

Review Article

Trans-Catheter Percutaneous Aortic Valve Implantation for Severe Inoperable Aortic Valve Stenosis: Where Do We Stand?

GEORGE LATSIOS, ULRICH GERCKENS, EBERHARD GRUBE

HELIOS Heart Center Siegburg, Department of Cardiology/Angiology, Siegburg, Germany

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Address:
George Latsios

*HELIOS Heart Center
Siegburg
Ringstrasse 49
53721 Siegburg, Germany
e-mail: glatsios@hotmail.com*

Why do we need percutaneous aortic valve implantation? One of the commonest heart diseases in the elderly is heart valve disease, especially aortic valve stenosis. It carries a poor prognosis and its prevalence also rises with the mean age of the population.¹ Aortic valve disease (AVD) is present in 26% and symptomatic aortic valve stenosis (AS) in 2% of persons aged 65 years or more, while in persons older than 75 years, AVD is present in 37% and AS in 2.6%.²

Calcified degenerative aortic valve stenosis is currently the most frequent native valve disease in Europe. Furthermore, it is most often seen in elderly patients with comorbidities.³ Once symptoms develop, in the form of angina, syncope or congestive heart failure, the prognosis in these patients deteriorates rapidly, with an estimated life expectancy of two to five years.⁴

Valve replacement is the definitive therapy for patients with severe AS who have symptoms or objective signs determining poor prognosis, such as left ventricular (LV) dysfunction.

The removal of the stenotic calcified aortic valve and its substitution with a purely mechanical or a bioprosthetic one leads to relief of symptoms and prolongation of life expectancy,⁴ with an acceptable

perioperative mortality in properly selected patients. However, in high-risk patients with baseline features such as LV failure, concomitant coronary artery disease, prior bypass graft surgery, chronic obstructive pulmonary disease, extra cardiac arteriopathy, renal failure and/or advanced age, the expected operative mortality ranges from 10% to even 50% in some high-risk patient subgroups.⁵ The EuroSCORE⁵ and more recently the STS Predicted Risk of Mortality score⁶ enabled cardiologists and cardiothoracic surgeons to classify patients as either “good” or “high” surgical risk candidates for conventional open heart surgery.

In the latter group, surgery is often not performed. In the Euro Heart Survey, up to 33% of patients in NYHA functional class III/IV with a diseased aortic valve were declined for surgery or were never considered as surgical candidates, in view of their projected short life expectancy and associated comorbid conditions.³ Balloon aortic valvuloplasty is now rarely used, mainly because of its limited long-term efficacy.^{7,8} Alternative techniques for the treatment of high-risk patients were therefore required.

Based on this need, percutaneous treatment of aortic valve disease with implantation of stent valve prosthesis has been evaluated in animal models over the

past decade.⁹⁻¹¹ In 2002, the first human implantation of a balloon-expandable aortic valve prosthesis was performed¹² (trans-catheter percutaneous aortic valve implantation - TAVI) in a patient with aortic valve stenosis considered inoperable due to severe comorbidities. Initial reports with this new percutaneous valve have been promising, though the optimal device¹³⁻¹⁴ and procedural technique are still evolving, and the restriction of TAVI candidates to end-stage inoperable patients has clouded the interpretation of the feasibility and safety of this procedure.¹⁵⁻¹⁶

In this article we present the two currently available technologies for non-surgical percutaneous treatment of aortic valve stenosis, i.e. trans-catheter implantable valves. Two devices are under clinical investigation for TAVI. One device is the Edwards-Sapien valve (ESV: Edwards Lifesciences, USA), which consists of three pericardial leaflets, initially equine and currently bovine, mounted within a tubular, slotted, stainless steel, balloon-expandable stent. It is currently available in 23 and 26 mm sizes, which need, respectively, 22 and 24 F introducer sheaths. The other device is the Medtronic CoreValve Revalving System (MCV: Medtronic, Minneapolis, USA), which has three pericardial leaflets, initially bovine and currently porcine, mounted in a self-expanding, nitinol frame. It is available in 26 and 29 mm sizes, which go through an 18 F introducer (Table 1). After clinical trials, these two systems received a CE certification in early 2007 (Figure 1).

Three other systems, made by the following manufacturers, have also been studied in Germany. However, so far their use has not been generalized.

1. Sadra Medical, Inc.
2. Direct Flow Medical, Inc.
3. Ventor Technologies Ltd., (now under Medtronic, Inc.).

We will briefly discuss the patients' screening process, which is required before the implantation procedure, as well as the steps of the procedure itself; besides the usual retrograde transfemoral artery route, alternative routes of implantation will be also discussed.

Finally, we will summarize the published cumulative data regarding the immediate success rates of the TAVI procedure and follow up of these patients.

Screening process

In general, the screening process consists of two parts. In the initial phase, the diagnosis and its severity should be confirmed by means of history and standard cardiological examinations (normal transthoracic echo, transesophageal echo [TEE], and coronary angiography). At the same time, the inoperability of the patient should be established and ideally agreed on by a team consisting of an experienced interventional cardiologist, a cardiothoracic surgeon and a cardio-anesthesiologist. Although it is possible that TAVI is an equally good procedure to open-heart surgical aortic valve replacement, the latter still remains the "gold" standard. So, until more data and longer follow up become available, TAVI should be strictly limited to patients considered inoperable, due to various reasons, the most common of which are the following:

Table 1. Trans-catheter aortic valve replacement. Characteristics of CE approved devices.

Product	Edwards-Sapien Valve, ESV	Medtronic CoreValve, MCV
Stent material	Stainless steel	Nitinol
Valve material	Bovine pericardium	Porcine pericardium
Release mechanism	Balloon expansion	Self expandable
Implantation: access	Trans-femoral (and trans-subclavian)	Trans-femoral (and trans-apical)
Sheath size	22 F to 24 F according to valve size	18 F
Femoral artery diameter	>7-8 mm according to valve size	≥6 mm
Suitable aortic annulus sizes	>19 mm, ≤25 mm	>20 mm ≤27 mm
Anesthesia	Yes	No (transfemoral)
Worldwide number of implantations	>6000	>6000

1. Age >75 years and high predicted perioperative mortality: EuroSCORE >20 or STS score >10.
2. Chronic pulmonary disease, with long-term use of bronchodilators or steroids.
3. History of chest wall radiation with subsequent severe adhesions.
4. Liver cirrhosis with portal hypertension.
5. Renal failure (especially on dialysis).
6. Porcelain aorta.
7. Degenerative neurocognitive dysfunction.

The second part of the screening process of a possible candidate for TAVI is to make sure that certain anatomic criteria are fulfilled. Firstly, the peripheral arteries (iliac/femoral) should be of sufficient size (diameter >6 mm for both 26 mm and 29 mm MCV, >7 mm for the 23 mm and >8 mm for the 26 mm ESV), relatively free of calcification or extensive tortuosity. In most cases, simple angiography at the level of the abdominal aorta with peripheral vessel run-off suffices to delineate the anatomy. Multi-slice computed tomography (MSCT) with 3D reconstruction provides additive information that cannot be readily given by angiography, such as vessel calcification, vessel wall pathology and tortuosity. In such a study the left subclavian artery and the aortic arch should always be also looked at.

However, perhaps the most significant anatomic criteria that have to be met have to do with the dimension of the aortic annulus and the ascending aorta. Correct sizing of the valve is critical to minimize the potential for paravalvular leakage and to avoid prosthesis migration after placement: however, no consensus exists¹⁷ as to what is the “gold standard” method for measurement of the aortic annulus.

Perhaps the easiest method, combining practicality with reproducibility, is aortography with a measuring pigtail. Aortography during valvuloplasty can assist in the assessment of the AV annulus size by the degree of regurgitation evident around the balloon. Multi-planar TEE, currently utilized in many centers, has been found to show larger values than trans-thoracic echocardiography.¹⁸

Our choice for measuring the diameter and obtaining further information on the shape of the aortic annulus, as well as the relation between the annulus and the ostia of the coronary arteries, is MSCT.¹⁹ By this method we can also calculate other important parameters, such as the total amount of calcium and its distribution in each aortic cusp. It seems that the post-implantation aortic regurgitation and the need for

permanent pacing correlate with the above mentioned parameters, as these are accurately and objectively determined by MSCT.^{20,21}

Procedure

Regarding the anesthesiological aspects of the TAVI procedure, during the transfemoral MCV prosthesis implantation the patient is mildly sedated but otherwise alert and not intubated; the trans-subclavian access is an exception. In the majority of ESV programs general anesthesia is still used for transfemoral and transapical implantations; in the transfemoral approach this is anticipated to change with the introduction of smaller profile devices.

The modifications in the procedure will be discussed extensively.

We no longer use extracorporeal percutaneous femoro-femoral bypass or any other form of assist device, as was the case in the initial implantation cases.

Periprocedural TEE monitoring has historically been used to help correctly position the valve as well as to detect complications. Nowadays, we use TEE only in the cases where the patient is intubated, since it does not add information to the precise deployment of the balloon- or self-expandable prosthesis; furthermore, the various complications can be recognized by fluoroscopy alone and/or hemodynamic data.

The following initial steps are common for both types of prosthesis (ESV and MCV):

- A pacemaker lead is placed in the right ventricular apex, through either the femoral vein or the internal jugular vein. This will serve two purposes: a) as a temporary pacemaker, until permanent pacemaker implantation, in the case of new onset rhythm disturbances (left bundle branch block or atrioventricular block II or III) after aortic valve balloon valvuloplasty or after implantation of the prosthesis; and b) for rapid (~180 bpm) ventricular pacing, as a means of effective heart standstill, during aortic valve balloon valvuloplasty as well as during deployment of the ESV. It should be noted that the MCV is deployed slowly, over a few minutes, and during this time the patient is in complete hemodynamic stability, except for the few seconds that the valve is occlusive but non-functioning.
- Through the diseased and stenotic calcified aortic valve, the LV is wired, usually with the help of an AL1 or AL2 diagnostic catheter with a normal or

hydrophilic straight tip guidewire. Then, a 0.035" super stiff guidewire (usually an Amplatz Super Stiff) is placed in the LV apex, over a pigtail catheter.

- Subsequently, the valve is dilated with a standard balloon catheter (aortic valvuloplasty). The size of the balloon chosen depends on the annulus size, as well as the size of the prosthesis we plan to implant. As a general rule, the size of the balloon is larger than those used in pure aortic valve valvuloplasty, since complete opening of the native valve is intended.
- Immediately afterwards, the prosthesis is advanced and positioned at its intended anatomic position. The advancement of the prosthesis through the 18 F (MCV) or 22-24 F (ESV) sheath, the peripheral vessels, the aortic arch and finally through the valve is accomplished using the push-and-pull technique over the super stiff guidewire. Use of a special catheter (Flex Catheter, Edwards Lifesciences) facilitates the passing of the valve by the somewhat bulkier ESV devices.
- Accurate placement of the prosthesis is achieved by fluoroscopy and injection of small amounts of contrast through a pigtail catheter positioned in the aortic root.
- Aortography is performed at baseline and after valve placement to assess paravalvular regurgitation. Angiography is also performed after valve deployment to ensure coronary and/or bypass graft patency.
- In cases where the regurgitation is more than moderate, there are options available. In the case of under-expansion, a further post dilatation of the already implanted prosthesis can be carried out safely and efficiently, effectively reducing the regurgitation. The MCV prosthesis can also be "pulled" by means of a GooseNeck Snare catheter in case of deep implantation.
- The common femoral artery, depending on the size of the prosthesis to be implanted, can be either prepared surgically (more usual with the ESV) or approached percutaneously (more usual with the MCV). Femoral access at the level of the common femoral artery can be verified by various methods or "tricks" (echo-guided, fluoro-guided with dye injection, or by puncturing through the visible loop of a contralaterally placed pigtail catheter). Manipulation of the introductory sheaths should be careful. Depending on the size of the device, closure of the vascular access site can be carried out

surgically or using a percutaneous closure device (Prostar 10 XL, Abbot).²² In the latter cases, the sutures are prepositioned after predilatation of the artery with a 9 F sheath, and before introducing the 18 F sheath.

After the procedure, all patients are transferred to the intensive care unit for continuous monitoring. The temporary pacemaker cable remains for 24 to 48 hours, after which it is either removed or replaced by a permanent pacemaker, if required by the patient's condition.

Alternative access modalities for TAVI

These approaches are useful in patients with symptomatic severe aortic stenosis who cannot undergo the usual transfemoral procedure for a variety of reasons:

1. Peripheral (iliac and femoral) arteries: severe calcification, tortuosity, small diameter (<6 mm for MCV, <7 or 8 mm for ESV), previous aorto-femoral bypass.
2. Aorta: severe angulation, severe atheroma of the arch, coarctation, aneurysm with mural thrombus.
3. Presence of bulky atherosclerosis of the ascending aorta and aortic arch

Trans-apical access (ESV)

This is an antegrade procedure (in contrast to the usual retrograde). A small incision is made in the left thoracic wall, and the LV apex is exposed. Subsequently it is punctured, the prosthesis delivery sheath is positioned inside the LV and the rest of the procedure follows in a manner similar to the one already described. At the end, the puncture site is surgically sutured.

Trans-subclavian access (MCV)

The (usually left) subclavian artery is surgically exposed through a small incision in the mid-clavicular line. The sheath is advanced all the way to the aortic arch, and the procedure is carried out avoiding vascular access to the lower extremities. Again, at the end, the puncture site is surgically sutured.

Procedural results

Up to the current time (October 2009) more than 10,000 patients have been implanted worldwide with

one of the two available systems already mentioned (ESV and MCV). In this way, they were treated for severe symptomatic aortic valve stenosis, otherwise considered inoperable.

Cumulative data on each of the device's performance, i.e. acute procedural success, procedural complications and procedural and 30-day mortality, are continuously recorded in the form of registries. These are the SOURCE registry²³ for the Edwards-Sapien Valve (1038 patients in 32 European centers between November 2007 and January 2009) and the 18 French Expanded Evaluation Registry (data on file) for the Medtronic CoreValve (1483 patients in 132 European centers between November 2007 and April 2009). Before proceeding to a more thorough analysis, we must stress that a direct comparison between the two technologies should not be made, since differences exist regarding access site management, annulus size considered appropriate, population comorbidity status, and finally various degrees of expertise in the learning curve of each technique (Table 2).

SOURCE registry

The 1038 patients had a mean age of 82.6 years with a mean logistic EuroSCORE of 27%. Overall successful implantation of the ESV at 32 European centers was demonstrated, with high device success and low 30-day mortality rates. The data showed a 30-day survival rate of 93.7% in trans-femoral procedures, and 89.7% in trans-apical procedures – rates that were better than the predicted surgical survival. Procedure safety was proved, since incidences of valve malposition (1.5%), coronary obstruction (0.6%), stroke (2.5%), and conversion to surgery (2.7%) were all very low. The need for permanent pacemaker implantation at 30 days was 7%, and significant aortic regurgitation

at the end of the procedure was observed only in a minority of patients (4.7%). Major vascular complications were 10.6% in the transfemoral and 2.4% in the transapical arm.

In all cases, the trans-aortic valve gradient was reduced, as measured either invasively or with standard echocardiography. Valve function was good, with a final valve area ranging from 1.5 to 1.8 cm².

18 French expanded evaluation registry

The 1438 patients (55% female) had a mean age of 81 ± 6 years with a mean logistic EuroSCORE of 23%. The successful MCV implantation rate reached 98.5%, although about two thirds of the 132 centers (61.9%) were still in training. The 30-day survival rate was 89.7%; however, only 6.7% of the patients died from a cardiac cause. Access site bleeding occurred in only 2.9% (1.9% of experienced centers), despite the fact that the MCV implantation procedure is a purely interventional one and the 18 F sheath hole is not controlled by open vascular surgery but rather using percutaneous techniques.

The procedure was safe, since valve migration or dysfunction never occurred (0%), while incidence of myocardial infarction (0.9%), stroke (2.2%), and conversion to surgery (0.8%) were all very low. The need for permanent pacemaker implantation was 7% in the first 24 hours after the procedure and rose to 25% at 30 days.

Regarding the efficiency of the procedure (“treatment”), TAVI with the MCV prosthesis resulted in a reduction of the mean aortic gradient from 48 mmHg pre- to 8 mmHg post-implantation, which corresponded to an increase in effective aortic valve area from 0.65 cm² pre- to 1.55 cm² post-implantation. This translated in improvement in the patients' symptomatology: half of them improved their NYHA func-

Table 2. Some key data regarding procedural and 30-day outcome of patients treated with trans-catheter aortic valve replacement for inoperable severe symptomatic aortic stenosis. Both are CE approved devices since 2007.

	SOURCE Registry Edwards-Sapien Valve	18 FEE Registry Medtronic CoreValve
No. of patients	1038	1438
Age (mean ± SD)	82 ± 6	81 ± 6
Logistic EuroSCORE	27%	23%
Procedural success	94.1%	98.5%
30-day mortality	8.5%	10.3%
30-day stroke	2.5%	2.2%
Permanent pacemaker	7.0%	25% (15%-40%)
Vascular access complications	9.3%	2.9%

tional class by 1 level (47%), and another one third by 2 or even 3 levels (35%).

Long-term follow up

The first-in-man experience was in 2002 for the ESV

and in 2005 for the MCV prosthesis. In 2007 both devices gained CE approval for the treatment of severe symptomatic aortic valve stenosis, if the estimated surgical risk was considered too high. As already mentioned, despite the multi-morbid condition of the patients implanted with either the ESV or the MCV, acute 30-day

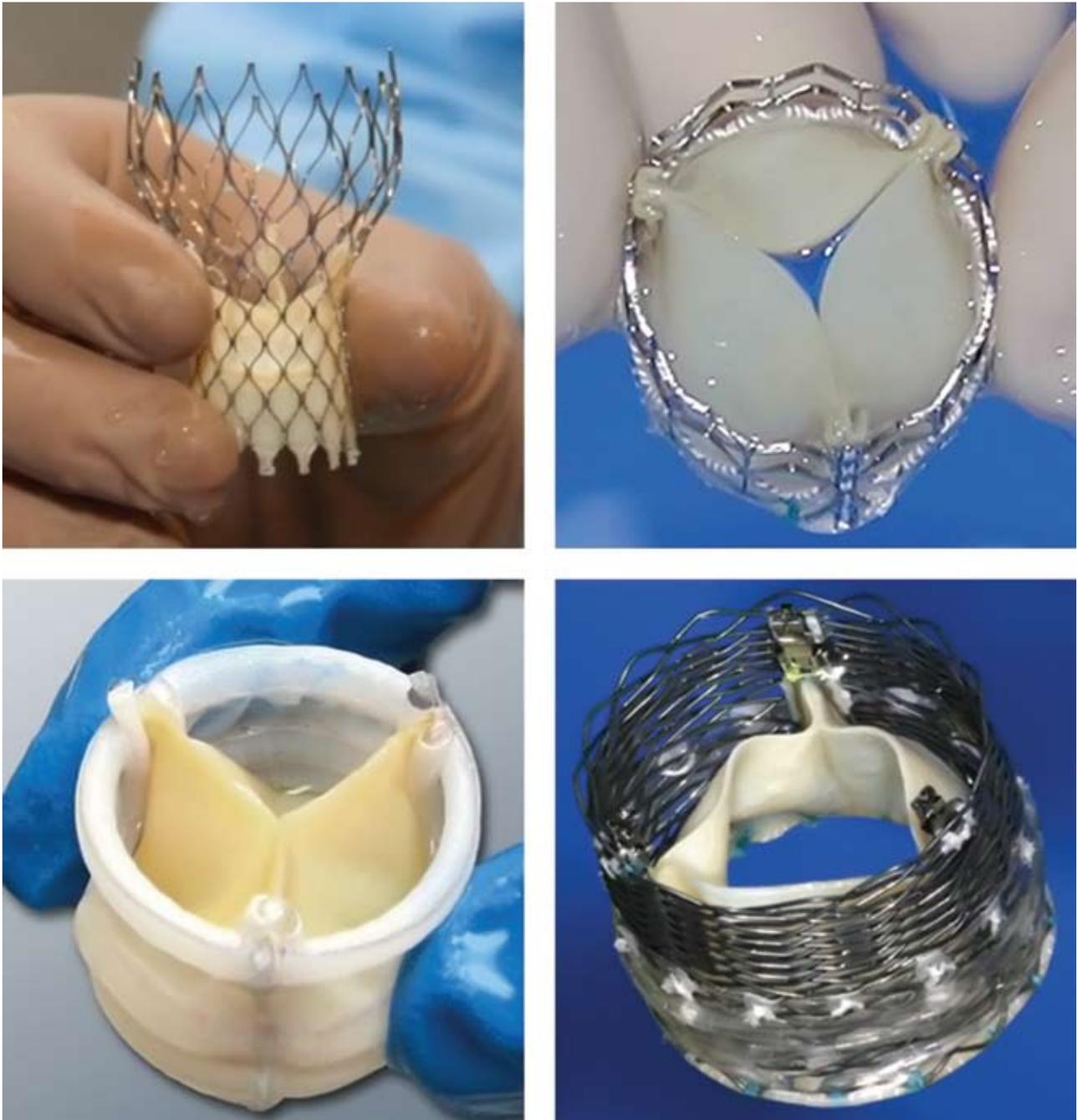


Figure 1. Various percutaneously placed prostheses for the treatment of aortic valve stenosis. The Medtronic CoreValve and Edwards-Sapien (top left and top right, respectively) are CE certified, while the Direct Flow and the Sadra (bottom left and right, respectively) have been implanted successfully in FIM trials.

results demonstrated efficacy and safety better than the estimated surgical mortality in the same patients.

One significant question is the long-term safety and performance results of TAVI. Therefore, we have reported²⁴ the first validated 12-month long-term outcomes after TAVI using the 18 F MCV prosthesis.

Between May 2006 and April 2007, 126 patients underwent elective MCV prosthesis implantation with the third-generation 18 F device in 9 institutions in various countries. In 112 patients 12-month follow up was completed. Procedural success (absence of valve failure or malfunction) was achieved in 86.5% of the cases. The implantation resulted in a reduction of the mean gradient from 48 mmHg pre- to 8 mmHg post-implantation (30 days), a decrease that lasted over the 12-month follow-up period (10 mmHg). This corresponded to an increase in aortic valve area from 0.72 cm² to 1.78 cm² at 30 days. Again, this result remained unchanged during the 12-month follow-up period (1.74 cm²). The majority of the patients improved their NYHA functional status, a constant finding during follow up. At one year, 89% of the patients were in NYHA class I or II.

The 12-month mortality rate was 28.6% (17.0% cardiac and 11.6% non-cardiac), a result reflecting the comorbidities of these patients and the acute procedural / 30-day results (15.2% all cause mortality). After the initial 30 days, the rates of stroke, myocardial infarction and major arrhythmia were quite low (0.9%, 1.8%, 3.6%, respectively). Follow up of the initial patients recruited in the FIM CoreValve study shows that in this 5-year period the prosthesis has shown no sign of malfunction or structural deterioration.

Results regarding the 1-year follow up of patients implanted with the ESV prosthesis have also been reported (PARTNER EU trial).²⁵

Between April 2007 and January 2008, 130 patients underwent elective ESV prosthesis implantation in 9 institutions in various countries, 61 through the transfemoral and 69 through the transapical approach. Device success (successful delivery and deployment of device, valve area >0.9 cm² and regurgitation ≤2+) was achieved in 91% of cases. The implantation resulted in a reduction of the mean gradient from 47 mmHg pre- to 10 mmHg post-implantation (30 days), a decrease that lasted over a 6-month follow-up period (10 mmHg). This corresponded to an increase in aortic valve area from 0.7 cm² to 1.6 cm² at 30 days. The same area of 1.5 cm² was calculated at half year. More than half of the patients (60%) improved their

NYHA functional status, immediately after the procedure and at 6 months.

The combined 1-year survival in this pivotal ESV trial is only 62%; however, this differs significantly between the two delivery cohorts. In the transfemoral implantation population, 1-year mortality is 25% (stroke 7%, myocardial infarction 4%), while in the transapical approach it is 51% (stroke 6%, myocardial infarction 6%); according to the investigators, this reflects the comorbidities of these patients.

Conclusions

There is certainly a great need in cardiology for the development of an effective interventional method for the treatment of degenerative calcified aortic valve stenosis. This need arises not only from the large number of patients who are considered inoperable for traditional open heart surgery, but also from the troublesome and potentially complicated course of thoracotomy, extracorporeal circulation, prolonged mechanical ventilation, etc.

After the initial safety and efficacy trials, the latest studies demonstrate a high rate of procedural success and low 30-day mortality in a large cohort of high-risk patients undergoing trans-catheter aortic valve implantation. Long-term results and improvement in design and techniques will clarify many of the questions pending. Also, a randomized trial between percutaneous and surgical aortic valve replacement is already under way to shed further light.

To date, percutaneous aortic valve replacement is one of the latest innovations in invasive cardiology, offering a new therapeutic option to many patients who until now have not been treated adequately.

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