

## Historical perspective: 10<sup>th</sup> year anniversary of TAVI

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If the development of transcatheter aortic valve implantation (TAVI) for the treatment of calcific aortic stenosis (AS) can be considered a “success story” today, it is nothing short of a miracle as the project appeared totally unrealistic in the early 1990s. Over the course of the history of medicine we have repeatedly seen disruptive innovations that at first look unfeasible and unacceptable. It is quite thrilling, therefore, to observe the current expansion of this technology worldwide only 10 years after the first-in-man (FIM) TAVI procedure performed in Rouen on April 16<sup>th</sup>, 2002, an event that was wonderfully celebrated on May 13<sup>th</sup> 2012 in the presence of more than 500 colleagues coming to Rouen from throughout the world.

When we think again about that first TAVI case, a 57-year-old man, it is fascinating to recognise that the patient would probably have been turned down for a TAVI today. He presented in cardiogenic shock with major left ventricular dysfunction (the ejection fraction was 12%) and multiple comorbidities contraindicating AVR. Aorto-femoral bypass occlusion and severe contralateral atherosclerosis prevented the use of the transfemoral retrograde access. He also had an intraventricular floating thrombus. TAVI was performed using the antegrade transseptal approach. This unplanned approach added stress to the procedure which however was completed in a straightforward manner, without complication. Haemodynamic and echocardiographic results were improved incredibly and valve function was excellent on transoesophageal echocardiography. As expected from our post-mortem observation of 1993, there was no impairment of the coronary ostia or the mitral valve, no atrioventricular block and only mild paravalvular aortic regurgitation. This first case confirmed the feasibility of TAVI in a human using transcatheter techniques, and the international reaction to this spectacular case defied imagination.

The development of TAVI, which was specifically addressed by us to overcome the issue of early balloon aortic valvuloplasty restenosis, has been a 20-year odyssey. In 1993, we validated on post-mortem studies the concept of intravalvular stenting in calcific AS. The first prototypes of balloon-expandable valves were developed by a start-up company, “Percutaneous Valve Technologies” (PVT), and tested in an animal model in 2000. The device consisted of a tri-leaflet bovine pericardial valve mounted in a single size (23 mm) stainless steel balloon-expandable stent. The same device was used for the FIM TAVI case and, thereafter, with slight structural changes in two prospective series: first in our centre, and then in the USA and Italy, using only the transseptal approach. In these patients, the initial prognosis was compromised by the gravity of the comorbidities and extremely short-term life expectancies. It is thus stupefying to have observed a prolongation of life for several years in some of these patients – up to four, five or even six and a half years – all patients remaining in good clinical condition.

TAVI entered a new era in 2004 with the acquisition of PVT by Edwards Lifesciences (Irvine, CA, USA). Rapid improvements were made to the valve prosthesis and delivery systems and new approaches were developed. The development of the Edwards SAPIEN valve, a modified model of the Cribier-Edwards valve with two sizes, 23 mm and 26 mm, and the transition from the transseptal approach to the retrograde transfemoral approach were critical to the advancement of the procedure. The delivery system incorporated a deflectable Retroflex catheter for the transfemoral retrograde approach, initially evaluated by Webb et al in Vancouver. Simultaneously, the minimally invasive transapical approach was developed using another delivery system (Ascendra), evaluated by Walther et al in Leipzig. These spectacular advances allowed for considerable expansion of TAVI in terms of patients treated and procedural success.

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In 2004, an alternative device, the CoreValve (Medtronic, Minneapolis, MN, USA), a porcine pericardial valve mounted in a self-expanding nitinol stent, was launched and its use spread rapidly in Europe. With the two devices, thousands of high-surgical-risk patients were enrolled in feasibility studies, leading to the CE mark in 2007 for both devices. Thereafter, acceptance and expansion of TAVI was amazing. In line with the statements by the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), several hundred high-risk patients were included in post-marketing registries conducted with the two models of valves, and using the different approaches, including the European SOURCE registry (1,032 patients, 38 centres) with the Edwards SAPIEN valve. These registries contributed to better appraisal of patient screening, improvements in technical modalities and better prevention and management of complications. The immediate and long-term results kept improving with experience and advancing technologies; the procedural success rate progressively reached >95%. Excellent haemodynamic results, comparing favourably with the results of surgical AVR, lasting functional improvement and improved survival were consistently observed. Complications were also shown to decrease with experience, reaching an acceptable level in this high-risk population, and were similar for both valve models with the exception of a more frequent incidence of conduction disturbances with the CoreValve. Overall, the results of TAVI became more predictable. A mortality rate of 6-10% at one month and a 1-year survival rate of 80% could be seen after transfemoral TAVI in the SOURCE registry.

The results of the pivotal PARTNER randomised study with the Edwards SAPIEN prosthesis, which was organised beginning in 2009 in 26 centres in the USA, and including 1,056 high-surgical-risk patients, were eagerly anticipated. At one and two years, the results confirmed that in non-operable patients TAVI is highly superior to standard therapy, markedly reducing the rate of all-cause mortality and repeat hospitalisation. This same study demonstrated that in high-surgical-risk patients, TAVI is not inferior to surgical AVR in terms of all-cause mortality. As a consequence of these results, TAVI was approved by the FDA in November 2011 for non-surgical candidates; approval for high-risk-patients is hopefully pending. Subsequent to FDA approval, about 400 centres should open for TAVI within a couple of years in the USA and active training has already been initiated in a number of existing ones. A CoreValve US pivotal trial is currently on-going in 40 institutions throughout the USA.

Innovations in valve and delivery systems are unceasing. Since 2010, the SAPIEN XT valve, which includes a cobalt chromium highly resistant frame, a new valve and leaflet design and an additional valve size (29 mm), has been available in Europe. This comes with new smaller size delivery systems (NovaFlex) which increases the rate of transfemoral access to 80% of patients, and an improved delivery system for the transapical approach. Several other advances are already in use or under evaluation, including a smaller valve size (20 mm) and other valve models by Edwards. The new

AcuTrack delivery system for CoreValve implantation and new valve sizes should also further improve the accuracy of valve placement while increasing the scope of patients treated. There is no doubt that these rapidly evolving technologies will markedly contribute to the expansion of TAVI in the near future.

To date, it is estimated that over 50,000 patients in more than 500 European centres have benefited from TAVI using the two models of prosthesis, and the technique continues to evolve, a fact which obviously supports the clear-cut clinical need for this technology. It has already been observed that lower-risk patients in Europe are receiving TAVI and that clinical outcomes are better. Extension of TAVI to intermediate-risk patients will be evaluated in European studies (the SURTAVI trial) as well as in the PARTNER 2 Trial in the USA. The extension of the indication to younger and low-risk patients, not to say to all AS patients, would certainly require further technical improvements and better prevention of severe complications, particularly vascular, haemorrhagic and cerebral complications, as well as conduction abnormalities and paravalvular leak. It would also require a greater knowledge of the long-term durability of valves and platform systems.

Reductions in sheath size and new approaches (transaortic) are expected to further decrease haemorrhagic and vascular complications, which occur in 2-30% of patients undergoing TAVI and have a negative impact on the short-term clinical follow-up. Neurological event rates, reported to range from 1.7-7% remain an issue. The cause of stroke is multifactorial but most periprocedural and post-procedural strokes may be of embolic origin, as shown by post-TAVI magnetic resonance imaging. Approaches to embolic prevention include porous membranes covering the carotid ostia and carotid filters, which deserve further investigation, and a search for optimal periprocedural and post-procedural antiplatelet strategies. Complete heart block is frequently reported after TAVI. It is apparent that the 9-36% rate of new pacemaker implantation with the CoreValve is much higher than the 3-12% rate reported with the Edwards device. Lower device implantation into the left ventricular outflow tract against the interventricular septum may increase the risk of heart block. Better positioning with improved delivery systems might decrease the incidence of this complication. Moderate to severe (>grade 2) paravalvular aortic regurgitation is observed in <10% of cases and is typically due to bulky calcification, technical sizing or positioning errors. Better determination of aortic valve anatomy and calcification, optimal valve size and positioning using advanced imaging techniques, as well as new upcoming prosthesis design, might decrease the rate of paravalvular aortic insufficiency in the near future.

Importantly, it is unknown whether the favourable midterm durability of the currently used devices will be confirmed in the long term. Although clinical follow-up remains limited, structural device failure has only been reported anecdotally. Valve + platform durability has to be addressed in longer-term follow-up. Furthermore, whether TAVI will offer similarly good results in congenital bicuspid valves, which occur more frequently in younger patients, remains uncertain.

Other indications for TAVI have emerged recently, with the treatment of degenerated bioprostheses. The first results are highly encouraging, but formal evaluation of valve-in-valve therapy is planned in the upcoming SAPIEN XT PARTNER 2 and CoreValve REDO studies.

Finally, a number of next-generation devices are in early clinical evaluation. The aims are to reduce delivery catheter profile, facilitate accurate positioning, reduce paravalvular leaks and allow for retrieval. Although these new devices might represent the future of TAVI, minimal information is available to date on efficacy, procedural outcomes and durability.

One can proudly observe the excellence and unequalled partnership generated by TAVI. Cardiologists, cardiac surgeons, anaesthesiologists, imaging specialists, geriatricians, nurses and technicians have learned to work together towards a unique goal: making TAVI possible while being safe and successful with optimal patient

outcome. An optimal multidisciplinary collaboration for patient screening and procedures as well as formally trained and experienced physicians are the keys to success. Each indication for TAVI is a matter of good clinical sense and it should be reserved to patients in whom a good outcome is likely.

Within five years, an extension of indications to lower-risk patients can be expected, as well as an explosion of centres and investigators worldwide. Simplified and safer techniques will soon be available, with rapid and consistent technological improvement. Although work still needs to be done to improve techniques and outcomes further, the future of TAVI looks bright. Even though surgical aortic valve replacement remains today the gold standard for a majority of patients, there is no doubt that TAVI will be able to offer to an ever increasing number of patients an alternative way of improving outcomes and quality of life.