Replacing the valve, restoring the flow: Effects of transcathester aortic valve implantation
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CHAPTER 11

AN UP-TO-DATE OVERVIEW OF THE MOST RECENT TRANSCATHETER IMPLANTABLE AORTIC VALVE PROSTHESES


* Both authors contributed equally
ABSTRACT

Over the past decade Transcatheter aortic valve implantation (TAVI) has evolved towards the routine therapy for high-risk patients with severe aortic valve stenosis. Technical refinements in TAVI are rapidly evolving with a simultaneous expansion of the number of available devices. This review will present an overview of the current status of development of TAVI-prostheses; describes the technical features and applicability of each device and the clinical data available.
INTRODUCTION

Background
For patients with severe aortic valve stenosis, considered inoperable or high-risk for surgery, transcatheter aortic valve implantation (TAVI) is a firmly established minimal invasive treatment option. In TAVI, the aortic valve is not excised; instead, a bioprosthetic valve is implanted over the native valve via a transcatheter procedure. The first TAVI was performed in Rouen by dr. Cribier in 2002. A transseptal antegrade approach was used for aortic valve insertion in the first cases later followed by a retrograde approach, with a successful delivery in 90% of cases. In 2005, gradual expansion of treatment with the two initial prostheses, the balloon-expandable Edwards SAPIEN and the self-expanding Medtronic CoreValve, followed. The safety and efficacy of the Edwards SAPIEN and the Medtronic CoreValve were established through well-designed randomized control trials (RCT). The Placement of Aortic Transcatheter Valves (PARTNER) trials showed non-inferiority of TAVI compared to surgical aortic valve replacement in high risk patients and superiority compared to conservative management, including balloon valvuloplasty. Since these first TAVI trials, the technology has been embraced and the number of procedures has expanded rapidly. Since 2012 TAVI has been incorporated into the international guidelines for treatment of severe symptomatic aortic valve stenosis, and has evolved towards the routine therapy for patients unsuitable for surgery or with high-operative risk and more than 200,000 procedures have been performed worldwide. Various approaches for TAVI have emerged: the retrograde transcatheter route (mainly transfemoral, -subclavian, -axillary), the directly aortic approach, via a ministernotomy and the antegrade transapical cardiac route, via a mini lateral thoracotomy. Preprocedural imaging of the transfemoral trajectory and cardiac anatomy with a computed tomography (CT)-scan has become key in the preoperative assessment for these minimally invasive procedures. Currently, the retrograde transfemoral approach is the most frequently exploited and least invasive technique and can be performed under local or general anesthesia. However not all patients have a suitable femoral access due to small diameters, calcifications or tortuosity of the femoral and iliac arteries. Over the years, femoral delivery systems decreased in sheath size, however a minimal arterial lumen diameter of less than 5.5 to 6 mm, found at CT-scan remains the most important limitation for a transfemoral approach. Valid alternatives are the transapical approach, first described in 2006 or the transaortic approach as described with the CoreValve, or with the Edward Sapien.

Outcomes
The initial exploratory studies evaluated TAVI procedures, outcomes, complications and predictors of adverse outcomes, all in their own manner. After the first experience, postop-
ervative complications, management and long-term outcomes became subject of debate. Although on all-cause mortality TAVI proved to be non-inferior to surgical aortic valve replacement, it was traditionally associated with a higher incidence of vascular complications and echographically determined postprocedural paravalvular regurgitation as compared to conventional cardiac surgery. Therefore, both complications have been introduced as the “Achilles heel” of TAVI procedures.

A major breakthrough in the research field was the consensus document of the Valve Academic Research Consortium (VARC) in 2011 with a revision in 2012 (VARC 2). The VARC comprises an independent collaboration between US and European Academic Research organizations and cardiology and cardiac surgery societies. Their consensus criteria were developed to improve comparability and interpretability of study results. Important complications were identified, partly based on what was known from conventional surgery. Furthermore, the first research endpoints were defined in the VARC consensus document. The VARC-2 criteria describe updated definitions of important endpoints including mortality, myocardial infarction, stroke, bleeding complications, acute kidney injury, vascular complications, conduction disturbances and arrhythmias, and prosthesis performance. In addition, quality of life (QOL) and echocardiographic criteria are provided for the evaluation of prosthetic valve function including QOL-questionnaires, criteria for re-stenosis, paravalvular regurgitation and regular follow-up assessment.

**Prostheses**

Various anatomic considerations are to be taken into account in developing transcatheter devices, such as the access to the diseased valve, adjacent structures, the coronary arteries, the pressure regimen which complicates anchorage of the device, and finally, considerations regarding underlying disease. Since the first TAVI procedure, multiple prostheses have been developed and adapted. Prosthesis function and characteristics can have a crucial influence on indications as well as prognosis. In conventional valvular surgery, assessment of device function has always been of considerable interest. This has resulted in valuable advancements in device development. In the rapidly expanding field of TAVI evaluation of prostheses is therefore of uttermost importance.

Currently several new generation valves have been introduced in an attempt to refine the procedure and reduce common TAVI complications. We will evaluate both the prostheses used with the initial TAVI experience and the most commonly used new generation prostheses with a glance on possible future devices.
### Tabel 1: overview of TAVI prostheses

<table>
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<tr>
<th>Prosthesis</th>
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<th>valve material</th>
<th>balloon expandable/ self expandable</th>
<th>approach</th>
<th>CE Mark</th>
<th>first in human</th>
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<td>Porcine pericardium</td>
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<td>transfemoral</td>
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<td>2004</td>
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<tr>
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</tbody>
</table>

### Initial prostheses

**Sapien/Sapien xt**

The first TAVI was performed in 2002 with the Cribier–Edwards valve (Edwards Lifesciences Inc., Irvine California, USA). After this initial experience, the Edwards Company developed the Edwards SAPIEN. The first randomized controlled trial in TAVI (PARTNER I), as mentioned above, was conducted with this prosthesis. The PARTNER randomized trial, cohort B of 358 patients confirmed the superiority of the transfemoral TAVI, compared
with standard medical therapy with regard to overall survival and cardiac functional status. Cohort A showed non-inferiority of TAVI compared to surgical aortic valve replacement in 699 patients with high surgical risk. The Edwards SAPIEN received CE mark in 2007, and FDA approval in the USA in October 2012. The Edwards SAPIEN prosthesis consists of 3 bovine pericardial leaflets, mounted on a stainless steel stent. Using a crimpler, the prosthesis is crimped around the catheter and is expanded by inflation of a balloon during rapid pacing. Radial force ensures fixation to the aortic annulus. The prosthesis can be implanted by retrograde or antegrade approach. The Edwards SAPIEN-XT subsequently followed the SAPIEN valve. The stainless steel frame was replaced by cobalt chromium making the frame thinner, stronger and compressible. The refinement of the stent frame has resulted in a lower prosthesis profile with a smaller diameter delivery system that depends on valve size. Important progress in reducing vascular adverse events was made with the introduction of the subsequent SXT-THV, as demonstrated in the PARTNER IIB trial. Recently the 5 year results of the PARTNER I trial were published as follow-up data of cohort A with 699 patients with high surgical risk, as well as of cohort B with 358 inoperable patients.

In patients participating in cohort A, the risk of all-cause mortality in the TAVI group was 67.8% compared with 62.4% in the patients treated by surgical aortic valve replacement. Moderate or severe aortic regurgitation was significantly more frequent in patients treated by TAVI (14 vs 1%) and was associated with an increased 5-year risk of mortality in the TAVI group. In addition the durability of the prosthesis was reported; hemodynamic benefit after TAVI was proven by echocardiographical assessment. There was no evidence of structural valve deterioration and the mean gradient over the prosthesis remained low (11mmHg). In the patients participating in cohort B, the risk of all-cause mortality at 5 years was 71.8% in the TAVI group versus 93.6% in the standard treatment group. Of the survivors in the TAVI group, 86% had New York Heart Association (NYHA) class 1 or 2 symptoms compared with 60% in the standard treatment group.

CoreValve
The CoreValve (Medtronic Inc., Minneapolis, Minnesota, USA) prosthesis is one of the two pioneer prostheses in TAVI technology. It was the first transcatheter prosthesis that received a CE mark for transfemoral implantation in May 2007 and received FDA approval in January 2014. The first generation CoreValve system consisted of bovine pericardium. All more recent generations of the prosthesis consists of three porcine pericardial leaflets, mounted on a self-expanding nitinol stent. The stent is composed of shape memory alloy, acquiring its final shape once released. Three segments can be identified; an upper and lower segment with radial forces to provide stability and to anchor the stent, and a middle segment that contains the three leaflets and maintains alignment of the leaflets by circumferential forces. The prosthesis is crimped by hand, compressed into a sheath and positioned by removal of the sheath, usually during rapid ventricular pacing. This valve can
only be delivered by retrograde approach. The Pivotal Trial, conducted in the US was the landmark trial for the CoreValve\textsuperscript{28}. Patients with symptomatic severe aortic stenosis were classified in an extreme- or high-risk cohort. Primary end point was a combined endpoint of all-cause mortality at 1 year. The CoreValve high-risk trial is the only randomized trial of TAVI vs surgical aortic valve replacement to show superior survival of TAVI. This was achieved with a numerically lower rate of major stroke and statistically superior changes in aortic valve function from baseline to 1 year. A significantly reduced risk of 1-year mortality by TAVI with CoreValve was reported (14.2% \( v \) 19.1%; \( p = 0.04 \))\textsuperscript{19}. A permanent pacemaker was implanted in 23.7% of patients\textsuperscript{19}. The incidence of a new permanent pacemaker is high compared to other prostheses. The origin of cardiac conduction disorders after TAVI is thought to be compression of the endocardium containing the conduction system by the prosthesis, the prosthesis-tissue interaction\textsuperscript{29}. Both the course of the left bundle branch as well as the proximity of the right atrium and the atrioventricular node to the implanted prosthesis, increase the risk for conduction disorders after TAVI\textsuperscript{30}

The CoreValve remains the signature Medtronic prosthesis; alterations in prosthesis frame height and delivery system were realized, under the same name. Recently, the all-cause mortality up to 5 year was reported with rates of 21% at 1 year, 29% at 2 year and 55% at 5 year\textsuperscript{31}. Prosthetic valve degeneration was 1.4% at 5 years. At follow-up, 17% required implantation of a permanent pacemaker. The CoreValve is currently evaluated in the surgical replacement and transcatheter aortic valve implantation (SURTAVI) trial, comparing TAVI to surgical aortic valve replacement in intermediate-risk patients with severe aortic stenosis (NCT01586910: full details available at www.clinicaltrials.gov, (last verified June 2015)). In 2013 CoreValve announced the first implants in the CoreValve Evolut R Clinical Study. The Evolut R is a recapture-enabled valve and delivery system providing the option to recapture and reposition the CoreValve Evolut R valve during deployment\textsuperscript{32}. Furthermore, the nitinol frame of the CoreValve Evolut R has been redesigned with consistent radial forces, potentially reducing stress on the left bundle branch. With this new delivery system transfemoral TAVI can be safely performed in patients with iliofemoral diameters as small as 5.4 mm\textsuperscript{33}.

**Self-expandable versus Balloon expandable devices**

Both the Medtronic CoreValve and the Edwards SAPIEN/SAPIEN-XT have been used widely since the first TAVI procedure in 2002; however differences in hemodynamic performance as well as device success have been reported\textsuperscript{38-40}. The three major experiences published thus far; the Milan experience, the Pragmatic study and the French TAVI registry, showed no significant differences in both cardiovascular mortality and all-cause mortality\textsuperscript{29, 41, 42}. However likewise there are studies with contradictory results; describing that patients who underwent CoreValve implantation had both lower all-cause mortality (1.9% \( v \) 14.3%; \( p = 0.032 \)) and cardiovascular mortality (0.0% \( v \) 14.3%; \( p = 0.006 \)) at 30 days follow-
up\textsuperscript{43}, and an in 2014 published randomized trial, describing that device success was significantly more likely with the balloon-expandable rather than the self-expanding valve system (95.9\% vs 77.5\%), with a lower risk on aortic regurgitation (4.1\% vs 18.3\%). In this randomized trial, placement of a new permanent pacemaker was less frequent in the balloon-expandable valve cohort\textsuperscript{44}. At present, it should be concluded that the debate on balloon versus self-expanding systems remains ongoing.

Current trials and prostheses

\textit{Sapien 3}

The Edwards Sapien 3 valve (Edwards Lifesciences Inc., Irvine California, USA) is a next generation balloon expandable valve with a design based on the Sapien/ Sapien XT. The valve was first used in January 2012 and received CE-mark in January 2014\textsuperscript{45} with FDA approval in June 2015. The prosthesis can be used for transfemoral, transaortic and transapical access. It is currently available in four sizes: 20, 23, 26 and 29 mm and for the transfemoral access delivered in a low profile access sheath of 14F (or 16F (29mm device). The possibility to deliver prosthesis with a 14F sheath may lower vascular complication rates. The design of the valve leaflets and material remained bovine pericardium with ThermaFix Tissue Treatment, which should reduce calcification of the prosthesis. The frame struts at the top of the valve are wide angled and composed of four rows and columns for radial strength. Compared to earlier generation Edwards prostheses, the enhanced frame geometry allows lower delivery profiles with concomitant higher radial strength. This serves to maintain the circularity after deployment. The height of the valve is increased compared to older Edwards valves. If a similar implantation technique is used this increased height may lead to more stent extension in the left ventricular outflow tract, which is an important predictor of pacemaker implantation\textsuperscript{46}. The reported 30 day incidence of pacemaker implantation for the Edwards 3 are indeed at the high end of normal for Edwards valves with currently reported rates ranging from 4.0\% to 17.2\%\textsuperscript{45, 47}. This is relatively high compared to the results of a search among studies using the older generation Edwards SAPIEN, reporting a median pacemaker rate of 6\% (IQR 5-7)\textsuperscript{48}. In older generation Edwards valves the lower two-third of the frame was already covered with an internal polyethylene terephthalate (PET) skirt. An innovative aspect of this new Edwards prosthesis is the outer skirt of PET, aimed to reduce paravalvular leakage\textsuperscript{49}. Thus far this adjustment seems to be effective with reported low rates of ≥ mild postprocedural paravalvular regurgitation of 7\% compared to 42\% in the Edwards XT group\textsuperscript{50} and compared with other studies with earlier generation valves\textsuperscript{51}. Further studies are required to show the clinical impact of these hemodynamic improvements. Recently reported all-stroke rates are similar to incidences described for older valve types, varying from 1.1\% to 5.7\%. However the reported most meaningful incidence of disabling stroke is relatively low varying between 0\% and 2\%\textsuperscript{12, 47, 52, 53}.
Currently the PARTNER II S3 RCT enrolls intermediate-risk and high-risk patients to evaluate the safety and efficacy of the SAPIEN 3 system on short and long term. Patient data will be collected for 5 years after valve replacement. (NCT01314313 full details available at www.clinicaltrials.gov, last verified April 2015)

**Portico**

The self-expanding Portico (St. Jude Medical, St. Paul, Minnesota, USA) THV has a radiopaque, nitinol stent. CE Marking was issued in 2012 for the 23 mm valve and in 2013 for the 25 mm valve. The stent design has wide-open struts at aortic level to limit the risk of coronary ostial occlusion. The stent can be resheathed up to 80% of deployment, making reposition of the valve after almost complete placement possible. The valve leaflets are made of bovine pericardium and are treated with the Linx anti-calcification technology (St. Jude Medical). The valve is made of porcine pericardium and is implanted and deployed at annular level and extends no more than 5 mm into the left ventricle. The valve is manually loaded on the catheter. The placement catheter has a diameter of 18F at the valve-loading segment, whereas the catheter itself has a 12F diameter.

The initial experience showed the repositionability of the prosthesis, with a recapture and repositioning in 4 patients. Ten percent had moderate paravalvular regurgitation in this small series. No patient required pacemaker implantation. Ventricular (rapid) pacing is not required during valve deployment. In September 2014 St Jude temporarily halted the implementation of valves worldwide for safety issues and evaluation of reduced valve leaflet mobility reported on CT-scans. However, the issue seemed not to occur specifically in the Portico, moreover it was described as a class problem, including surgical prosthesis. As a result, in June 2015 FDA has cleared St. Jude Medical to resume its study of the Portico.

**Jenavalve**

The self-expanding JenaValve (JenaValve Technology GmbH, Munich, Germany) received CE approval for TAVI in aortic valve stenosis in September 2011. It is the only prosthesis that received CE-mark for aortic regurgitation (September 2013). The now certified JenaValve is a transapical positioned prosthesis, composed of a nitinol self-expanding stent and three native porcine aortic valves. The device provides the option of repetitive repositioning before final release. Rapid pacing is not necessary for positioning of this prosthesis. The JenaValve contains a clipping system that fixates the stent to the diseased native valve leaflets, a feature that creates the opportunity to implant the valve in minimally calcified aortic valves. This is in contrast to the aforementioned Edwards SAPIEN and Medtronic CoreValve devices, in which radial forces exerted on the aortic annulus provide alignment and fixation. A transfemoral JenaValve is currently being evaluated. The largest series to date using the JenaValve involves 88 patients, 79 patients with severe aortic stenosis and 9 with severe aortic regurgitation. This German experience reports a device success of 91%, and 10% 30-day mortality.
A JenaValve prosthesis for transfemoral use (The JenaValve TAVI Plus system) has been successfully implanted in animal experiments and currently still a subject of research and will be available in three sizes: 23, 25 and 27 mm, delivered with an 18Fr catheter consisting of a sleeve which houses the prosthesis and a shaft that releases initially the feelers and finally the prosthesis during valve deployment.

**Lotus**

The first in-man implantation of the Lotus Valve system (Boston Scientific Corporation, Marlborough, Massachusetts, USA) was in 2007. The system is CE marked, however in the United States it is still an investigational device. It consists of a valve prosthesis, pre-attached to the delivery catheter. The prosthesis is composed of three bovine pericardium leaflets mounted in a braided nitinol frame. Currently the only access route is transfemoral. The delivery and anchoring method is based on controlled mechanical expansion; by rotating the delivery handle manually, the prosthesis is unsheathed, the device radially expands and shortens to achieve the final dimensions. The prosthesis is repositionable and retrievable even after full expansion, and the frame is designed with a central radiopaque marker to enable precise positioning. To minimize leakage, the valve is covered with an adaptive seal. The prosthesis is designed to function early during deployment and rapid pacing is not required, resulting in minimization of the hemodynamic changes during the procedure.

Recently the REPRISE II, published 30 day outcomes in 120 patients. Successful valve implantation was achieved in all patients with a significant improvement in functional NYHA classes. The rate of paravalvular leakage was 1.0% of the patients, which is considerably lower than rates described in literature. Opponents of repositioning during TAVI argue that extra manipulation during the procedure may induce strokes. However this could not be directly deduced from the REPRISE II; 30-day incidence of disabling stroke was 1.7% compared with 3.2% major strokes in a weighted meta-analysis of studies using mainly Sapien and CoreValve. Furthermore stroke rates in the REPRISE II differed not significantly between patients with and without repositioning attempts. A major complication of the Lotus valve seems to be the high rate of permanent pacemaker implantations after a TAVI of 28.6%, which is similar to the rates reported after CoreValve implantation but considerably higher than the pacemaker implantation rates in trials with the Edwards SAPIEN valve. The results have to be confirmed in larger trials and will be directly compared with other valve systems in the Reprise III, starting as a randomized controlled trial of the Lotus and CoreValve prostheses. (NCT02202434 full details available at www.clinicaltrials.gov, last verified July 2015). Some interventionalists argue that the high rates of pacemaker implantation imply that the first clinical Lotus implantations should be performed in patients who already have a permanent pacemaker. This will allow the operator to adjust to the implantation technique without negative consequences for the patient.
Acurate
The Acurate (Symetis, Ecublens, Switzerland) is a self-expandable supracoronary prosthesis. The delivery systems consist of a flexible shaft, for the transapical approach equipped with two radio opaque markers and for transfemoral use with an 18 French sheath with radio opaque stent holder. The prostheses comprise three porcine leaflets, mounted on a nitinol stent with an inner and outer impermeable skirt, designed to prevent paravalvular regurgitation. The prostheses consist of stabilization arches, an upper and lower crown. Once deployed, resheathing, repositioning and retrieval are not possible. Initially the valve was developed for the transapical access route and received the CE mark in 201165-67, with now more than 1200 transapical implants. The prosthesis for transfemoral access followed, with a CE mark in 2014. The first-in-man study for a transaortic system is expected to start in 2015.

For the transapical device clinical follow-up results of 40 patients, showed a 30-day device success rate, as defined by VARC 1, of 92.5%, with two valve-in-valve procedures and one moderate leakage after implantation. At 6 months follow-up 96.7% demonstrated either none/trivial or mild paravalvular regurgitation. A multicenter registry on 250 patients reports a 30-day mortality rate of 6.8%. At least moderate paravalvular regurgitation was reported in 2.3% of patients68, 69. A comparison between the transapical systems of Edwards Sapien and Acurate among 103 propensity matched pairs, showed more redilation after treatment with the Acurate device (40% vs 9%)70. The first-in-man trial for the transfemoral route reports procedural success of 95% in 20 patients, with two pacemaker implantations (10%).

Medtronic Engager
The Engager (Medtronic Inc., Minneapolis, Minnesota, USA) is a transapical implantable prosthesis, consisting of 3 bovine pericardial leaflets, mounted on a self-expandable nitinol frame. The prosthesis consists of a main frame and a support frame. The main frame is sewn to a polyester sleeve. The support frame contains three control arms to fixate and position the prosthesis. The prosthesis is available in 23mm and 26mm size71. After a successful feasibility study72 a European pivotal trial was conducted with a total of 61 patients73. Overall device success, defined by modified VARC criteria, was achieved in 94.3%. All cause-mortality was 9.9% at 30 days. The CE mark was received in February 2013.

Direct flow
The Direct Flow (Direct Flow Medical Inc., Santa Rosa, California, USA) has an entirely non-metallic framework double ring design, with upper (aortic) and lower (ventricular) ring balloons of Dacron polyester. In between the inflatable rings is the bovine pericardial valve. The rings can be pressurized independently through position-fill lumens with saline and contrast solution, inducing immediate visibility when inflated. The prosthesis
is repositionable and retrievable before anchoring, by deflation of the cuffs. Rapid pacing is not required for implantation since the valve leaflets are functional during expansion. A specific feature of the Direct flow medical is the ability to perform TAVI with minimal or no contrast; a feature especially favorable in patients with an impaired renal function. The Discover trial was the first multicenter nonrandomized study of the Direct Flow Medical\textsuperscript{74}. The VARC-defined device success rate was 93\% and 30-day freedom from VARC-defined safety event rate was 91\% with an all-cause mortality rate of 1.0\% (1 of 100) at 30 days. In January 2013 the direct flow medical has received CE Mark.

**Future valves at a glance**

**Centera**
The Edwards CENTERA (Edwards Lifesciences, Irvine, California, USA) is a self-expandable prosthesis with a radiopaque nitinol frame pre-packaged on a catheter\textsuperscript{75}. The design of the valve leaflets (bovine pericardium) is the same as the previous valves from the Edwards company, with an outer skirt consisting of polyethylene terephthalate, similar to the Edwards Sapien 3 prosthesis. The valve will be available in 23, 26 and 29 mm sizes. The design of the nitinol stent has a low frame height designed to minimize the risk for conduction disorders. Furthermore, the prosthesis does not extend into the ascending aorta for anchoring or self-alignment\textsuperscript{76}. The prosthesis has a motorized, battery-powered, delivery system with a detachable handle. This handle allows positioning by a single-operator with repositioning during loading and deployment.

The Centera received CE mark in 2014. The first experience with the Edwards CENTERA was gained in Canada and Germany with 15 patients; the reported survival was 87\% at 30 days and 80\% at 1 year. Paravalvular aortic regurgitation at 30-day follow-up was moderate in 1 (8\%) patient. Currently, a trial in the US as well as Europe is evaluating the Centera in the Safety and Performance Study of the Edwards CENTERA Self-Expanding Transcatheter Heart Valve (NCT01808274 full details available at www.clinicaltrials.gov, (last verified July 2015)).

**Colibri**
The Colibri prosthesis (Colibri Heart Valve, Broomfield, Colorado, USA) is a balloon expandable TAVI system for transfemoral use. It is a dry, pre-mounted, pre-crimped and pre-packaged valve, currently only manufactured in 24 mm. The porcine pericardium leaflets are folded, reducing number of sutures needed (<200 in Colibri, >1500 other systems). It is delivered through a 14 French sheath, allowing a transfemoral approach in patients with smaller vasculature and possibly reducing the risks for access route complications. The Colibri received CE mark in 2014. The first in-man case has been presented in 2012\textsuperscript{77}, long term outcomes are awaited.
Inovare
The Inovare (Braile Biomédica, São José do Rio Preto, Brazil) transcatheter aortic valve is implanted by transapical or transfemoral approach. The prosthesis consists of a bovine pericardium mounted in a cobalt-chromium valve and is balloon expandable. It received CE mark in 2014. The initial experience with the valve describes a successful implantation through transfemoral approach in six cases.

Trinity
TRINITY heart valve system (Transcatheter Technologies GmbH, Regensburg, Germany) is a prosthesis consisting of bovine pericardium mounted on a self-expanding nickel-titanium alloy frame. The prosthesis is repositionable and retrievable and can be implanted without the need for rapid ventricular pacing. Trinity underwent an in vivo animal trial in 2010 and in the first-in-human study it was implanted by transapical approach. Currently the prosthesis is available for either a transapical or transarterial catheter. CE mark for the trinity heart valve system was provided in 2015.

AorTx
The AorTxF valve (Hansen Medical Inc., Mountain View, California, USA) consists of a solid nickel-titanium alloy frame which is formed into a convex triangular shape. To eliminate stress at hinge points, the frame is hinged at three points to allow rotational crimping. The valve delivered via an 18F system and can be recaptured and repositioned. First in human implantation occurred in 2006 with eight patients. In 2015, CE mark was received for the Aortx.

Venus A-Valve
The Venus A-valve (Venus MedTech, (Hangzhou), Inc., Hangzhou, China) is a self-expanding prosthetic heart valve with porcine pericardium leaflets, developed and manufactured in China. It is delivered with an 18-20 F retrievable system via a transfemoral, transaortic or transaxillary/subclavian route. Currently the safety and performance of the Venus-A is evaluated in 80 patients in a clinical trial initiated from Beijing (NCT01683474. full details available at www.clinicaltrials.gov, (last verified January 2015). Endpoints are the safety and clinical benefit in 30 days, 6 months and 1 year. The primary outcome is all cause mortality and major stroke at 12 months post-procedure. Data is expected early in 2016. First public results of 15 patients (11 femoral and 4 aortic) were presented in 2013 on a conference in Hong Kong and showed a procedural success rate of 93.3% (14 patients). Thirty day outcome showed a pacemaker rate of 33.3% (5 patients), 1 major vascular complication and 1 major bleeding (6.7%) and no strokes. Already the prosthesis was used in a observational descriptive study describing the morphological characteristics of aortic valve stenosis in a China. This study included 120 patients of
whom 47.5% had a native bicuspid valve. Besides an extensive description of anatomy and morphology in this population, the procedure outcome is not discussed.

**Hydra Aortic Valve**
The Hydra Aortic Valve is a self-expandable prosthesis (Vascular Innovations Company, Bang Tanai, Nonthaburi, Thailand), developed and produced in Thailand, with the aim to generate a more affordable TAVI prosthesis for this country's patients. The prosthesis consists of bovine pericardium leaflets sutured to nitinol stent frame. To allow deployment and anchoring adjusted to the shape of the aorta. It the frame has three adjustable tentacles at the outflow trajectory. The prosthesis will be available in 3 sizes; Hydra22 for annulus sizes 18-20 mm, Hydra26 for 20-24 mm and Hydra30 for annulus size ranging from 24-28 mm. It will be delivered through an 18F catheter and will be retrievable after positioning until 70% deployment. The first multicenter, prospective trial is expected to start in November 2015 as a non-randomized investigational study among 70 patients in order to assess the safety and performance of the Hydra. (NCT02434263 full details available at www.clinicaltrials.gov, last verified April 2015).

**Optimum**
The Optimum TAVI system or the Thubrikar TAVR system (Thubrikar Aortic Valve Inc., Norristown, Philadelphia, USA) is a self-expanding prosthesis consisting of bovine pericardium leaflets mounted on a nitinol frame, developed with a low. Currently a 23 mm prosthesis is available and the company is planning on creating a 20 and 26 mm valve. It is claimed that the prosthesis is “designed for durability”, mimicking the natural aortic valve geometry. To date, animal studies, durability testing and human cadaver studies have been completed with success.

**Heart leaflet technology**
The heart leaflet technology (Heart leaflet technologies Inc., Maple Grove, Minnesota, USA) valve is a self-expanding prosthesis, composed of tricuspid porcine pericardial tissue. The prosthesis is implanted at the annular level and has an elastic wire frame with nitinol mesh, supporting the prosthetic valve and keeping it fixed within the native annulus. The company developed an integrated braided polyester liner to prevent regurgitant flow around the valve. First-in-man studies have been successfully performed and the Heart Leaflet Technology is awaiting FDA and European approval for clinical trials.

**Allegra**
The Allegra (New Valve Technology AG, Muri, Switzerland, is a self-expandable prosthesis, implanted transfemorally through an 18F sheath. The prosthesis consists of a short nitinol stent frame with a valve made of bovine pericard. Permaflow technology allows early
functionality of the valve by avoiding outflow obstruction during implantation and annular fixation is ensured through radial forces and the A single arm pilot trial was performed in 2013 and presented in 2014. In this trial 21 patients were included, with a procedural success of 91% (19 patients). Thirty day survival rate was 95%, pacemaker the implantation rate was 19.1% and there were 5 patients with minor vascular complications (23.8%). Postprocedural aortic regurgitation was graded mild in 13 patients, moderate in 2 patients; there were no cases of severe aortic regurgitation.

**Triskele**

The Triskele (UCL TAV™, University College London, London, United Kingdom) consists of a stent composed of a nickel–titanium alloy designed to enhance anchoring and sealing without excessive radial pressure on the annulus. A promising durability of the prosthesis is claimed since the leaflets of the valve are composed of a biocompatible polymeric nanocomposite, which is believed to have higher resistance to calcification. The prosthesis is fully retrievable and repositionable. The valve is still only in research phase.

**PercValve**

The PercValve (Advanced Bioprosthetic Surface, Ltd., San Antonio, Texas, USA) is a self-expandable prosthesis. It is designed as a monolithic valve with leaflets consisting of nanosynthesised e-nitinol mounted on a ‘thin film’, elastic nickel-titanium alloy frame. Animal studies demonstrated complete endothelialization of the valve leaflets within 10 days. This potentially reduces valve thrombosis and subsequent thromboembolic events. The prosthesis is delivered via a 10F delivery catheter by antegrade approach. In contrast to the majority of second-generation devices, it is not repositionable or retrievable.

**5-YEAR VIEW**

The field of transcatheter aortic valve procedures has expanded rapidly in the past decade. TAVI has proven to be superior to the conventional treatment for inoperable aortic stenosis and should be strongly considered for patients who are at high risk for surgical aortic valve replacement. As a result of clinical experience and continuous improvement in outcomes a gradual clinical shift is seen in TAVI towards intermediate-risk patients with severe aortic stenosis. However, this highly competitive field, technical refinements of the devices are mandatory to further decrease severe or frequently occurring complications (Table 2), exceeding the impact of complication management.
### Table 2: Overview of TAVI prostheses

#### Clinical studies

<table>
<thead>
<tr>
<th>Prosthesis</th>
<th>Indication</th>
<th>Valve material</th>
<th>Balloon expandable</th>
<th>Approach</th>
<th>CE Mark</th>
<th>First in human (year)</th>
<th>Mean age patients</th>
<th>Patients</th>
<th>Year of publication</th>
<th>Device success rate</th>
<th>30 days mortality</th>
<th>Long term mortality</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic CoreValve</td>
<td>AoS</td>
<td>Porcine pericardium</td>
<td>Self-expandable</td>
<td>Transfemoral</td>
<td>2007</td>
<td>2004</td>
<td>83.1 ± 7.1</td>
<td>390</td>
<td>2014</td>
<td>3.3%</td>
<td>1 yr: 14.2%</td>
<td>1 yr: 14.2%</td>
<td>Barker, Reardon (Pivotal trial US)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>81.5 ± 6.3</td>
<td>353</td>
<td>n/a</td>
<td>7.4%</td>
<td>1 yr: 21%, 2yr: 29%, 3yr: 38%, 4yr: 48%, 5yr: 55%</td>
<td>Barbanti 2015</td>
<td></td>
</tr>
<tr>
<td>CoreValve Evolut R</td>
<td>AoS</td>
<td>Porcine pericardium</td>
<td>Self-expandable</td>
<td>Transfemoral</td>
<td>2013</td>
<td>2012</td>
<td>82.8 ± 6.1</td>
<td>60</td>
<td>2015</td>
<td>78.6%</td>
<td>0%</td>
<td>n/a</td>
<td>Manoharan</td>
</tr>
<tr>
<td>Edwards SAPIEN XT</td>
<td>AoS</td>
<td>Bovine pericardium</td>
<td>Balloon expandable</td>
<td>Transfemoral/transapical/transaortic</td>
<td>2011</td>
<td>2011</td>
<td>xx ± xx</td>
<td>101</td>
<td>2015</td>
<td>98%</td>
<td>1.0%</td>
<td>n/a</td>
<td>PARTNER II</td>
</tr>
<tr>
<td>Edwards Sapien 3</td>
<td>AoS</td>
<td>Bovine pericardium</td>
<td>Balloon expandable</td>
<td>Transfemoral/transapical/transaortic</td>
<td>2014</td>
<td>2014</td>
<td>84.4</td>
<td>101</td>
<td>2015</td>
<td>98%</td>
<td>1.0%</td>
<td>n/a</td>
<td>Sapien 3 CE Intermediate Risk (presentatie Web), PARTNER II</td>
</tr>
<tr>
<td>Portico</td>
<td>AoS</td>
<td>Porcine pericardium</td>
<td>Self-expandable</td>
<td>Transfemoral</td>
<td>2012</td>
<td>2011</td>
<td>xx ± xx</td>
<td>63</td>
<td>2015</td>
<td>98%</td>
<td>1.0%</td>
<td>n/a</td>
<td>PARTNER II</td>
</tr>
<tr>
<td>JenaValve</td>
<td>AoS</td>
<td>Porcine native aortic valve leaflets</td>
<td>Self-expandable</td>
<td>Transfemoral/transapical</td>
<td>2011</td>
<td>2009</td>
<td>xx ± xx</td>
<td>31</td>
<td>2014</td>
<td>96.8%</td>
<td>12.9%</td>
<td>6 months: 19.3%</td>
<td>Seiffert 57,58</td>
</tr>
<tr>
<td>JenaValve AoR</td>
<td>AoR</td>
<td>Porcine native aortic valve leaflets</td>
<td>Self-expandable</td>
<td>Transfemoral/transapical</td>
<td>2013</td>
<td>2009</td>
<td>73.8 ± 9.1</td>
<td>31</td>
<td>2014</td>
<td>96.8%</td>
<td>12.9%</td>
<td>6 months: 19.3%</td>
<td>Seiffert 57,58</td>
</tr>
</tbody>
</table>
Lotus Valve system
AoS Bovine pericardium self-expandable transfemoral 2013 2007 84.4 ± 5.3 120 2014 99.2% 4.2% n/a Meredith 2014

Acurate (Symetis)
AoS porcine native aortic valve leaflets self-expandable transapical 2011 2009 80.9 ± 6.3 250 2014 98% 6.8% n/a Kempfert

Acurate (Symetis)
AoS porcine native aortic valve leaflets self-expandable transfemoral 2013 85.3 ± 3.7 20 2012 95% 0.0% n/a FIM study

Medtronic Engager
AoS Bovine pericardium self-expandable transapical 2013 2008 81.9 ± 3.7 60 2013 84.9% 9.9% n/a Holzhey: multicenter engager pivotal

Direct Flow Medical
AoS Bovine pericardium inflation of ring transfemoral balloons 2013 2006 83.0 ± 5.7 75 2013 93% 1.3% n/a Schofter 2014, direct flow

Edwards CENTERA
AoS Bovine pericardium self-expandable transarterially 2014 2011 xx ± xx 2013 100% 13% 1 year: 20% Binder

Inovare valve AoS Bovine pericardium balloon expandable transfemoral/ transapical 2014 2008 65.8 ± 20.2 6 2012 100% not described Pontes 2013

The Colibri Heart Valve, UCL TAV, Perc Valve, Vanguard Valve, Trinity and the Heart Leaflet Technology have limited or no public clinical data and are therefore not incorporated in this overview.
EXPERT COMMENTARY: EMERGING TECHNOLOGIC REFINEMENTS

The shortcomings in the first generation transcatheter prostheses led to design modifications and the development of second-generation transcatheter prostheses. Thus far, the decreased sheath sizes and sheath characteristics of the newer generation prostheses, improved percutaneous vascular access\(^90\) and will further decrease vascular complications. Prevention of paravalvular leakage has been achieved by optimal sizing using CT imaging. Further improvement has been accomplished by application of a sealing skirt on new prosthesis. However, additional improvements of the devices are mandatory specifically when moving towards treatment of low risk younger patients and should include further downsizing of the delivery systems, technical features to continue simplifying the procedure, shortening the operator's learning curve. Furthermore, enabling unobstructed coronary access, either for acute or planned PCI, is mandatory\(^65\). Reducing the necessity of a new pacemaker implantation is obviously preferable wherever possible. This might be achieved by decreasing the radial forces on the endocardium and the conduction system as well as shortening of the frame and a decreased implantation depth. Although occurring with a relatively low incidence, a reduction of peri- or postprocedural stroke is required in the future of TAVI. Protection devices might play a role, although their efficacy is currently not established yet\(^91-93\). Safer delivery systems and medical regimes including antithrombotic medication are other potential targets in minimizing stroke incidence\(^84, 95\). Finally, decreasing the invasiveness, number of puncture sites, the need for endotracheal intubation ventilation and subsequent extubation, will potentially optimize outcome. The durability of the prostheses remains an important feature, particularly if in the nearby future indications will shift and younger patients will be considered for TAVI. Durability is determined by the design of the prosthesis, the used tissue and frames, the crimping, the treatment of the valve tissue, gradients across the valve and multiple patient characteristics. It is important that mechanical pressure and stress do not lead to structural valve deterioration, including accelerated calcification, degeneration, frame fatigue or prosthesis tearing, and that the good hemodynamic performance of the prosthesis persists on long term. As the novelty of the procedure precludes large trials on long-term durability, the only available durability data are the described mid-term (5-years) results, which look promising\(^31, 36, 37\). Moreover the long-term (10 years), late-term (15 years), and very-late-term (20 years) outcome data are awaited. Nonetheless, for surgical aortic bioprostheses excellent long-term durability has previously been reported. This induces optimism about the durability of transcatheter aortic prostheses, since similar tissue fixation techniques are utilized.
EXPERT COMMENTARY: EXPANDING INDICATIONS

Presumably, part of the above mentioned improvements will decrease complication rates and result in an expansion of clinical indications for TAVI such as younger, lower risk patients that may benefit from this treatment\textsuperscript{[96, 97]}. In addition, TAVI can be used for patients with specific risk factors deeming inoperability, and for expanding indications such as multiple valve procedures\textsuperscript{[98]} aortic regurgitation, valve-in-valve procedures\textsuperscript{[99-104]} and bicuspid aortic valve stenosis\textsuperscript{105}. Specifically, the valve-in-valve possibility may induce a shift in age from mechanical to biological surgical prosthesis. Appropriate selection of patients based on outcome predictors will further help to maximize the benefit of TAVI and reduce mortality.

Table 3: Most desirable features of devices

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repositionability</td>
</tr>
<tr>
<td>Retractable</td>
</tr>
<tr>
<td>High durability and long device lifetime</td>
</tr>
<tr>
<td>Proven safety of device</td>
</tr>
<tr>
<td>Non-thrombogenicity</td>
</tr>
<tr>
<td>Dynamic responsiveness</td>
</tr>
<tr>
<td>Prosthesis-tissue interaction</td>
</tr>
<tr>
<td>Small delivery sheaths</td>
</tr>
</tbody>
</table>
CONCLUSIONS

Combining individual patient characteristics with device characteristics to achieve the optimal hemodynamic result is essential for the best choice of prosthesis for the individual patient. Evaluation of devices combined with individual patient characteristics will improve the selection of patients, selection of devices and optimize outcomes. Therefore, in this rapidly changing area of transcatheter valve implantations the future direction will be guided by assessing data on the safety and durability of the devices in long-term follow-up studies.

Figure 1: From left upper corner to right; Edwards SAPIEN, Edwards SAPIEN XT, Edwards SAPIEN 3, Medtronic CoreValve, Medtronic Evolut-R, Boston Lotus, JenaValve, Medtronic Engager, Edwards CENTERA. Reproduced with permission from Edwards Lifesciences, Medtronic Inc a subsidiary of Medtronic plc, Boston Scientific and JenaValve.
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Chapter 11


