

NOVEL THERAPIES

The Next Era of Transcatheter Aortic Valve Implantation (TAVI): Fully Repositionable, Re-Sheathable and Retrievable Prostheses?

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ABBREVIATIONS

AS = aortic stenosis
AV = atrio-ventricular
CE (mark) = Conformit Europtene
LVOT = left ventricular outflow tract
PPM = patient-prosthesis mismatch
PVR = paravalvular regurgitation
TAVI = transcatheter aortic valve implantation
TCT = Transcatheter Cardiovascular Therapeutics

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) is a great alternative treatment option in high surgical risk and inoperable patients with severe symptomatic aortic stenosis (AS). TAVI is a rapidly emerging technique with a constantly expanding body of evidence. However, the devices, which are commercially available and are currently used widely, have several major limitations. In particular, the inability to reposition/retrieve/resheath valves, in addition to several patient selection and procedural limitations, such as the occurrence of moderate to severe paravalvular regurgitation (PVR), the risk of annular rupture, atrioventricular (AV) conduction abnormalities with subsequent pacemaker requirement, vascular complications and associated bleeding, coronary ostial obstruction by the valve, stroke, as well as complex delivery processes, are expected to be overcome with the newer generation valves. Consequently, a number of new transcatheter valve choices have been developed either for clinical study or are in the pipeline, that it is hoped to bring meaningful clinical outcomes compared with the currently commercially available technology. Early data on design modifications have shown significant reductions in adverse outcomes from TAVI.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular disease in the industrialized world. It is more common among the elderly population with critical AS affecting 3% of those greater than 75 years of age.¹ Despite the fact that its prevalence is constantly increasing, a large percentage (~30%) of these patients decline or are denied surgical replacement of the aortic valve due to prohibitive or increased surgical risk, mostly related to comorbidities. The symptoms of the disease comprise syncope, angina and heart failure. The prognosis of the disease is poor, while the clinical condition of the patients is rapidly deteriorating. In particular, 50% of patients with syncope die within 5 years if they remain untreated. Similarly, 50% of patients with angina die within 2 years and 50% of patients with heart failure die within one year. Most of them are elderly patients who either have comorbidities or cannot undergo

Conflict of Interest: Dr. Vavuranakis has the following potential conflict of interest to report: serving as proctor of Medtronic, Inc.

surgery (inoperable). Therefore, the introduction of transcatheter techniques and their ability to be performed in both “high-risk” and inoperable patients expanded the management options in these patients.

In 1965, the first catheter-mounted valve was reported to be implanted via the femoral artery into the descending aorta of an animal model, and in 1986, the first catheter based intervention for AS was balloon valvuloplasty as described by Alain Cribier.² The first catheter-mounted stented valve implantation in humans was performed in 2000, when a platinum–iridium stent with a bovine jugular valve, was implanted into the pulmonary artery of a boy with pulmonary atresia by Bonhoeffer and his colleagues.³ However, the first transcatheter implantation of aortic valve (TAVI) was performed in 2002 via an antegrade transvenous approach using the historic Percutaneous Heart Valve™ (Percutaneous Heart Valves, Inc., NJ, USA), and the first retrograde transarterial approach was performed in 2003.⁴

Since that time, TAVI has emerged as a very challenging treatment option with more than 60,000 TAVI devices being implanted using both the antegrade transapical approach and retrograde transfemoral and transaortic approaches, due to avoidance of sternotomy and cardiopulmonary bypass. This potential resulted in many technological advances associated with both the valve sizes and morphological characteristics as well as with the sheath sizes.

OVERVIEW OF VALVE TYPES

HISTORICAL VALVES AND COMMERCIALY AVAILABLE VALVES (FIRST GENERATION)

The historical valves, the Percutaneous Heart Valve™ (Percutaneous Valve Technologies, NJ, USA), the Paniagua Heart Valve™ (Endoluminal Technology Research, Miami, FL) and the Cribier-Edwards Transcatheter Heart Valve™ (Edwards LifeSciences, Irvine, CA, USA) were balloon-expandable valves.⁵

The first commercially available valves were the Edwards SAPIEN THV™ (Edwards LifeSciences, Irvine, CA, USA) (Figure 1) and the Medtronic CoreValve™ (Medtronic, Minneapolis, MN, USA). The latter was the only self-expandable valve. In particular, CoreValve™ (Figure 2) consists of a supra-annular bovine (first-generation model) or porcine (second- and third-generation models) pericardium valve mounted on a self-expanding nickel-titanium alloy frame. The frame works with a ‘cell’ design with three distinct zones of varied loop strength and radial force. Additionally, the high radial force of the central portion, supra-annular positioning of the leaflets further minimizes disruption of leaflet configuration and coaptation. The cell structure of the stent also facilitates conformation to anatomical variance and functions to minimize coronary ostia obstruction.⁶ Rapid ventricular pacing, routinely needed for expansion of valves mounted on stents,



FIGURE 1. Edwards SAPIEN THV™ valve (Edwards LifeSciences, Irvine, CA, USA).



FIGURE 2. Medtronic CoreValve™ (Medtronic, Minneapolis, MN, USA) consists of supra-annular bovine (first-generation) or porcine (second- and third-generation models) pericardium valve mounted on a self-expanding nickel-titanium alloy frame.

is not required for both the 26- and 29-mm sized CoreValve models, while pacing at rates of 140 beats per minute is still recommended for the 31-mm device type. Furthermore, the ability to reposition and retrieve the valve up to 1/3 of valve length deployment is also claimed. The available sizes of CoreValve prosthetic sizes are the 26-, 29- and 31-mm which are delivered via an 18Fr Accutrack™ long sheath through the femoral artery.⁷ The design, however, necessitates a retrograde approach, eliminating the possibility of transapical access. However, when femoral access is contraindicated, the subclavian^{8,9} and direct aortic approaches are now approved and established routes for delivery of this type of valve.¹⁰

The aforementioned commercially available devices, that are currently used widely, have several major limitations. To be more precise, the inability to reposition/ retrieve/ resheath

these valves may result in device embolization or malpositioning. In addition, several patient selection and procedural factors constitute major limitations of the procedure. In particular, patient-prosthesis mismatch (PPM) may lead to the occurrence of moderate to severe or severe paravalvular regurgitation (PVR), which has been associated with increased mortality at two-year follow-up.¹¹ This may require corrective techniques,¹²⁻¹⁴ such as post-balloon valvuloplasty, valve-in-valve deployment, “Snare (Lasso) technique, “Remove and Reinsert” technique or surgery.

At the First Department of Cardiology of Hippokraton Hospital in Athens, where the CoreValve Medtronic system has been used since August 2008, reposition techniques¹²⁻¹⁴ (“Snare” technique, “Remove and Reinsert” technique “valve-in-valve”, “balloon withdrawal”) were required in 11% of cases. In all cases, the final angiographic result did not reveal significant PVR, immediately or during the short- and long-term follow-up of patients.

Furthermore, PPM entails the risk of annular rupture due to the high radial forces associated with aggressive oversizing of the valve prosthesis, especially where balloon expansion or balloon valvuloplasty is required.¹⁵ Valve and leaflet tissue may also provoke coronary ostial obstruction, embolization and consequent myocardial infarction.

Moreover, atrio-ventricular (AV) conduction abnormalities may develop due to the intimate co-location of the left bundle with the base of the interleaflet triangle separating the non-coronary and right coronary leaflets of the aortic valve with subsequent need for permanent pacemaker implantation.^{6,16} In addition, vascular complications and associated bleeding are a not infrequent complication of placing large-bore sheaths in femoral arteries, especially in often-elderly patients with calcific atherosclerotic disease of the peripheral vasculature.¹⁷⁻¹⁹ Finally, stroke is a significant risk when compared to similar cohorts undergoing cardiac surgery. The risk of stroke likely relates to embolization of friable material at the time of intervention.²⁰

The above limitations are expected to be overcome with newer generation valves that will be discussed below.

COMMERCIALLY AVAILABLE SELF-EXPANDABLE DEVICES: SECOND-GENERATION

Medtronic Evolut™ (Medtronic, Minneapolis, MN, USA)

Evolut™ is the second-generation CoreValve™ which retains most of the design features of its precursor, including cell geometry and preserved skirt height (Figure 3). Nevertheless, a number of important technical alterations have been made. To be more precise, overall height has been reduced, due to a 10 mm shortening of the outflow tract and tailored shape to improve fit and the capacity for valve retrieval.²¹ Additionally, the porcine leaflets were treated with alpha-amino oleic acid to inhibit calcification, a process that has been extended across the



FIGURE 3. Medtronic Evolut™ (Medtronic, Minneapolis, MN, USA) is the second-generation CoreValve™ which cell geometry and preserved skirt height. However, overall height has been reduced, due to a 10 mm shortening of the outflow tract, and tailored shape to improve fit and the capacity for valve retrieval.

entire CoreValve™ family. A first-in-man case report in 2012 described the successful implantation of a 23 mm CoreValve Evolut™, delivered using an 18Fr AccuTrack™ delivery system. CE-Mark approval was obtained later that year.

JenaValve (JenaValve Technology GmbH, Munich, Germany)

JenaValve™ is a porcine aortic root valve mounted on a low profile *self-expandable* nickel-titanium alloy frame designed for anterograde transapical implantation. The leaflets are identical to those used in the stentless Ilan™ and the stented Aspire™ valves (Vascutek, Inchinnan, Renfrewshire, UK). A unique aspect of this valve is that it relies on “clip fixation” of the prosthesis to native aortic valve leaflets (Figure 4). This reduces the requirement for high radial forces and larger contact area for securing the device to the aortic annulus complex structures. As a result, a shorter stent design minimizes complications related to the extension of the valve into the aorta and the left ventricular outflow tract (LVOT), such as AV conduction defect and coronary obstruction, respectively. Other features include three positioning ‘feelers’ extending into the aortic root sinus for self-positioning and providing tactile feedback, flexible stent posts to minimize leaflet stress and leaflets that function early in deployment negating requirement for rapid ventricular pacing. The delivery system of the valve includes a flexible 32Fr sheathless delivery catheter that obviates the need for excessive crimping and profile-minimizing modifications.¹⁰

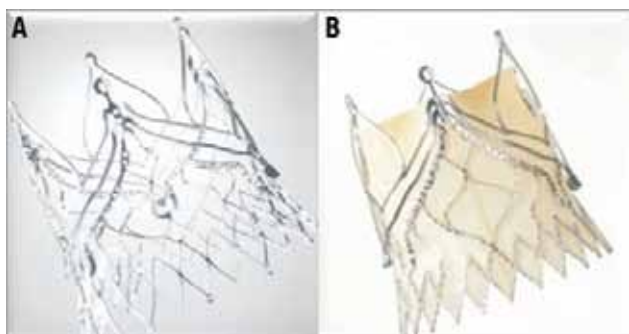


FIGURE 4. JenaValve (JenaValve Technology GmbH, Munich, Germany) is a porcine aortic root valve mounted on a low profile self-expandable nickel-titanium alloy frame designed for antero-grad transapical implantation.

The Jena Valve™ was first implanted in 2009²² and a multi-center prospective CE-Mark study resulted in approval in 2011.²³ A post-market registry (JUPITER) is ongoing. A feasibility and safety study of the transfemoral route with view to CE-Mark approval was planned in 2013.

Symetis Acurate™ (Symetis SA, Ecublens, Switzerland)

The Symetis Acurate™ uses a porcine aortic root valve mounted on a self-expandable nickel-titanium alloy stent. The shape of the stent body is an hourglass (Figure 5). This facilitates the annular fit and three stabilization arches provide tactile feedback during positioning and prevent tilting during deployment. An upper crown provides axial fixation and contributes to self-positioning. A polyethylene terephthalate (PET) skirt is found on the proximal part of the stent body, both inside and outside to prevent PVR. Additionally, this aspect of the



FIGURE 5. Symetis Acurate™ (Symetis SA, Ecublens, Switzerland) uses a porcine aortic root valve mounted on a self-expandable nickel-titanium alloy stent. The shape of the stent body is an hourglass. An upper crown provides axial fixation and contributes to self-positioning.

valve minimally protrudes into the LVOT to decrease AV conduction disturbance. The delivery system of the valve is loaded and housed on a 28Fr delivery device for antero-grad transapical access. Consequently, loading of the valve does not require excessive crimping. Additionally, the conical shape of the delivery catheter purportedly facilitates self-centering.¹⁰

Deployment is performed via a rotational knob, which, initially, partially unsheathes the valve and releases the stabilization arches followed by the upper crown. Accidental full release is guarded by a safety pin. Physiological orientation is facilitated by markers that allow for TAVI and native commissural alignment and consequently minimize coronary ostia compromise. The valve is *repositionable and re-sheathable* by reverse rotation of the delivery knob prior to release.¹⁰

Limitations of the valve positioning, include the requirement for preceding aggressive valvuloplasty due to the lower radial forces during self-expansion of this valve. Additionally, stabilization arches make the Symetis Acurate™ of uncertain value for valve-in-valve procedures. In particular, the results of a first-in-man trial (n = 40) and pilot study (n = 50) were combined for submission for CE-Mark approval which was achieved in 2011.²⁴ A post-marketing surveillance registry was established (Symetis Aortic Valve Implantation Registry) with favorable early results after 150 patients.

Early results for a transfemoral system which has recently undergone first-in-human trials (n = 20) were presented at the TCT 2012 Miami conference and were consistent with the transapical results. The delivery system used has an 18Fr outer diameter and the valve is available in three sizes to accommodate annulus sizes of 21–27 mm. A CE-Mark study for the transfemoral approach began in late 2012¹⁰ and final approval was given in 2013.

Portico™ (St. Jude Medical, St. Paul, MN, USA)

The Portico™ valve is a self-expanding nickel-titanium alloy stent with treated bovine pericardium leaflets, designed to be *fully resheathable, repositionable and retrievable*. The stent design is similar to the Medtronic CoreValve™ but with a more open cell structure (Figure 6). A porcine pericardium (chosen for its thin profile) sealing cuff is attached to the inside of the frame to minimize the risk of PVR. However, in contrast to the CoreValve™, cardiac conduction abnormalities are less frequent, probably due to a lower leaflet profile and a more vertical ventricular end of the stent, reducing both protrusion into and radial force onto the LVOT.²⁵ Furthermore, the prominent overlap of the leaflets allows full coaptation despite distorted and non-circular anatomy, of particular importance due to the lower leaflet profile resulting in intra-annular positioning. Finally, leaflets function early in deployment and thus remove the need for rapid ventricular pacing.

The Portico™ was first implanted in humans in 2011 in a small feasibility study of 12 patients in Canada and 10 patients in Ireland. A pivotal study began in December 2011 resulting

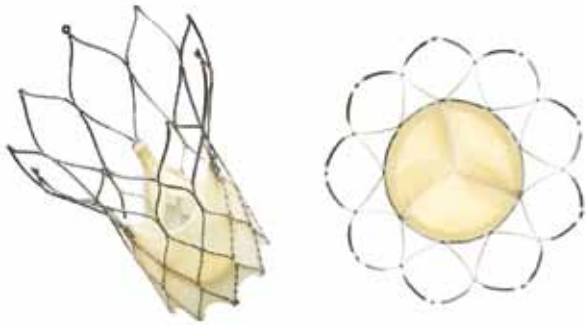


FIGURE 6. Portico™ (St. Jude Medical, St. Paul, MN, USA) is a self-expanding nickel-titanium alloy stent with treated bovine pericardium leaflets, designed to be fully resheathable, repositionable and retrievable with a more open cell structure comparing to the Medtronic CoreValve™.

in CE-Mark approval in 2012 for transfemoral or transapical delivery (18Fr and 24Fr sheaths respectively).²⁶

Sadra Lotus™ (Boston Scientific, Natick, MA, USA)

Sadra Lotus™ consists of a woven nickel-titanium alloy stent housing bovine pericardium leaflets for transfemoral delivery. The valve is pre-loaded on an 18Fr delivery system for the transfemoral approach and has full *repositioning and resheathing* capacity (Figure 7). The first-in-human implantation of the Lotus valve was in 2007, with impressive ongoing results at 5-year follow-up.²⁶ These positive results were supported by early data from a pilot study in 2012, the REPRIS I trial (n = 11).²⁷ Recruitment for the REPRIS II trial is now completed with the Lotus valve showing good performance in the REPRIS II trial.²⁸

Edwards CENTERA™ (Edwards LifeSciences, Irvine, CA, USA)

Edwards CENTERA™ is the first *self-expanding* valve produced by Edwards LifeSciences. It is composed of a nickel-titanium alloy frame and treated trileaflet bovine pericardium. The stent features a unique shape with the ventricular edge of the valve flared to 29-mm, tapering into the 26- mm ‘waist’ and ‘bellying’ out to 28-mm (for the 26-mm valve) (Figure 8). This purportedly facilitates self-centering of valve in the annulus, improved fit and therefore reduces PVR. Additionally, it minimizes protrusion on either side of the annulus. Unlike the CoreValve™, this valve is not functional until fully deployed and thus requires rapid ventricular pacing due to considerable LVOT obstruction. Although the CENTERA™ is *repositionable and recapturable* until final deployment, it is only resheathable if less than 70% deployed.²⁹ The valve is delivered transarterially with a single-operator, motorized system via a 14Fr sheath (Edwards LifeSciences). A CE-Mark clinical approval trial was begun in late 2012.²⁹

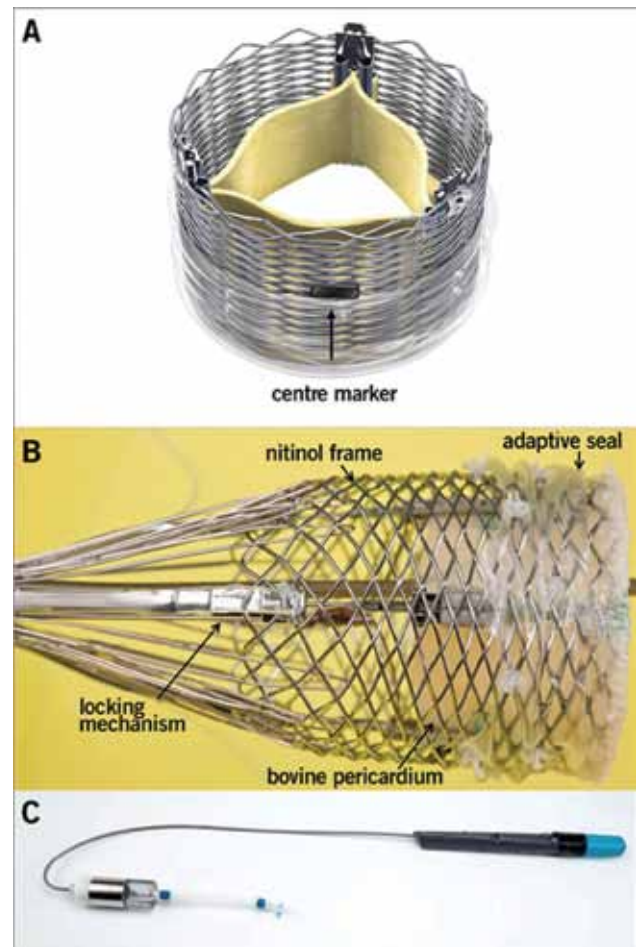


FIGURE 7. Sadra Lotus™ (Boston Scientific, Natick, MA, USA) consists of a woven nickel-titanium alloy stent housing bovine pericardium leaflets for transfemoral delivery.



FIGURE 8. Edwards CENTERA™, the first self-expanding valve produced by Edwards LifeSciences, is composed of a nickel-titanium alloy frame and treated trileaflet bovine pericardium. The stent features a unique shape with the ventricular edge of the valve.

Direct Flow Medical Aortic Valve™ (DFM Inc., Santa Rosa, CA, USA)

Direct Flow Medical Aortic Valve™ is a bovine pericardium valve with an entirely non-metallic framework relying on sequential inflation of dual rings (ventricular followed by aortic) to anchor the prosthesis to the native valve annulus (Figure 9). The valve is *fully repositionable* by deflation of the cuffs prior to final anchoring. The purported advantage of such a design is minimization of valve migration, dislodgement and PVR. This valve also has the theoretical potential to reduce cerebrovascular events as the dual rings ‘trap’ the native leaflets and may minimize embolization. Moreover, rapid ventricular pacing is not required, due to the fact that the valve leaflets are functional upon expansion. The first-generation DFM valve was evaluated in a feasibility and safety study in 31 patients.^{30,31} The safety and efficacy of the second-generation system are currently being assessed in the CE Mark, multi-center DISCOVER trial³² and were verified in 2013.



FIGURE 9. Direct Flow Medical Aortic Valve™ (DFM Inc., Santa Rosa, CA, USA) is a bovine pericardium valve with an entirely non-metallic framework relying on sequential inflation of dual rings (ventricular followed by aortic) to anchor the prosthesis to the native valve annulus.

Medtronic Engager™ (Medtronic, Minneapolis, MN, USA)

Medtronic Engager™ is the first valve from Medtronic for transapical access and anterograde approach. It employs a *self-expanding* nickel-titanium alloy frame incorporating scalloped, full thickness, bovine pericardium leaflets (Figure 10). The Engager™ valve is delivered via a 29Fr transapical delivery system and a direct aortic delivery system is under development. The Engager™ underwent first-in-man implantation in 2008.²⁶ The Engager™ CE pivotal trial began as a prospective, multi-center study involving 120 patients. The 30-day results on the first 60 recruited patients have been impressive most notably with regard to marked reduction in PVR, an improvement in keeping with the other second-generation transapical valves (Acurate™ and JenaValve™).³³ The valve obtained CE mark approval in 2013.



FIGURE 10. Medtronic Engager™ (Medtronic, Minneapolis, MN, USA) is the first valve from Medtronic for transapical access and anterograde approach. It employs a self-expanding nickel-titanium alloy frame incorporating scalloped, full thickness, bovine pericardium leaflets.

NEW ENTRIES

The **AorTx™ valve** (Hansen Medical Inc., Mountain View, CA, USA) has a solid nickel-titanium alloy panel frame formed into a convex triangular shape that is hinged at three points to allow rotational crimping and eliminate stress at hinge points. The valve cusps do not come in contact with the frame during valve opening, which may confer leaflet durability (Figure 11). The valve has an 18Fr delivery system and has the potential to be *recaptured and repositioned*. First in human implantation occurred in 2006 (n = 8).¹⁰

The **HLT™ valve** (Heart Leaflet Technologies Inc., Maple Grove, MN, USA) has porcine leaflets mounted on a *self-expandable* nickel-titanium alloy wire stent (Figure 12). The valve sits in an intra-annular position and it is suitable for the transfemoral route via an 18Fr delivery catheter and is available in 21- and 23-mm sizes. The valve is fully repositionable and retrievable. Additionally, the leaflets are sewn to flexible post to reduce valve and tissue stress. First-in-human implantation was performed in 5 patients in 2011. It was planned for this new design to undergo pilot trial at the end of 2012.^{10,34}

Additionally, there are other valve devices that have not been fully developed such as **Vanguard II™** (ValveXchange Inc., Aurora, CO, USA) which is a second-generation transcatheter valve, for which a CE-Mark approval trial began in 2012.¹⁰ Similarly, the **Trinity Heart Valve™** (Transcatheter Technologies GmbH, Regensburg, Germany) (Figure 13) is a repositionable and retrievable valve with bovine pericardium mounted on a self-expanding nickel-titanium alloy frame. It has been implanted transapically in a beating heart (without the need for rapid ventricular pacing).¹⁰ The **UCL TAV™ valve** (University College London, London, UK) comprises leaflets composed of a novel biocompatible polymeric nano-composite recently developed and patented by University College Lon-

NEWER GENERATION VALVES FOR TAVI

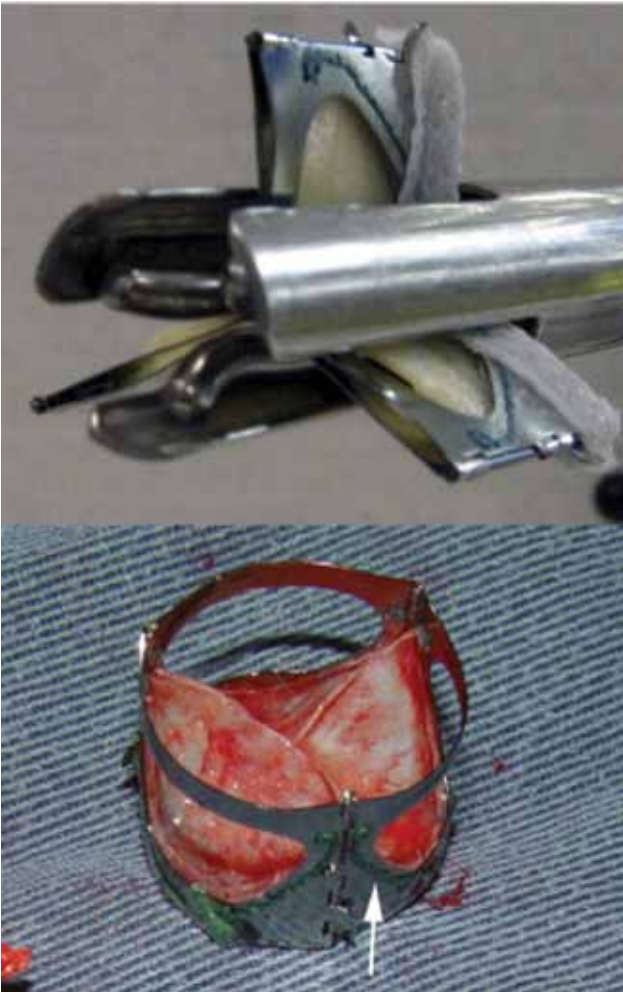


FIGURE 11. The AorTx™ valve (Hansen Medical Inc., Mountain View, CA, USA) has a solid nickel-titanium alloy panel frame formed into a convex triangular shape that is hinged at three points to allow rotational crimping and eliminate stress at hinge points.

don, which exhibits superior mechanical and surface properties and has higher resistance to calcification (Figure 14). The UCL TAV™ is also *fully retrievable and repositionable*.¹⁰ Finally, the **tissue-engineered heart valves** have relied on a nickel-titanium alloy stent housing a biodegradable synthetic scaffold onto which autologous bone-marrow mononuclear cells are implanted (Figures 15 & 16). The inherent advantage of this is that the valve maintains repair/regenerative capacity potentially overcoming problems related to reduced durability secondary to calcification and mechanical stress. This concept



FIGURE 12. The HLT™ valve (Heart Leaflet Technologies Inc., Maple Grove, MN, USA) has porcine leaflets mounted on a *self-expandable* nickel-titanium alloy wire stent. Additionally, the leaflets are sewn to flexible post to reduce valve and tissue stress.



FIGURE 13. Trinity Heart Valve™ (Transcatheter Technologies GmbH, Regensburg, Germany) is repositionable and retrievable, and has bovine pericardium mounted on a self-expanding nickel-titanium alloy frame.

has been applied to pulmonary valves and vascular grafts, with the latter having received FDA approval for clinical application. Proof-of-concept for application to TAVI has recently been reported in an ovine model.³⁵

CONCLUSION

To conclude, there has been rapid and profound evolution of the valve technology, that it is hoped to bring meaningful clinical outcomes compared with the currently commercially available technology. Early data on design modifications have shown significant reductions in adverse outcomes from TAVI.

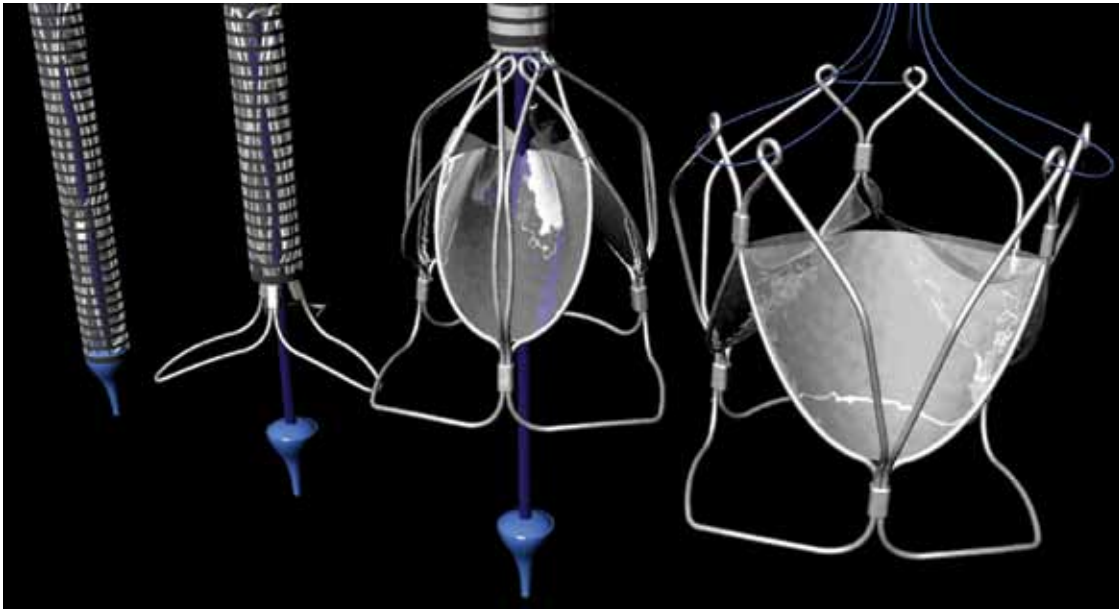
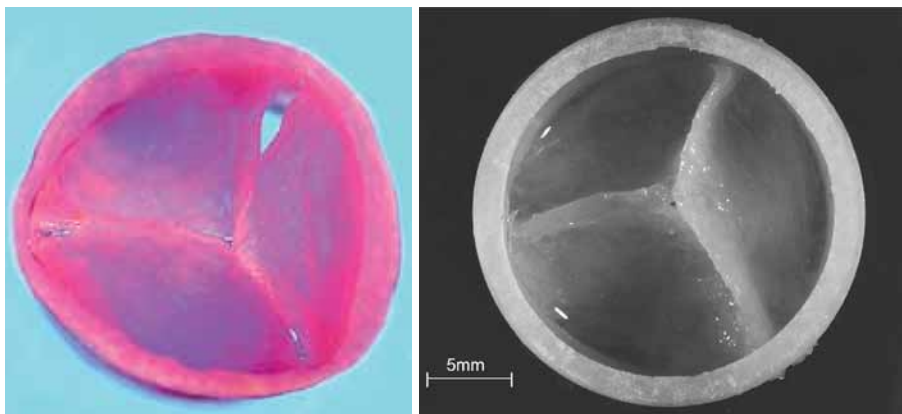


FIGURE 14. The UCL TAV™ valve (University College London, London, UK) comprises leaflets composed of a novel biocompatible polymeric nano-composite recently developed, which exhibits superior mechanical and surface properties and has higher resistance to calcification.



FIGURES 15 & 16. The tissue-engineered heart valves have relied on a nickel-titanium alloy stent housing a biodegradable synthetic scaffold onto which autologous bone-marrow mononuclear cells are implanted. Proof-of-concept for application to TAVI has recently been reported in an ovine model.

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