CoreValve (R) transcatheter self-expandable aortic bioprosthesis

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EXPERT REVIEWS

CoreValve® transcatheter self-expandable aortic bioprosthesis

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Transcatheter aortic valve implantation has been designed to treat patients affected by severe symptomatic aortic stenosis considered extremely high risk for surgical aortic valve replacement. The CoreValve® (Medtronic Inc., MN, USA) is a multilevel self-expanding and fully radiopaque nitinol frame with a diamond cell configuration that holds a trileaflet porcine pericardial tissue valve and anchors the device in the native anatomy. CoreValve was the first percutaneous valve to be granted the CE mark for transfemoral implantation in May 2007 and the CoreValve US Pivotal Trial is actively underway. The CoreValve is available in four sizes (23, 26, 29 and 31 mm) to serve a broad range of patients' annulus from 18 to 29 mm. All the valves fit into an 18-Fr size catheter. Currently, more than 35,000 patients have been treated in more than 60 countries worldwide from the femoral artery, the axillary artery and, more recently, from a direct aortic approach, with excellent results up to 4-year follow-up.

Keywords: aortic stenosis • catheter-based valve intervention • CoreValve® • structural heart disease • transcatheter technique

Severe aortic stenosis (AS) is the most frequent form of valvular heart disease in Western countries. It is rarely rheumatic in etiology in Western countries and the most common cause is degenerative calcification of the aortic valve (AV). Parallel to increased life expectancy and increase in the elderly population, symptomatic AS has become an increasing health problem with a prevalence of 5% in patients over the age of 75 years [1,2], and is currently the most frequent reason for AV replacement (AVR) in patients with AS [3]. The prevalence of AV abnormalities as detected by population-based echocardiographic study increases with age, with 2% of people 65 years of age or older having isolated calcific AS, whereas 29% exhibit age-related AV sclerosis without stenosis [3]. In the Cardiovascular Health Study, in which 5201 men and women older than 65 years were examined, 26% of study participants had aortic sclerosis, with a slight predominance of the disorder in men.

Patients affected by AS can be asymptomatic until late in the course of the disease. However, once the cardinal manifestations of AS (i.e., angina, syncope and heart failure) appears the prognosis is poor. Generally, patients with degenerative calcific AS present symptoms in the seventh through ninth decades. Angina usually occurs in two-thirds of the patients with critical AS and is precipitated by exertion and relieved by rest. Syncope is due to decreased cerebral perfusion during exertion. Exertional dyspnea and orthopnea are usually late symptoms. Other late manifestations of severe AS include atrial fibrillation and pulmonary hypertension. The survival after symptoms onset is approximately 2 years in patients with heart failure, 3 years in those with syncope and 5 years in those with angina [4].

AVR, the standard treatment for these patients, is a Class I recommendation by the American College of Cardiology (ACC) Foundation/American Heart Association and European Society of Cardiology guidelines, which reduces symptoms and prolongs life, and can also be performed with acceptable mortality in elderly patients [5]. Since 1960, when the first AVR was performed, different advancements have been made not only in prosthetic technology, including improvement in hemodynamics, durability and thromboresistance, but also in cardiac surgery techniques. These included best myocardial protection, root enlargement for the management of the small aortic root with improvements in both operative as well as long-term results. Current options for AVR include mechanical

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valves, bioprosthetic and, less frequently, homograft and autograft. Mechanical bileaflet valves are today extremely durable with excellent hemodynamics and minimal thrombogenicity. Mechanical valves require anticoagulation mostly based on vitamin K antagonists, while bioprosthetic valves usually require only antiaggregant therapy, and thus have a lower risk of bleeding. Long-term durability of bioprosthesis varies substantially with patients' age; new valves are free from leaflet dysfunction up to 18 years. Recently, many centers have moved toward tissue valve replacement also in younger patients because of improved durability and antiaggregant therapy. Although it is well accepted that standard AVR provides the most beneficial outcomes in patients with AS, the outcomes of very high-risk populations remains sparse. The perception by the cardiological community of associated comorbidities, especially age greater than 80 years and low ejection fraction, on poor outcomes after AVR has led clinicians to pursue other nonsurgical options for this patient cohort [6]. In the Euro Heart Survey, it was noted that 33% of older patients with severe symptomatic AS were denied surgery [7,8]. Reports of AVR in elderly patients showed high operative mortality rates between 7 and 12% [9,10], and identified different risk factors for mortality, such as significant left ventricular dysfunction, previous chest surgery or radiation, severe chronic obstructive pulmonary disease, liver or renal failure, and diffuse atherosclerosis [10–13]. Transcatheter AV implantation (TAVI) has been designed to treat this group of elderly, symptomatic AS patients at high risk for surgery. The first balloon expandable percutaneous AV implantation was tested in 1992 by Andersen *et al*. in an animal model [14]. The subsequent initial human implantation was successfully performed by Cribier *et al*. in 2002 that implanted a balloon expandable equine pericardial leaflet stent valve via an antegrade approach, in a 57-year-old man affected by severe AS and cardiogenic shock [15]. At the present time, most data available on TAVI are based upon two specific devices: the balloon-expandable Edwards SAPIEN prosthesis (Edwards Lifesciences, CA, USA) and the self-expandable CoreValve® prosthesis (Medtronic Inc., MN, USA).

The procedures may be performed from the femoral artery [16,17] from a transapical approach [18], the axillary artery [19] and more recently from a direct aortic approach [20].

CoreValve description

Design conception and iterative prototyping of CoreValve bioprosthesis took place during 1997–2002 and first-generation device technical, preclinical, animal and cadaver work was completed by early 2004. The Medtronic CoreValve consists of three unique components: a self-expanding support frame with a trileaflet porcine pericardial tissue valve, a 18-Fr catheter delivery system and a disposable loading system.

Nitinol frame & bioprosthesis

The CoreValve is a multilevel self-expanding and fully radiopaque nitinol frame with a diamond cell configuration that holds a trileaflet porcine pericardial tissue valve and anchors the device in the native anatomy (Figure 1). This noncylindrical frame design incorporates three different diameters with three totally different degrees of radial and hoop strength [17].

The lower portion of the memory shaped nitinol frame exerts a high radial force for secure valve intra-annular anchoring. Its constant outward force minimizes the possibility of recoil and also allows the frame to adjust to the native annulus size and shape within its size design parameters.

The middle part of the frame contains the valve leaflets. The supra-annular positioning of the prosthetic valve ensures proper valve function even if the lower portion of the frame is noncircular as it conforms to the native annulus. In addition, the frame's concave apposition to the sinus avoids the coronaries and allows both unimpeded coronary blood flow and coronary catheter access postimplantation. As such, the hourglass frame design avoids the need for rotational positioning since the upstroke of the valve commissures remain removed from the coronaries at all times.

The upper part (positioned into the ascending aorta) is the largest diameter portion of the nitinol frame and has low radial force. It increases the prosthesis fixation and its primary function is to assure optimal alignment of the prosthesis to the blood flow. The very top of this section also features two loops that serve to load the valve into the delivery catheter.

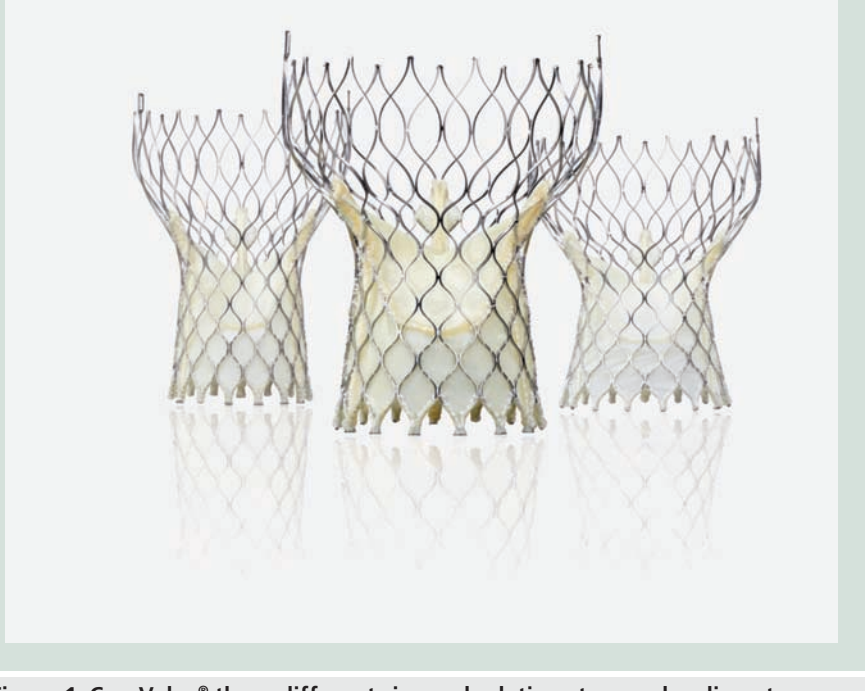

Figure 1. CoreValve® three different size and relations to annulus diameters.
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The single-layer porcine pericardial tissue valve was specifically engineered for transcatheter delivery and to respond to the primary design requirement of minimizing profile in the compressed state of the device, so that it can fold into smaller catheters without the risk of tissue damage. The valve, retaining a traditional three-leaflet configuration, is made of single-layer pericardial elements that are sewn together and then sewn to the frame with polytetrafluoroethylene sutures. The valve is constructed of six individual pieces (three skirt elements and three-leaflet elements) of porcine pericardium treated with standard tissue fixation and sterilization techniques [21].

Porcine pericardial tissue is approximately half the thickness of bovine tissue (Figure 2), this minimal tissue thickness leads to substantial 'space savings' in the folded configuration, while yielding identical or superior density, elasticity consistency, flexibility, cellular structure and tissue strength characteristics [21–23]. Magnified imagery demonstrates how bending induces less buckling in porcine leaflets than in bovine leaflets (Figure 3). Leaflet stress is further reduced through CoreValve's tall commissures and deep-angled leaflet cuts. A critical requirement for durability with TAVI is ensuring adequate frame expansion and circularity at the level of the valve, particularly since the difference between the sagittal and coronal annulus diameters in nearly half of TAVI patients is greater than 3 mm. If the frame is under-expanded at the level of the valve, leaflet misalignment induces high stresses, which can lead to prolapse, fatigue and potentially delamination, calcification and valve failure. CoreValve's supra-annular design minimizes ellipticity at the valve level for more optimal leaflet coaptation and performance.

The CoreValve is available in four sizes (23, 26, 29 and 31 mm) to serve a broad range of patients' annulus from 18 to 29 mm (Figure 1 & Table 1). All the valves fit into an 18-Fr size catheter [21].

The 18-Fr delivery system

The CoreValve delivery system (Figure 4) is an over-the-wire catheter and accommodates a 0.035″ wire. The distal part of the catheter features an 18-Fr housing capsule that accommodates the bioprosthesis, 12-Fr catheter also containing the 15-Fr, AccuTrack. AccuTrack provides an additional layer that isolates the retractable delivery sheath from the introducer and patient anatomy, thus providing a stable platform for deployment and assuring an easy navigation through the vasculature and access into the native AV. The AccuTrak Stability Layer is fixed at the handle and extends down the outside of the retractable catheter shaft, the AccuTrak Stability Layer is designed to allow the retractable sheath to move back freely, reducing the retrograde movement of the valve during deployment.

The AccuTrak Stability Layer is comprised of a 15-Fr braided layer that fits over the proximal 12-Fr braided shaft and extends to approximately 80% of the length of the deployment sheath.

The handle of the delivery system has two different control elements, a rotating knob for slow progressive sheath movement, used during standard valve deployment, and a slide knob for rapid sheath movement. The catheter tip is radiopaque and the distal part of the housing capsule features an additional positioning marker that allows the physician to monitor capsule position during valve implantation [21].

Catheter-loading system

CoreValve's third-generation loading system is fully disposable. It serves to load the bioprosthesis, under temperature conditions of approximately 0–8°C by immersion in cold saline, into the catheter housing cone in a consistent and nontraumatic manner.

It comprises five individual elements (inflow cone, inflow tube, outflow cone, outflow cap and outflow tube), which are applied in sequence by a single loader-operator.

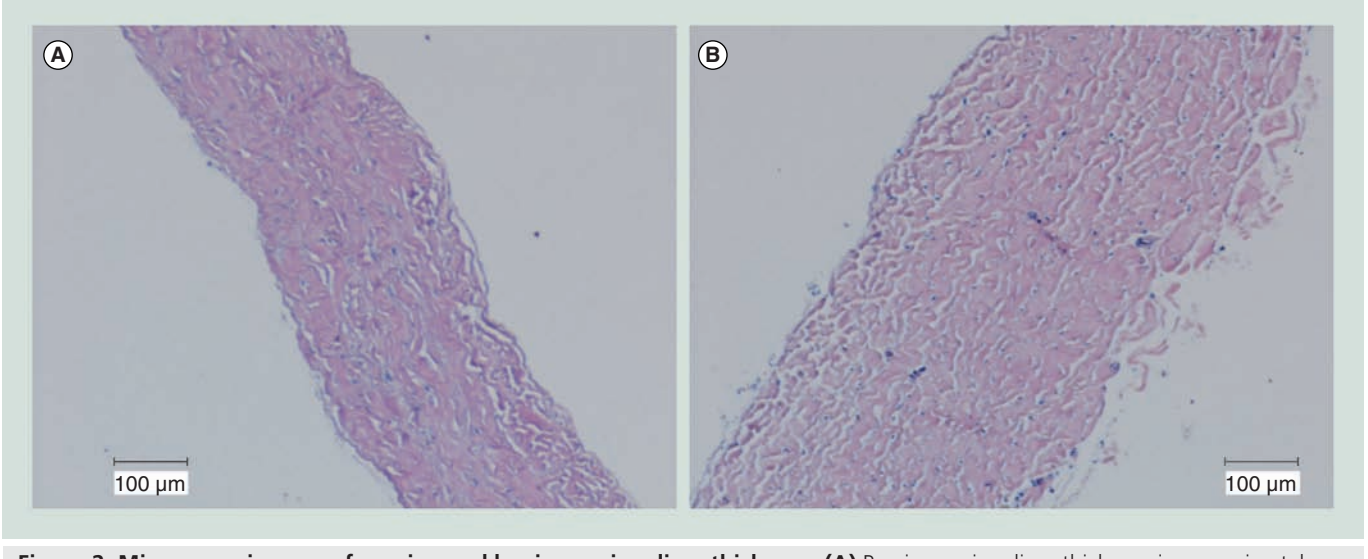

Figure 2. Microscopy images of porcine and bovine pericardium thickness. (A) Porcine pericardium thickness is approximately half that of **(B)** bovine and structurally very similar.
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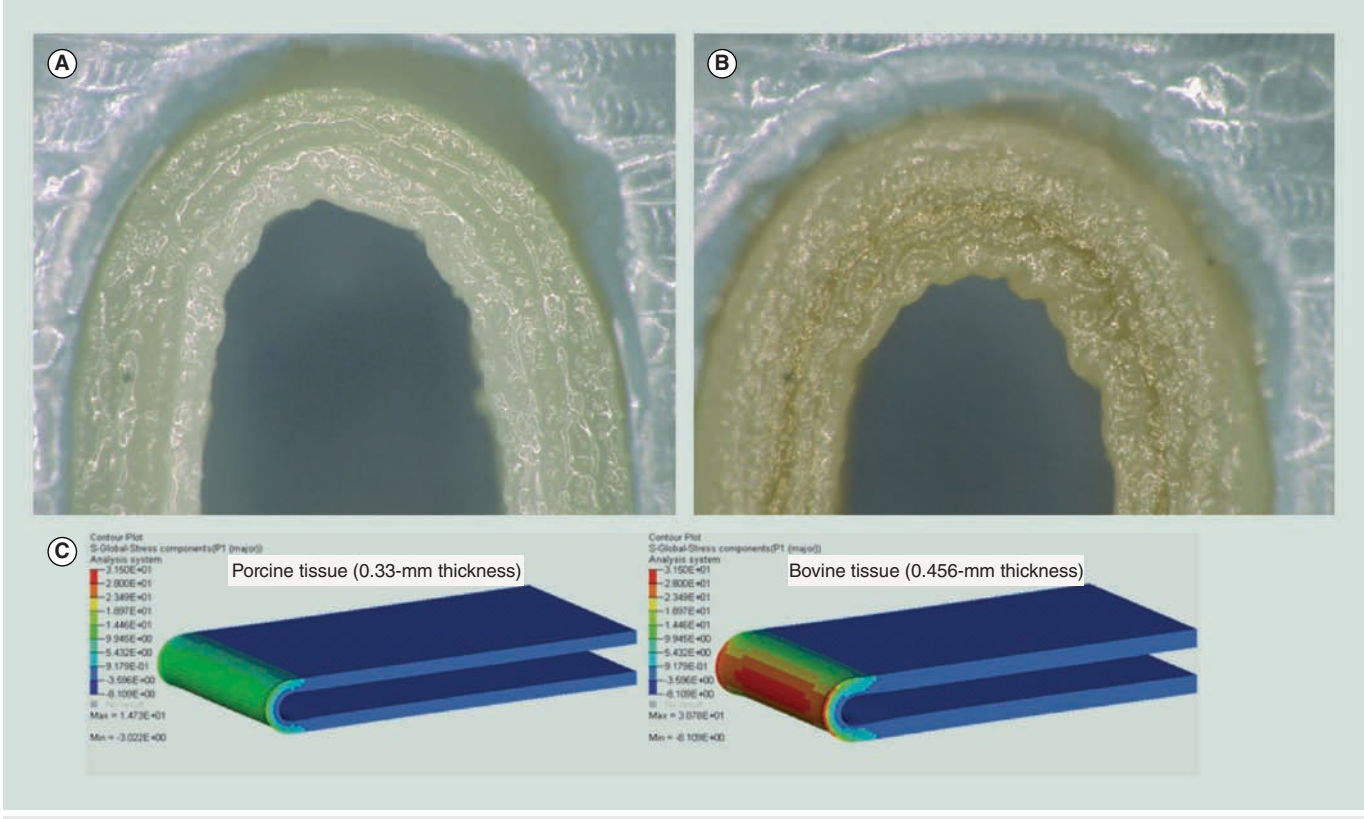

Figure 3. Despite being nearly identical in strength, porcine pericardium has a pronounced advantage to bovine pericardium in pliability. Magnified imagery (magnification 175×) demonstrates how bending induces less buckling in **(A)** porcine leaflets than in **(B)** bovine leaflets. **(C)** Finite element analysis demonstrates porcine pericardium experiences less bending stresses than bovine pericardium.
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Clinical profile & postmarket studies

While the first-generation CoreValve used bovine pericardial tissue and was constrained within a 24-Fr delivery sheath, the second-generation device incorporated a porcine pericardial tissue valve within a 21-Fr sheath. The current third-generation CoreValve prosthesis is a porcine pericardial tissue valve preloaded and compressed in a 18-Fr outer diameter catheter.

The first implantation of the self-expanding CoreValve was reported by Grube *et al*. in 2005 who provided the treatment to a 73-year-old woman with severe calcified AS, New York Heart Association (NYHA) class IV heart failure, and reduced left ventricular systolic function who was declined surgical AVR because of extensive comorbidity [24]. At 2-week follow-up, her initial hemodynamic improvement persisted and she improved to NYHA class II.

In the pilot study, 25 patients underwent CoreValve implantation under general anesthesia with extracorporeal support (extracorporeal percutaneous femoral–femoral bypass) using the retrograde approach via a surgical femoral artery cut-down [24,25]. All the patients had been deemed unsuitable for open standard surgical AVR. The patient cohort was elderly (mean age: 80 ± 5 years) with NYHA class III–IV (96%), a mean AVA of 0.72 ± 0.13 cm^2 and a median logistic EuroSCORE of 11%. The authors reported an 84% procedural success rate, with a reduction in mean AV gradient; cardiovascular and cerebral events occurred in eight patients (32%), with a 20% in-hospital mortality (five patients). At 30-day follow-up, all patients experienced functional improvement in NYHA class, and 17 out of 18 patients (94%) had none or only mild aortic regurgitation (AR), and no adverse events occurred after discharge. The first ten patients were treated using the first-generation 24-Fr device, whereas patients 11–25 were treated using the second-generation 21-Fr device; and as expected, major vascular complications were significantly higher with first-generation 24-Fr (five patients, 50%) compared with one out of 15 patients (7%) treated with the second-generation device. The investigators subsequently provided their experience with the second- and third-generation (18-Fr) devices, in a total of 86 patients (30 men, mean age of 82 years); 50 patients received

Table 1. CoreValve® size and annulus treatable size.

CoreValve size (mm)	Treatable annulus diameter (mm)
23	18–20
26	20–23
29	23–27
31	26–29

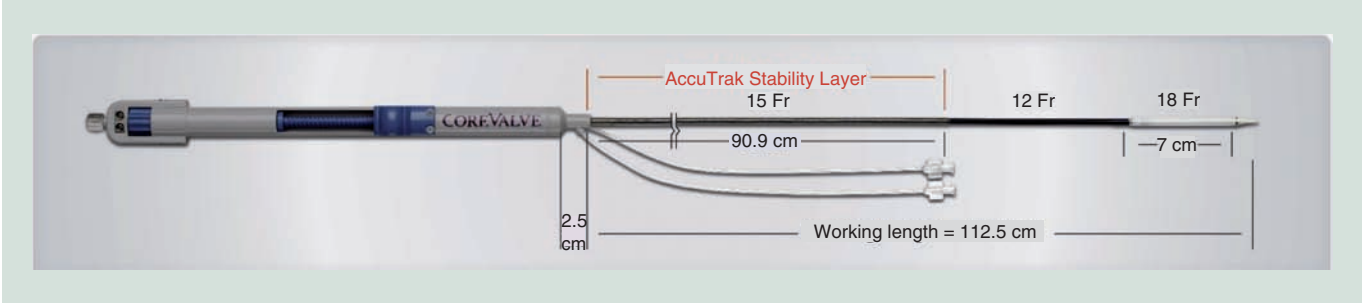

Figure 4. The CoreValve® delivery system is an over-the-wire catheter and accommodates a 0.035″ wire.
The distal part of the catheter features an 18-Fr housing capsule that accommodates the bioprosthesis, immediately behind the valve housing capsule the catheter shaft steps down to 15-Fr and the AccuTrak begins. The handle of the delivery system has two different control elements, a rotating knob for slow progressive sheath movement, used during standard valve deployment, and slide knob for rapid sheath movement.
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the 21-Fr and 36 the third-generation 18-Fr. The use of the 18-Fr device obviated the need for extracorporeal circulatory support, providing a major advance in the technique. Acute device success was achieved in 76 (88%) out of 86 enrolled patients with no difference between the two groups, no patients suffered greater than 2+ AR and procedural mortality was 6%, overall 30-day mortality rate was 12%; the combined rate of death, stroke and myocardial infarction was 22% [25].

Based on these results, the CoreValve ReValving™ system became the first percutaneous valve to be granted the CE mark in May 2007 for transfemoral implantation. After this approval, a multicenter expanded evaluation registry was created, and results were published by Piazza *et al*., a total of 646 patients (54% were female) with a mean age of 81 ± 6.6 years were treated [26]. Procedural success was achieved in 97% of the patients, and all patients had ≤2+ AR. Procedural death occurred in 1.5% of the patients. The combined incidence of procedural death, myocardial infarction or stroke was 2.5%. Vascular access site complications (dissection or tear) were reported in 12 out of 646 patients (1.9%).

National registries

Italian Registry

The first 663 consecutive patients enrolled in the Italian Registry have shown a procedural success and procedural mortality of 98 and 0.9%, respectively [27]. Intraprocedural death occurred in six patients (0.9%). The composite of procedure-related major adverse cardiovascular and cerebrovascular events was 2.1%. Major access site complications were observed in 13 patients (2.0%). A permanent pacemaker was implanted in 16.6% of patients within 2 weeks from the procedure and 17.4% at 30 days. The cumulative incidences of mortality were 5.4% at 30 days, 12.2% at 6 months and 15.0% at 1 year. The 3-year follow-up of the first 181 patients showed an all-cause mortality at 1, 2 and 3 years of 23.6, 30.3 and 34.8%, respectively. Cardiovascular death at 1, 2 and 3 years were 11.2, 12.1 and 13.5%, respectively. The actuarial survival free from a composite of death, major stroke, myocardial infarction and life-threatening bleeding was 69.6% at 1 year, 63.5% at 2 years and 59.7% at 3 years [28]. Interestingly, no report of structural valve deterioration up to 3 years has been reported.

Belgian Registry

In 2011, results of the Belgian National Registry were published [29]; all the 15 Belgian centers performing TAVI participated in the registry. Three hundred and twenty-eight patients were enrolled, 141 patients underwent CoreValve implantation, 94% (n = 133) were treated transfemorally and 6% (n = 8) by the subclavian approach. Procedural mortality was 2% and procedural success rate was 98%. The need for a new definitive pacemaker implantation was 22% (31 out of 138); the incidences of major complications were: renal failure 7% (nine out of 138), clinical stroke 4% (five out of 138) and transient ischemic attack 1% (one out of 138). Overall 1-year survival was 78% in the CoreValve transfemoral-treated patients and 100% in the CoreValve subclavian-treated patients. No prosthetic structural deterioration or nonstructural dysfunction was observed during follow-up.

UK Registry

The UK TAVI Registry collected prospectively all TAVI procedures performed within the UK on 870 patients undergoing 877 TAVI procedures up until December 31, 2009, with a mortality tracking in 100% of patients as of December 2010 was recently published [30]. CoreValve was implanted in 452 patients, 41% were proctored cases and almost 90% of cases were performed through the transfemoral route. Procedural success rate was 98.2% (444 out of 452), the incidence of stroke was 4% (18 out of 448) and myocardial infarction occurred in 1% of patients (five out of 447). Major vascular complications were reported in 6.2% of patients (28 out of 451). The requirement for a new permanent pacemaker was 24% (110 out of 451). Some degree of paravalvular AR (angiographic grade ≥1) occurred in 61% of patients, with this being moderate or severe (AR >2) in 17.3% (76 out of 439). Thirty-day mortality was 5.8% (26 out of 452). Survival at 1 and 2 years was 78.3 and 76.1% respectively.

French Registry

The French Aortic National CoreValve and Edwards Registry is a multicenter national registry conducted in 16 French centers between February 2009 and June 2009 and collects 244 consecutive TAVI patients [31]. The CoreValve was implanted in

78 patients using the transfemoral (n = 67%) or the subclavian artery (n = 12%) approach; 30-day mortality was 15.1% in the transfemoral group and 8.3% in the subclavian access group. Major complications included arterial iliofemoral vessel dissection or rupture in three patients (4.5%), subclavian thrombosis in one case and retroperitoneal hematoma in one patient. Stroke occurred in three patients (3.6%) and a pacemaker was implanted in 20 patients (25%). Marked improvement of symptoms was observed in the vast majority of patients at 1 month, mean aortic gradient remained low (10 mmHg) and an increase in ejection fraction was also observed and a decrease in pulmonary systolic pressure.

Spanish Registry

In the Spanish Registry, a multicenter prospective study that enrolled from December 2007 to July 2009, 108 patients were treated with Medtronic CoreValve and five patients were treated through the subclavian artery [32]. The average logistic EuroSCORE was 16%, with 21.3% of patients scoring ≥20%. The procedure was completed successfully in 106 cases (98.1%). In one patient, a second valve had to be implanted on top of the first one during the same procedure. None of the patients presented residual angiographic AR above grade 2, hemodynamic peak-to-peak gradient after the procedure was 2.4 mmHg. Vascular complications occurred in six patients (5.6%), three patients needed urgent operations, two due to failure of the percutaneous closure device and another due to iliac rupture. Definitive pacemaker implantation was carried out in 38 patients (35.2%). At 30 days, all-cause mortality and the rate of the combined end point of death, stroke, myocardial infarction or referral for surgery were 7.4 and 8.3%, respectively. The estimated 1-year survival rate calculated using the Kaplan–Meier method was 82.3% (for a median follow-up period of 7.6 months).

Medtronic CoreValve studies

ADVANCE Study

The CoreValve Advance International Post Market Study (Evaluation of the Medtronic CoreValve System in a 'Real-World' Patient Population) is one of the largest observational prospective post-market multicenter transcatheter valve trials (ClinicalTrials.gov identifier: NCT01074658) with 1015 extreme and high-risk patients with severe AS patients (mean age of 81 years, mean logistic EuroSCORE 19.2) enrolled at 44 experienced TAVI centers (>40 TAVI before joining the study) in 12 countries in western Europe, Asia and South America. All primary end point-related events were fully adjudicated according to the Valve Academic Research Consortium definitions by an independent Clinical Events Committee [33].

Excellent results from this trial were recently presented at the ACC's *61st Annual Scientific Session & Expo* in Chicago, USA [101]. Of the 1015 patients enrolled, 996 underwent CoreValve implantation, which was correctly positioned in 98.7% of cases and with a mean final gradient of less than 20 mmHg in 96.2% of cases. The procedural success rate was 97.8%, valve-related complications were extremely low, less than 0.5%. At 30 days, major adverse cardiac and cerebrovascular events had occurred in 8.3% of patients. Rates of total mortality and cardiac mortality were 4.5 and 3.4%, respectively. Strikingly, strokes occurred in just 2.9% of patients, while major bleeding occurred in 9.7%, and life-threatening or disabling bleeding occurred in 4% of patients. At 6 months, all-cause mortality was 12.8% and cardiovascular mortality was 8.4%. When mortality rates were analyzed further, unsurprisingly mortality was higher among patients with EuroSCOREs greater than 20, at 17.3% at 6 months.

US Pivotal Trial

The CoreValve US Pivotal Trial is actively underway. In the study, the CoreValve System is being investigated in two cohorts – patients at high and at extreme risk for surgical valve replacement. Together, the two cohorts will enroll more than 1600 patients. The primary objective is the safety and effectiveness of the Medtronic CoreValve System, as measured by a composite of all-cause death or major stroke at 12 months, in subjects necessitating AVR with predicted operative mortality or serious, irreversible morbidity risk of ≥50% at 30 days. The primary end point will be all-cause death or major stroke at 12 months (compared with performance goal).

Extreme-risk cohort

Subjects with symptomatic severe AS, necessitating AVR, with predicted operative mortality or serious, irreversible morbidity risk of ≥50% at 30 days, 487 nonrandomized patients, up to 200 patients with subclavian or direct aortic access. The extreme-risk cohort completed enrollment in January 2012. Extreme-risk patients will continue to be enrolled through continued access.

In the high-risk cohort, subjects had symptomatic severe AS, necessitating AVR, whose predicted risk of operative mortality is ≥15% (and whose predicted operative mortality or serious, irreversible morbidity risk is <50%) at 30 days, 790 patients were randomized 1:1 between CoreValve TAVI and surgical AVR.

Long-term durability

Although only few data are present in the literature about long-term second-generation valve durability, the CoreValve system's durability is documented at 3 years on a recent publication of the Italian experience by Ussia and colleagues about 181 patients who underwent TAVI from June 2007 to August 2008, reporting an all-cause mortality at 3 years of 34.8% with excellent valve hemodynamics and no cases of structural valve deterioration observed [28]. The actuarial survival free from a composite of death, major stroke, myocardial infarction and life-threatening bleeding was 69.6% at 1 year, 63.5% at 2 years and 59.7% at 3 years. Patients experiencing postprocedural major or life-threatening bleeding had a higher rate of mortality already seen at 30 days (21.6 vs 2.8%; $p < 0.001$) and this result was sustained at 3-year follow-up (62.2 vs 27.7%; $p < 0.001$).

Four-year results were presented by den Heijer and colleagues at the *European Society of Cardiology* in 2011, for 52 patients, with the second-generation CoreValve in Europe and Canada.

Four-year follow-up data were collected on 20 patients but 26 patients died, including 13 cardiac deaths. Overall survival was 58.5% at 2 years and 45.1% at 4 years. At 4 years, the surviving patients showed significant improvements in heart-failure symptoms. At 4 years, 57% of patients showed no regurgitation and 43% showed grade one regurgitation; mean CoreValve valve gradient decreased from 41 mmHg at baseline to 12 mmHg at 30 days and 10 mmHg at 4 years.

There were no strokes reported in the study population between 3 months and 4 years and no frame fractures, valve migrations, valve endocarditis or structural valve deteriorations leading to stenosis or regurgitation [33].

CoreValve TAVI procedure

The procedure should be performed in the cardiac catheterization laboratory or in a hybrid operating room with transesophageal echocardiographic and fluoroscopic guidance while the patient is under general anesthesia or in profound sedation and local anesthesia. To perform the operation, a multidisciplinary team involving interventional cardiology, a cardiac surgeon, an echocardiographist and anesthesiology is required. The CoreValve is the only system approved for three different transarterial access options: transfemoral, subclavian and direct aortic.

Transfemoral approach

Angiographic and CT scan evaluation of the femoral and iliac vessels is essential for appropriate patient selection. Ideally, we are looking for nontortuous vessels with minimal calcification. We must also ensure an adequate minimal diameter of the ileo-femoral arteries to accommodate the 18-Fr sheath.

A temporary pacing lead is advanced in the right ventricle through the femoral or jugular vein in patients without a permanent pacemaker to treat possible post-TAVI atrioventricular block. If percutaneous access is feasible, the procedure starts with the puncture of the worse femoral artery and introduction of a 40-cm braided 7-Fr sheath into the common femoral artery then a catheter is used to gain access to the contralateral artery in a crossover fashion. The best femoral artery is accessed by a single wall puncture, in the midline of the vessel, under fluoroscopic and contralateral angiographic guidance. Two 10-Fr ProGlide Suture-Mediated Closure System closure devices (Abbott Vascular Laboratories, Abbott Park, IL, USA) or one Prostar XL 10-Fr closure device (Abbott Vascular Laboratories) is placed within the vessel before any introducer sheath is sited; a 18-Fr introducer is then inserted over an Amplatz super stiff guidewire. The contralateral femoral is used to allow homodynamic monitoring during the procedure and for aortic root angiography and landmark guidance through a 6-Fr pigtail placed in the noncoronary sinus of valsalva. The CoreValve is then retrograde implanted, after native AV balloon valvuloplasty, under angiographic, fluoroscopic and possible transesophageal echocardiogram guidance. The self-expanding design of the CoreValve provides full valve functionality – without the need for rapid pacing – and partial repositionability prior to final release, providing time for evaluation and adjustment during the implant procedure. The valve is fully repositionable prior to annular contact and can be repositioned proximally up to 2/3 deployment (Figure 5). During CoreValve deployment the patient maintains normal blood pressure before annular contact and blood pressure returns to normal at 2/3 deployment (Figure 6). Since approval in May 2007, more than 35,000 patients have been treated with a femoral approach in more than 60 countries worldwide with the Medtronic CoreValve.

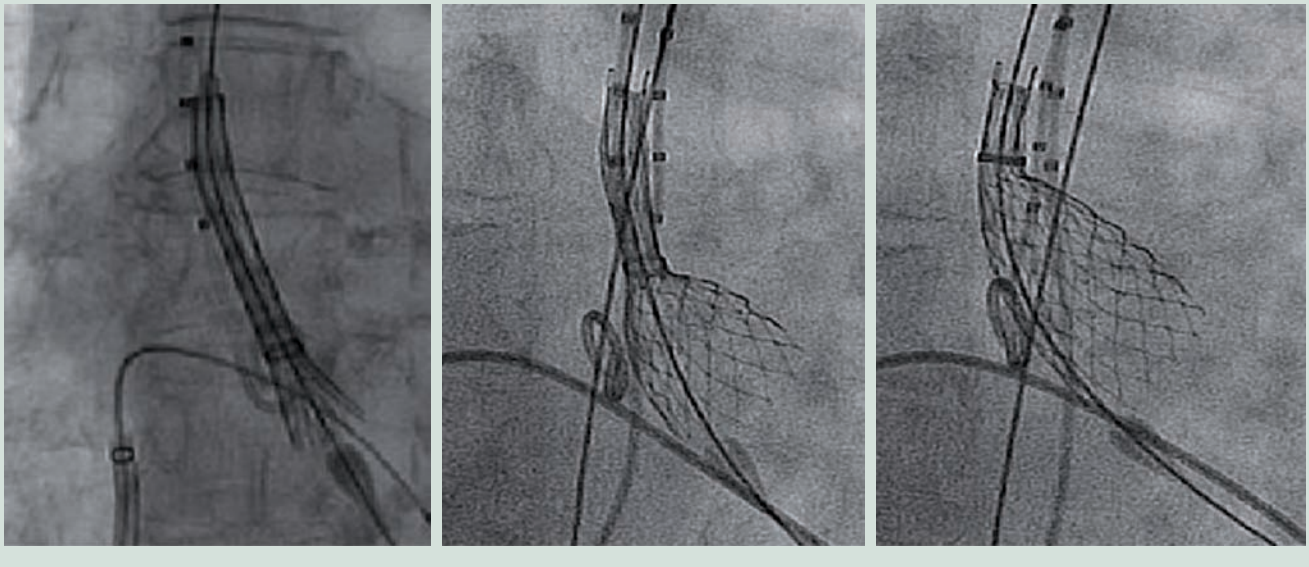

Figure 5. Different phases of CoreValve® deployment, the self-expanding design provides full valve functionality, partial repositionability prior to annular contact and can be repositioned proximally up to 2/3 deployment.
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Figure 6. During CoreValve® deployment the patient maintains normal blood pressure before annular contact and blood pressure returns to normal at 2/3 deployment.
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Trans-subclavian approach

The axillary artery is surgically isolated through a subclavicular incision of 3–5 cm just below the clavicle. Arterial cannulation is performed using the Seldinger technique through an oval shaped purse-string suture. The left axillary artery is usually preferred because it provides the best angle of deployment. Using the Seldinger technique, a 6-Fr sheath is first inserted into the axillary artery and after crossing the native AV, the 18-Fr sheath is inserted over an Amplatz super stiff guidewire, and a standard retrograde CoreValve implantation is performed [32,34].

Since the CE mark approval in December 2010, more than 950 patients have been treated in more than 150 centers with excellent results. In the literature, there are two principal papers reporting results from patients treated through a subclavian approach. Petronio and colleagues reported 54 patients from 13 centers across Italy; no specific complications for the subclavian access were reported, 30-day mortality was 0%, 6-month mortality rate was 9.4% [19]. Laborde and colleagues reported results from 79 patients from 41 centers in 13 countries. Moreover, 51 patients from five case series and 11 patients from ten case reports have been reported with excellent results [35]. Vascular complications occurred in six of the 62 patients (9.7%), one patient experienced aortic dissection with right common carotid artery occlusion and subsequent transient neurologic deficit. Subclavian artery dissection was seen in four out of 62 patients (6.5%); subclavian artery thrombosis developed in one patient, stroke occurred in two of the 62 patients [36]. The CoreValve system has been successfully implanted from the left subclavian in 14 patients with a patent LIMA graft but in two cases the LIMA was dissected requiring stent treatment of their native left anterior descending artery [36].

Direct aortic approach

The procedure is performed under general anesthesia, a double lumen endotracheal tube should be used for single left lung ventilation. The procedure should be performed through a right anterior minithoracotomy or through an upper ministernotomy. A basal ascending aorta aortography, by a graduated pigtail, is performed to measure the distance between the aortic annulus and the selected entry site in the ascending aorta. At entry site, level two aortic purse-string sutures for direct aortic access are placed in a standard fashion. Ascending aortic cannulation should be performed by directly inserting the 18-Fr sheath like a standard aortic cannula or with the Seldinger technique through the double purse-string sutures. In this case, a 6-Fr sheath is first inserted into the ascending aorta and after crossing the AV, and super stiff guidewire placement on the left ventricle, the 18-Fr sheath is advanced. At this point, a CoreValve bioprosthesis is then carefully introduced and retrogradely implanted under angiographic and fluoroscopic guidance in a standard fashion [37].

The EU CoreValve collaborative group on direct aortic approach collected a multicenter experience that comprises 93 patients implanted at 13 centers in eight countries in Europe, 44 of the procedures were performed through a ministernotomy and 49

through a right anterior minithoracotomy. Procedural success was achieved in 92 cases (98%). There were no procedural deaths and 30-day mortality was 9/93 (9.7%). The incidence of stroke was three out of 93 (3.2%) and 16 patients (17.2%) required a new permanent pacemaker [38].

Postoperative management & medication

We suggest that all patients with pre-existing reduced kidney function received intravenously isotonic saline hydration on the day before and after intervention.

A standardized premedication regimen consisted of aspirin 100 mg once daily and loading dose of clopidogrel 300 mg on the day before the procedure. A first-generation cephalosporin is generally considered the antibiotic of choice as prophylactic antibiotic therapy. Moreover, two units of concentrated red cells were reserved in consideration for the possibility of hemorrhagic complications.

Because patients who underwent transcatheter AVR (TAVR) are, by definition, frail older patients with multiple comorbidities and the procedure itself carries high risk of postprocedural adverse events than conventional percutaneous cardiovascular interventions, we believe that careful patient monitoring in a cardiac intensive care unit during the first 48 h seems to be extremely important to early detection and management of complications.

The temporary pacemaker electrode placed into the right ventricle through a jugular or femoral vein is generally maintained for 24- to 48-h postprocedure. Standard medical therapy included low molecular weight heparin until ambulation, acetylsalicylic acid (100 mg) and clopidogrel (75 mg) daily for 3–6 months.

Cardiac complications at the time of TAVI

Valve malposition

Deployment of the CoreValve prosthesis is performed in a controlled and step-wise manner.

Nevertheless, valve positioning remains one of the most challenging steps of the procedure. Correct evaluation for valve deployment is best evaluated using either transesophageal echocardiography or contrast angiography. Normally, the CoreValve prosthesis should be positioned approximately 4–8 mm below the AV annulus. A 'too low' implantation is defined as the distal edge of the valve frame positioned more than 12 mm below the annulus, into the left ventricular outflow tract. A 'too high' implantation is defined as the inflow aspect positioned above the annulus level.

Paravalvular regurgitation

Paravalvular regurgitation should be associated with a too low implantation of the valve, or to valve under-expansion due to the presence of severe native AV calcification or centro-valvular regurgitation, which may result from inadequate postimplantation balloon dilatation.

Pericardial effusion/pericardial tamponade

The causes of pericardial effusion are multifactorial. It is important to note that an effusion can occur promptly during valve implantation, but also can be delayed. The source of bleeding can be the right or left ventricle, or the aortic root. Injury of the right ventricle may result from perforation of the transient pacemaker wire. Injury of the left ventricle may result from perforation of the stiff guidewire. Aortic root rupture may occur after balloon valvuloplasty or after valve implantation, especially in elderly women with fragile tissue where bulky calcifications can perforate the aortic root.

Coronary obstruction

Coronary obstruction during CoreValve implantation is a rare entity, occurring in less than 2% of the patients. The reasons for this potentially catastrophic complication include displacement of native AV calcium deposits or valve leaflets displacement in front of the coronary ostia, embolization of calcium debris into one of the coronary arteries and too high CoreValve implantation causing coronary occlusion.

Conduction abnormalities

Considering the anatomic proximity of the conduction system to the AV, it is not surprising that conduction abnormalities, such as AV block or bundle branch block, are known complications of TAVI. Possible explanations include transient periprocedural inflammation, edema and mechanical stress due to balloon or nitinol frame trauma or myocardial necrosis in the basal interventricular septum due to ischemia.

TAVI cost–effectiveness

TAVI versus medical management

Watt *et al*. developed a two stage cost–effectiveness model comparing TAVI to medical management in extreme-risk patients [39]. In order to generate lifetime cost and benefit estimates, the extrapolation of survival data observed in the PARTNER US clinical trial were used [40]. The short-term model had a time horizon of 30 days while the long-term model had a 10-year time horizon. In comparison to medical management, individuals in the TAVI arm incurred an additional 10-year cost per patient of GB£25,200. The majority of TAVI-related costs correspond to the initial implant operation (£19,000) or perioperative intensive care unit care (£2500). However, the use of TAVI conferred savings in terms of balloon aortic valvuloplasty procedures (–£2400). The model predicted an increase in 1.56 quality-adjusted life years (QALYs) from TAVI when compared to medical management, resulting in an incremental cost-effectiveness ratio (ICER) of £16,200/QALYs. A sensitivity analysis produced an ICER range of £14,300–18,500/QALYs. The authors concluded that from a UK reimbursement perspective, in patients with severe AS who are deemed ineligible for surgical AVR, it is highly likely that TAVI represents a cost-effective treatment option.

Reynolds and colleagues [41] performed a cost–effectiveness analysis of TAVR compared with standard care among PARTNER trial cohort B patients [40,41]. They evaluated cost–effectiveness over a lifetime horizon in terms of both cost per year of life gained (primary analysis) and cost per QALY gained (secondary analysis). For patients treated with TAVR, mean costs for

the initial procedure and hospitalization were US$42,806 and $78,542, respectively. Follow-up costs through 12 months were lower with TAVR ($29,289 vs $53,621) because of reduced hospitalization rates but cumulative 1-year costs remained higher ($106,076 vs $53,621). The authors projected that over a patient's lifetime, TAVR would increase discounted life expectancy by 1.6 years (1.3 QALYs) at an incremental cost of $79,837. The ICER for TAVR was thus estimated at $50,200 per year of life gained or $61,889 per QALY gained. The authors concluded that TAVR increases life expectancy at an incremental cost per life-year gained well within accepted values for commonly used cardiovascular technologies.

Expert commentary

Severe AS is the most frequent form of valvular heart disease in Western countries, and with the growing elderly population, symptomatic AS has become an increasing health problem. AVR is the treatment of choice for these patients; however, the mortality rate associated with AVR increases substantially if multiple comorbidities, such as left ventricular dysfunction, previous cardiac operations, chronic obstructive pulmonary disease, liver or renal failure, and diffuse atherosclerosis are present. TAVI has been designed to treat this group of elderly, symptomatic AS patients at high risk for surgery. With increasing experience, and more than 50,000 patients treated, there is better insight regarding appropriate patient selection, access site evaluation and procedural technique. Furthermore, device manufacturers have provided significant technologic improvement. As a result, TAVI has become both safer and more successful, resulting in CE mark and US FDA approval in Europe and USA, respectively. The available data, supporting the use of CoreValve, are progressively growing. To date, CoreValve is an effective option to treat patients with severe AS at high surgical risk. It is currently the only transcatheter AV that has CE mark for three different access sites (femoral, subclavian and direct aortic). Continuous research and development on the CoreValve System is ongoing.

Five-year view

As one of the two market leaders, Medtronic CoreValve will possibly maintain a large market share, particularly because it is possible to use the same delivery system through three different access sites, and because other competitors have not yet obtained CE mark approval or, as in the case of Symetis and the Jena valve, they have CE mark limited only for the transapical approach.

Next-generation devices will have different improvements, such as low-profile sheaths, more accurate valve deployment and the ability to either reposition or even retrieve the prosthesis, reducing paravalvular leak. Next-generation 'CoreValve 2' technologies will utilize a self-expandable nitinol frame, high radial strength, repositionable and with a pericardial tissue prosthesis.

It will have some new characteristics; in particular, it will be repositionable, since it will be possible to sheath back the valve in the delivery catheter inside the patient's anatomy.

Owing to the encouraging results obtained with TAVI in high-risk patients, it is probable that a trend towards a global increase in the number of TAVI procedures will occur in the next few years. In the near future, as experience is gained and technology evolves, the patient population best served with TAVR is likely to change and three different areas will have specific consideration: the 'valve-in-valve' technique for patients with dysfunctional aortic bioprostheses, the use of TAVR in patients with stenotic biscupid AVs or affected by pure AR and application to lower-risk surgical patients.

It should not be forgotten that the cooperation between cardiologists, cardiac surgeons, anesthesiologists, echocardiographist, radiologists, nurses and all the different specialists involved in TAVI patients' care (the so-called heart team or team approach) is one of the most important parts of the entire TAVI process and its focus is the patient's physical and mental wellness. In conclusion, to continue to guarantee the extraordinary and, maybe, unpredictable success of this new procedure, the team approach should remain a key-point.

Financial & competing interests disclosure

G Bruschi is a consultant for Medtronic Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- Severe calcific aortic stenosis is a significant source of morbidity and mortality among the aging population.
- CoreValve was the first percutaneous valve to be granted the CE mark in May 2007 and the CoreValve US Pivotal Trial is actively underway.
- The CoreValve is available in four sizes (23, 26, 29 and 31 mm) to serve a broad range of patients' annulus from 18 to 29 mm. All of the valves fit into this 18-Fr size catheter. The most recent addition (summer 2012), is the 23-mm inflow model and is for the treatment of patients with annulus between 18 and 20 mm.
- CoreValve is the only valve on the market with CE approval for three different access sites: femoral, axillary and direct aortic.

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