwards valve, and they subsequently developed a method by which the sheath was directly inserted into the myocardium and a wire was passed through the aorta to implant the device. Their technique was based on the established method of transmitting blood from the apex during aortic dissection surgery. Unlike the percutaneous approach, a 33Fr sheath was used initially, which led to problems such as postoperative left ventricular hemorrhage and hematoma.

At present, the 26Fr Ascendra™ system and the Ascendra 2™ with increased operability are available. Although the transapical approach does not involve arterial complications, recent results show no decrease in chronic MACCE, suggesting that patients with more severe arteriosclerosis are being selected.

Figure 3. ReValving System® for percutaneous transcatheter aortic valve implantation. (Left) Self-expanding valve stent (26mm and 29mm). (Right) Delivery system: 12Fr shaft with 18Fr tip structure.
Increased Success Rate, Durability, and Expanding Range of Indications

In May 2009, the Source Registry data were reported at EuroPCR and the results for 1,038 patients from 32 sites were a success rate of 90.1% and a 30-day mortality rate of 8.5%, indicating that the outcome had improved dramatically compared with the initial results. The logistic EuroSCORE of the patients ranged from 25.7 to 29.2 (higher in the transapical approach group). Long-term durability evaluations of the bioprosthetic valves are still ongoing; however, the longest reported clinical follow-up in Rouen is greater than 6 years without any valve dysfunctions.

The PARTNER Trial: AoRTic TraNscatheter Valve Placement Trial

This is a non-inferiority trial of TAVI with the Edwards SAPIEN® vs surgical aortic valve replacement, with drug treatment in another arm. Enrollment was completed in 2009 and the results will be published in late 2010. Depending on the outcome, the US Food and Drug Administration is expected to approve the use of this prosthetic valve in 2011.

CoreValve ReValving System

Background In 2004, 2 years after Edwards Lifesciences developed and clinically applied the Cribier-Edwards prosthetic valve, Grube et al from Germany developed a self-expanding percutaneous aortic valve, together with the CoreValve ReValving System®, and clinically applied it in India. Their “ReValving system” originally used a 25Fr sheath, but reduction of the sheath size to 21Fr and then to 18Fr was achieved, together with improvement of the clinical results (Figure 3).

Initial Implantation Technique Grube et al first performed implantation with cardiopulmonary bypass (Figure 4). Although this technique differed from the concept of requiring no surgery and treatment under local anesthesia, as proposed by Cribier, it was required in the initial cases for the safe placement of the self-expanding stent valve in an ideal position and because marked blood pressure reduction or shock was expected during adjustment of the valve position while unsheathing and expanding the stent with a rotator. After the diameter of the sheath was reduced, implantation under local anesthesia was initiated. Although rapid pacing was initially required, this is no longer necessary.

Reduction in Equipment Size and Treatment Results Although the initial system was 25Fr, a reduction in diameter to 21Fr was achieved and an 18Fr system is currently used, but a 16Fr system is now under development, which would lead to a decrease in complications. The results of a multicenter trial published in 2008 (646 patients) showed a very high success rate of 97% and a mortality rate of only 1.5% for the technique. The overall 30-day mortality rate was 8.0% and the incidence of MACCE was 9.3%. The ReValving System (Medtronic) recently achieved over 5,000 implantations around the world. In all trials, unlike the prosthetic valves made by Edwards Lifesciences, many patients have required permanent pacing after implantation because of the complete heart block induced during the procedure. Reports
to date suggest that 10–50% of patients require a permanent pacemaker after implantation with the ReValving system, most likely because the atrioventricular conduction pathway is compressed at the left ventricular outflow tract and damaged by the tip of the device extending along the longitudinal axis. Some patients develop recurrent left bundle branch block after prosthetic valve placement, which resolves with time, and those with preoperative right bundle branch block often need a postoperative permanent pacemaker.15 Although the 18Fr system of Medtronic had the advantage of less complications at the access site compared with the device made by Edwards Lifesciences, both companies have provided an 18Fr system since March 2010.

New Possibilities The ReValving System uses the smallest sheath among the percutaneous prosthetic valves being implanted to date, but can not deliver the catheter if the iliac artery or aorta is very tortuous. Therefore, an approach via the subclavian artery that takes advantage of the 18Fr size of the system has been devised.16 Also, in patients with prosthetic valve dysfunction after surgical aortic valve replacement, treatment by a “valve in valve” method has been initiated, with the ReValving System being used to add a new valve to the prosthetic valve.15

Second-Generation TAVI

Although the first-generation prosthetic valves have been mainly used to date (Table), the second generation of percutaneous prosthetic valves has been developed and applied clinically. Companies have made various efforts to improve the ease of implantation, reduce aortic valve incompetence, and reduce the sheath diameter. One of the most important points is a new design that allows for retrieval. Although the first-generation prosthetic valves cannot be retrieved after being implanted, the second-generation valves can usually be retrieved after placement unless the valve has become completely detached.

Summary

This review of TAVI reflects current performance outside Japan. Many patients with severe AS requiring valve replacement will likely be treated using transcatheter-based, less-invasive modalities in the near future as valve performance continues to improve. Longer-term durability data is still needed, although clinical outcomes have stabilized with experienced operators. Because AS is expected to increase in the future as the population ages, we look forward to the safe introduction of this treatment option with adequate training programs.

References