

New frontiers in transcatheter heart valve technologies

The first prototype of a transcatheter heart valve prosthesis was developed as far back as 1965 by Dr Hywel Davies. More than 40 years on, the market for these devices, which offer a minimally-invasive alternative for replacing diseased heart valves to conventional surgery, is growing at double-digit rates. In this article, Sarah Zanon, senior clinical project manager of D-Target*, discusses the competitive landscape of the transcatheter aortic valve implant market and also opportunities in the area of transcatheter mitral valve repair

2007 saw the advent of two transcatheter aortic valve prostheses (TAVP) in the European market after receiving CE mark approval: the Sapien valve (Edwards Lifesciences) and CoreValve (developed by French company CoreValve, which was then acquired by Medtronic in 2009).

The impact of these devices on the heart valve (HV) market has been impressive. More than 40,000 TAVPs have now been implanted worldwide and their rapid adoption is a strong growth driver in the HV devices market. Average market growth for Europe is estimated at 20% per year through 2015, with Germany as the leading country, recording in 2010 almost 25% of all aortic valve replacements performed with TAVP. Increase in revenue is enhanced by the device's high average selling price (currently in the order of €25,000). As a reference, in 2010, Edwards TAVP sales amounted to \$206m and the 2011 outlook is in the range of \$300-340m, including an estimated \$20-25m for Q4 2011 after Sapien's launch in the US market. The company expect TAVP sales to hit \$1bn by 2013.

There is now also a redo procedure market for TAVPs, which involves replacing dehiscent bioprostheses with the valve-in-valve technique. Although this procedure is currently performed off-label, it might account for a relevant portion of implant sales in the near future.

The TAVP landscape: current players

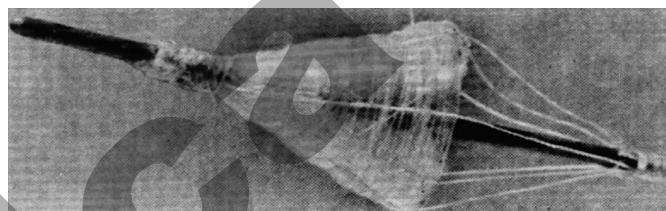
To date, four transcatheter devices are commercially available in Europe.

Edwards Lifesciences' Sapien valve (derived from pioneer PVT, acquired by ELS in 2004) is approved for both transapical and transfemoral approaches. Approved products family includes Sapien (stainless steel stent) and Sapien XT (Cobalt-chromium stent) models. Sapien is the only balloon-expandable based TAVP in clinical use or under development.

Medtronic's CoreValve system is a self-expandable (Nitinol stent) TAVP that is approved for delivery via three different approaches: transfemoral, subclavian and direct aortic.

The Jenavalve device by Jenavalve Technology (Munich, Germany) and Acurate TA by Symetis (Ecublens, Switzerland) was CE-mark in September 2011. Both are self-expandable porcine prostheses, approved for transapical procedures only. Transfemoral devices are under development.

In the US, only Edwards and Medtronic are active protagonists. Transfemoral Sapien valve has recently received



Dr Hywel Davies' "umbrella-like prosthetic valve mounted on a catheter", 1965

FDA approval for "patients who are not eligible for open-heart surgery for replacement of their aortic valve". In July, the FDA advisory committee favorably voted to endorse Sapien based on PARTNER (Cohort B) study outcomes. PARTNER study includes also Cohort A patients, randomizing either transfemoral or transapical approaches to surgical aortic valve replacement in high-risk surgical patients. Outcomes of Cohort A have been presented at TCT 2011 in San Francisco. Medtronic is currently conducting a pivotal randomised clinical trial in 40 US sites. It is anticipated that the enrollment will be completed by May 2012.

Transcatheter Aortic Valve Implantation (TAVI) Open issues

In light of available clinical data, it is realistic to consider that in five years, TAVI will represent the standard of care for inoperable (STS score >8) and high-risk (4 < STS score < 8) severe AS patients.

In order to expand TAVI to a broader, lower-risk population, some drawbacks will have to be addressed in the future development of the technology. Compared to traditional open-chest surgery, patients implanted with TAVP have higher rates of stroke (5% to 8% compared to 1-2% for surgical AVR), paravalvular leakages (moderate to severe up to 13%, as reported for PARTNER trial), interference with electrical conduction system (requiring up to 40% of permanent pace-maker implantation, depending on TAVP used) and vascular/LV apical complications (according to implant route). Consequently, TAVP reimbursement seems to be under critical review. Medicare and Medicaid Services have recently expressed concerns to make this new technology available to a large number of low volume and inexperienced centers.

In addition to these issues, there is also lingering concern regarding valve durability in TAVI. Unlike the surgical procedure, where the stenotic native valve is removed along with the surrounding calcifications before suturing the prosthesis, TAVI

overlaps the prosthesis to the existing irregular calcifications. Since a TAVP's working conditions are affected by implant site characteristics, the effective functioning of the device, and consequently its durability, are only partially predictable. Actual risk of earlier TAVP failure in human use is still to be assessed due to the lack of long-term clinical results.

First-gen TAVP vs second-gen

Classification of the eclectic TAVP variety already in clinical use or under development can be based on the design of the prosthetic stent and its way to interface with the implant site.

According to this criterion, first-generation devices are characterised by a very simple cylindrical stent structure fitting with the implant site as a cylinder inside a cylinder, the latter being the aortic root. The anchoring mechanism is substantially obtained by friction. Without calcification, these devices are prone to migrate and dislodge. Typically, TAVP in this group are Sapien and CoreValve, commonly considered the founding fathers of this technology. Their inaugural years of clinical use were affected by a low percentage of procedural success, mainly due to suboptimal positioning of the prosthesis and device migration. The reason for initial poor outcomes was referred to inadequate design unable to provide unique matching with the anatomy of the aortic root. In addition, the complexity of the procedure was deemed intrinsic and leading to unavoidable errors. Starting from this root cause analysis, a large number of new projects gave origin to second-generation devices. Some examples of second-generation TAVP, besides Jenavalve and Acurate TA, are Engager Valve of Medtronic (formerly Ventor), Lotus Valve of Sadra Medical (acquired by Boston Scientific in 2010), DMF Valve of Direct Flow Medical, and HLT System of Heart Leaflet Technologies. Regardless of the specific technological solutions, the common feature is the pursuit of anatomical fitting with the implant site by means of a sophisticated shape of the stent. The final goal of second-generation devices is to obtain a self-guided positioning device, making the result of implant procedure less dependent on the end-user. Furthermore, since the risk of malpositioning is still considered significant, great emphasis is generally given to intra-procedural recapturability and retrievability of the device, offering the operator a second chance of procedural success.

What is particularly noteworthy is that concurrent to second-generation TAVP development, remarkable improvements were accomplished to make the procedure easier and more reliable (eg use of rapid pacing, more accurate valve size assessment, etc). Moreover, imaging quality has significantly improved, leading to a higher rate of procedural success even with the first-generation devices. Therefore, it seems proper to wait for more clinical data before concluding that second-generation TAVP represents a true step ahead in safety and effectiveness.

This conclusion may be corroborated by one of the latest newcomers in TAVP arena, Portico by St. Jude Medical (first-in-man study in June 2011), which can be rightfully listed among first-generation device. Is it a sign that second-generation concepts should be subject to critical review? More likely, the above mentioned TAVI open issues will be fully addressed only by third-generation devices which are still at the very early stage of the R&D pipeline. As a pure speculation, it may be expected that third-generation TAVP will require strong

innovation in the materials used for both the stent and the functional component.

Mitral valve: a world of its own

While progress in TAVI technology has created a concrete alternative to traditional surgery, at least in a specific patient population, transcatheter treatment of mitral valve (MV) regurgitation fails to provide comparable results. The reason for delayed penetration cannot certainly be ascribed to a lack of demand. MV regurgitation is a vastly underserved market with the potential to highly outdo the aortic one. It is expected that transcatheter MV technology may increase the US TAVP market from the 48,000 surgeries per year (as estimated in 2006) to at least 350,000 overall cases per year when the technology is consolidated. Similar impact is expected in the rest of the Western world.

Several factors make transcatheter MV regurgitation treatment much more technically demanding than TAVI. Examples of challenges particular to transcatheter MV treatment include: the complex MV and sub-valvular anatomy, the absence of well-structured implant site (MV is positioned between two open chambers), the often multifactorial coinciding etiologies in MV disease, and the frequent occurrence of MV annulus prolapse.

The evident difficulties have led to a diversified spread of approaches from the outset, mainly MV repair, MV replacement, and heart chamber(s) remodeling. The latter approach is based on the hypothesis that remodeling the heart's left side (left atrium or ventricle, or both) can indirectly induce a corrective effect on MV. Cinching devices like Ample PS3 (left atrium remodeling) and Myocor iCoapsys (left ventricle remodeling) are two examples of this technique. Most of the research programs in this area have been discontinued or suspended.

More resources have been devoted to the development of transcatheter MV repair and replacement, which are considered more promising and efficacious.

Transcatheter MV repair

The development of transcatheter MV repair technology, characterised by extraordinary inventiveness, has a long history starting in the late 1990s. Several approaches, some already significantly exploited without concrete results, can be classified as:

- Coronary sinus approach, including Monarc System (Edwards Lifesciences, discontinued), Carillion Mitral Contour System (Cardiac Dimensions, CE mark granted in January 2009), PTMA (Viacor, first-in-man in June 2005)
- Edge-to-edge (Alfieri technique), including Mitraclip (developed by Evalve, acquired by Abbott in 2009, CE-mark granted in April 2008), Mobius (Edwards Lifesciences, discontinued)
- Annuloplasty through annulus plication, including MPAS (MitrAlign, FIM February 2008), Accucinch (GDS, FIM September 2009), Kardium Cinch (Kardium, in Feasibility Phase)
- Annuloplasty through RF annulus shrinkage, including QuantumCor (QuantumCor, in Preclinical phase), ReCor (Recor Medical, in Feasibility Phase)
- Cordal replacement, including DS 1000 (Neochord, in Pre-Clinicals), Mobius II (Edwards Lifesciences, clinical

evaluation stopped), V-Chordal Adjustable System (Valtech Cardio, in early clinical evaluation)

Despite more than 2,000 patients treated to date with any of the abovementioned devices, it appears unlikely that transcatheter MV repair will progress into daily clinical practice. Although surgery repair is generally the recommended treatment for MV disease, it is debatable that transcatheter MV repair may achieve similar results. This is due to a significant percentage of procedural failure and complications, frequent inadequate acute correction, and poor long-term efficacy, affected by a high rate of recurrent MV regurgitation. It can be argued that transcatheter MV repair did not produce expected results because it was erroneously considered the replica of surgical repair. Alas, transcatheter MV repair is not as effective as surgery. Each of the above listed therapeutic systems addresses only one specific aspect of MV dysfunction, whereas a cardiac surgeon has a large and diversified toolbox (different surgical techniques and implantable devices) for surgical MV repair.

Transcatheter MV replacement

The acknowledgement of transcatheter MV repair limits rekindled interest in transcatheter MV replacement, especially for the treatment of functional MV regurgitation. Start-up companies are in the process of developing transcatheter MV replacement products, like Endo Valve (a University of Pennsylvania spin-off acquired by Micro Interventional Devices in April 2011) and CardiAQ (based in Irvine, California, closed a series A funding round in January 2010, in early stage of

technical development). Also, there are rumors about direct involvement of worldwide cardiovascular leading companies, such as Medtronic and Edwards Lifesciences, in this area as well. New upcoming players include Valtech Cardio (founded in 2006 in Israel) with CardioValve, and Neovasc (Vancouver, Canada) with Tiara.

The renewed interest in transcatheter MV replacement should not be reason to underestimate the demanding technical hurdles related to this approach. Given the MV anatomical and pathological peculiarities, it would be strategically wrong to consider the successful concepts of TAVP suitable for MV application. Innovative solutions are required to properly address prosthesis anchoring and sealing in mitral position, as well as to mitigate the risk of SAM, i.e. the interference of native MV with systolic aortic flow. Furthermore, transcatheter technology has an intrinsic drawback when applied to diseased MV: the expansion of a prosthetic frame (applying a radial force outward) within a MV annulus subject to dilated progressive degeneration is a substantial contradiction in terminis.

Original and innovative solutions, far superior to aortic valve application, are firmly needed for transcatheter MV technologies. However, as with any challenge the human mind has had to face, the future holds fascinating and unexpected answers.

**D-Target is a medical device-focused clinical research organisation. It is an independent division of international CRO Premier Research.*

Join the discussion with

Clinica

Medtech Intelligence

NEWS, ANALYSIS & INSIGHT

Did you know that **Clinica Medtech Intelligence** is the major hub for discussion & interaction for medtech professionals through our **LinkedIn** group, while our **Twitter** account and **Email Bulletin** offer regular updates of the latest medtech developments?

Join us on LinkedIn: To join us simply search for **Clinica Medtech Intelligence** on the LinkedIn homepage

Follow us: Visit www.twitter.com/ClinicaMedTech for regular updates of the latest medtech developments

Clinica Bulletin: Register for free at www.clinica.co.uk/clinicabulletin

informa
business information