CLINICAL RESEARCH

Development of transcatheter aortic valve implantation (TAVI): A 20-year odyssey

Implantation de valves aortiques par voie percutanée : une odyssée de 20 ans

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Summary The development of transcatheter aortic valve implantation (TAVI) by our group has been a 20-year odyssey. In 1993, postmortem studies validated the concept of intravalvular stenting in calcific aortic stenosis. The first prototypes of balloon-expandable valves were tested in an animal model in 2000. The first-in-man implantation was performed in Rouen in 2002, rapidly followed by two prospective series in compassionate cases in our centre. TAVI took flight in 2004 in the hands of Edwards Lifesciences, with major improvements in devices and approaches. At the same time, the self-expanding CoreValve was launched. Thousands of high-surgical-risk patients were enrolled in feasibility studies, leading to the Conformité Européenne (CE) mark being granted in 2007 for the two devices. A number of postmarketing registries have shown dramatic improvements in procedural and midterm results and decreased complication rates, with more experience and improved technology. The results of the randomized PARTNER study in the USA recently confirmed the important place of TAVI in non-operable and high-surgical-risk patients. To date, more than 50,000 patients have benefited from TAVI worldwide (2300 patients in 33 centres in France in 2011) and the number is consistently increasing. An optimal multidisciplinary collaboration and formally trained experienced physicians are the keys to success. An extension of indications to lower-risk patients might be expected in the coming years but should be cautiously investigated. Ten years after the first-in-man case, TAVI is here to stay and the future is promising.

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Abbreviations: AS, Aortic stenosis; AVR, Aortic valve replacement; BAV, Balloon aortic valvuloplasty; TAVI, Transcatheter aortic valve implantation; THV, Transcatheter heart valve.
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Background

If the development of transcatheter aortic valve implantation (TAVI) by our group in France can be considered a “success story” today, it is nothing short of a miracle, as the project appeared particularly challenging—not to say totally unrealistic—at its origin in the early 1990s. It is quite thrilling, therefore, to observe the current acceptance and expansion of this technology worldwide, 10 years after the "heroic" first-in-man TAVI procedure performed in Rouen on April 16th, 2002.

We report here the main phases of this 20-year odyssey and briefly consider future prospects, as TAVI remains in a process of continuous development.

Birth of a concept

The starting point of this adventure took place at the end of the 1980s, with the evidence of the limitations of balloon aortic valvuloplasty (BAV), a technique that we had pioneered since 1985 [1] for the treatment of non-operable calcific aortic stenosis (AS). The goal of BAV was to provide a therapeutic option for patients considered at that time to be inoperable, often because age more than 75 years per se was a customary contraindication to aortic valve replacement (AVR) in the 1980s. BAV was associated with midterm improvement in quality of life [2], explaining its rapid adoption and explosive growth worldwide. However, the lack of survival benefit and a recurrence rate of 80% at 1 year [3,4] led to a dramatic decline in its use.

For us, addressing the issue of post-BAV valvular restenosis soon became an obsession. The idea of placing within the diseased valve a large-size stent containing a mounted prosthesis (stented valve) was rapidly considered an optimal potential option.

Actually, the concept of transcatheter heart valve implantation was not new. In the 1970s, several projects aimed at treating aortic regurgitation [5–7] remained experimental. In 1989, Henning-Rud Andersen first implanted an original model of a balloon-expandable catheter-mounted stented valve within the aorta of pigs, using a handmade mesh containing a porcine valve. The results, published in 1992 [8], were not followed by human application. Other experimental concepts emerged thereafter [9–11]. In 2000, Philip Bonhoeffer developed a stented valve made of a bovine jugular vein conduit inserted in a platinum-iridium stent, which was implanted in the pulmonary artery of lambs [12]. Bonhoeffer performed the first human implantation of this device in a right ventricle to pulmonary artery conduit in 2000 [13], followed by intense development of the technology in this indication. Simultaneously, we specifically addressed degenerative AS, a highly challenging indication, regarding the specificity of the calcific aortic valve and surrounding structures.

First observations, enthusiasm and frustration

In 1993 to 1994, we demonstrated in 12 fresh specimens of calcific AS that a Palmaz stent, 23 mm in diameter, could circularly open each native valve, regardless of the amount of calcification. The ideal height of the stent appeared to be 14 to 16 mm to avoid impinging on the coronary ostia, the intraventricular septum or the anterior mitral valve leaflet, thus duplicating the subcoronary position of any surgical bioprosthesis. The stents were well anchored within the aortic annulus, requiring a high traction force to be dislodged, thus
limiting the risk of embolization. This study, which validated the concept of aortic valvular stenting in a model of human calcific AS, was a fundamental milestone. However, at that time, the type of valve prosthesis and its physical properties were still at the drawing stage.

Over a 4-year period, the search for a biomedical company that was interested in the project failed completely. A long list of engineering issues and potential complications was consistently pointed out, including coronary obstruction, aortic and mitral valve complication, early dislodgement of the device, stroke, mechanical complications, etc. The project was even considered "the most stupid ever heard"!

Percutaneous valve technologies: the end of the tunnel

To accomplish this venture, a start-up company, "Percutaneous Valve Technologies" (PVT, NJ, USA) was finally formed in 1999. Engineers from Israel were able to design the first models of balloon-expandable transcatheter heart valve (THV), which consisted of a stainless steel stent integrating a tri-leaflet polyurethane valve. Considerable laboratory work was done before obtaining the first frozen THV model.

Animal trials: first promising results

With the help of my collaborator Helene Eltchaninoff, animal experiments on the sheep model started in September 2000 at the Centre d’experimentation et de recherche appliquée (CERA; Institute Montsouris, Paris). Through the brachiocephalic trunk, the first successful implantation of a THV within the native aortic valve was achieved, with excellent results and no complications. After this case, we had the inkling that it was the start of an important story. The presentation of this case at various meetings aroused memorable and encouraging enthusiasm from the medical community! More than 100 implantations at different cardiac sites were subsequently performed by us. Soon, with experience, we switched to bovine pericardium for the valve prosthesis. We learned a lot from this experiment, with case after case contributing to substantial improvements in the THV and in the delivery systems and implantation techniques. We also conceived an original model for the chronic evaluation of the THV in the systemic circulation [14], which demonstrated the persistence of excellent valve function and the integrity of the THV on pathological examination at 5 months.

First-in-human implantation

April 16th, 2002 — the date of the first-in-human implantation [15] — will remain a memorable day. A 57-year-old patient with severe AS presented in cardiogenic shock with major left ventricular dysfunction (the ejection fraction was 12%) and multiple comorbidities contraindicating AVR. After failed emergent BAV, TAVI appeared to be the last-resort option for this young patient. The indication was particularly challenging in this critically ill patient who also had subacute leg ischaemia related to an aortofemoral bypass occlusion and severe contralateral atherosclerosis preventing the use of the transfemoral retrograde access. All information concerning this never-used therapeutic option was given to the patient’s relatives and the patient himself, all of whom gave their consent with no hesitation. The procedure was performed the following day with my collaborators Helene Eltchaninoff and Christophe Tron, using the antegrade transseptal approach. This unplanned approach added stress to the procedure, although we had experience of using it in a few BAV cases with no arterial access. Actually, each step of the procedure was amazingly straightforward. Stabilizing the THV across the native valve was quite challenging, but after some time, we succeeded and rapidly deployed it. Haemodynamic and echocardiographic results were incredibly improved, with no transvalvular gradient and a return of blood pressure to normal, allowing discontinuation of vasopressors. There was no impairment of the coronary ostia or the mitral valve, no atrioventricular block and only mild paravalvular aortic regurgitation. On transoesophageal echocardiography, valve function was excellent. No words can express the emotion felt by the whole team. We were witnessing a true resurrection. Despite an episode of pulmonary embolism, the patient continued his clinical recovery. Unfortunately, the perfusion of his leg continued to worsen and after an above-knee amputation that never healed properly, the patient passed away 4 months after TAVI.

This first case confirmed the feasibility of implanting a THV in a human on the beating heart using transcatheter techniques, with perfect subcoronary position and no interference with the surrounding structures, thus translating our postmortem observation of 1993.

The international reaction to this spectacular case defied imagination. The deafening silence during the video presentation of this case in meetings was testament to the degree of emotion and stupefaction of the medical community. Clearly, this first-in-man case can be considered a breakthrough in the history of interventional cardiology.

First Rouen series

After three additional cases we obtained permission from the French Administration to start a feasibility trial at our centre. The programme was approved, but restricted to compassionate use. We recruited 16 patients into a first study (I-REVIVE trial), where the THV, further modified by the use of an equine pericardial valve, was implanted using either an antegrade or a retrograde (n = 7) approach [16]; 20 additional patients were recruited into a second series (RECAST trial), where the access was antegrade in all patients [17]. Each case was special and each implantation was incredible. These studies confirmed the feasibility of TAVI (80% procedural success) and the lasting haemodynamic and functional improvement after implantation. As expected, several of these critically ill patients died of their comorbidities within weeks or months but, amazingly, some survived beyond 2 to 5 years and even as long as 6.5 years in our most striking case, without any prosthesis dysfunction.
The incidence of 25% moderate-to-severe paravalvular aortic regurgitation was related to the unique 23-mm THV size available. The extension of the protocol to other centres in Europe and the USA clearly demonstrated the limitation of this unusual transseptal route in less experienced hands. Further expansion of TAVI clearly required technical improvements, simplification of the procedure, alternative approaches and a larger valve size.

Edwards Lifesciences: transcatheter aortic valve implantation (TAVI) takes flight

With the acquisition of PVT by Edwards Lifesciences (Irvine, CA, USA) in January 2004, TAVI entered a new era. Rapid improvements were made to the valve prosthesis and delivery systems and new approaches were developed for THV implantation.

The Edwards SAPIEN valve (initially the Cribier-Edwards valve) consisted of a tri-leaflet bovine pericardium valve, pretreated to decrease calcification, mounted in a balloon-expandable stainless steel stent. The prosthesis became available in two sizes: 23 and 26 mm. The delivery system incorporated a deflectable RetroFlex catheter, brilliantly conceived for the transfermal retrograde approach and initially evaluated by Webb et al. in Vancouver [18]. Simultaneously, the minimally invasive transapical approach was developed using another delivery system (Ascendra), evaluated by Walther et al. in Leipzig [19]. Unfortunately, French investigators could only access these technologies after 1 year of delay, in the setting of several European feasibility studies (REVIVE, PARTNER and TRAVERSE trials). The satisfactory results of these trials, despite specific complications with the two approaches, led to a growing acknowledgement and considerable expansion of TAVI worldwide.

Concurrently, another device had been progressing since 2004: the CoreValve [20] (now produced commercially by Medtronic, Irvine, CA, USA) had an autoexpandable nitinol stent containing a porcine pericardial valve, which allowed its transfemoral insertion through smaller sheaths sizes (21F then 18F) than the 22F and 24F sizes required for the Edwards devices—a major appealing feature for a number of teams. As an alternative to the transfemoral approach, the subclavian access was proposed with the CoreValve. The Conformité Européenne (CE) mark was obtained for both models of valve in 2007.

Setting up transcatheter aortic valve implantation (TAVI) in the therapeutic armamentarium for calcific aortic stenosis

Thereafter, acceptance and expansion of TAVI was amazing. In line with the statements by the European Association of Cardiothoracic Surgery (EACTS) and the European Society of Cardiology (ESC) [21], several hundred patients were included in postmarketing registries conducted with the two models of valves and using the different approaches, including the European SOURCE registry with the Edwards SAPIEN valve [22]. 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 more than 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 to 10% at 1 month and a 1-year survival rate of 80% could be quoted after transfemoral TAVI in the SOURCE registry [22].

The results of the pivotal PARTNER randomized study with the Edwards SAPIEN prosthesis, conducted from 2009 in 26 centres in USA and including 1056 high-surgical-risk patients, were eagerly expected [23,24]. Patients were divided into two cohorts: operable patients randomly assigned to TAVI (transfemoral or transapical) or AVR and non-operable patients randomly assigned to transfemoral TAVI or medical treatment. Briefly, 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 hospitalization at 1 year (with an absolute increase in survival of 20%), whereas in high-surgical-risk patients, TAVI is not inferior to surgical AVR in terms of all-cause mortality at 1 year. In view of these results, TAVI was approved by the FDA in November 2011 for non-surgical candidates; approval for high-risk-patients should hopefully occur soon. Subsequent to FDA approval, about 400 centres should open for TAVI within a couple of years in USA and active training has already been initiated in new centres.

Innovations in valve and delivery systems are ongoing. Since 2010, the new 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 delivery systems (the NovaFlex for the transfemoral approach is compatible with smaller sheath sizes [18F and 19F], 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 should also improve further the accuracy of valve placement. 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 50,000 patients in more than 500 European centres have benefited from TAVI with the two models of prosthesis and the technique continues to evolve. This obviously supports the clear-cut clinical need for this technology.

The situation in France

It is unfortunate that administrative constraints prevented France, which had been pioneering TAVI, from participating
in the development of the technology, with each technological advance being first evaluated in Canada or Germany. This led to slow growth of the procedure in our country until 2010. Thanks to many colleagues and partners from the industry, reimbursement of TAVI was obtained from our national insurance (Sécurité Sociale) in January 2010, with the subsequent approval of 33 TAVI centres throughout the country. Subsequently, the number of TAVI procedures exploded in France, reaching nearly 2300 patients for the year 2011 — a number still more than twofold lower than in Germany. Nevertheless, among a number of national registries, the French experience, as reflected in the FRANCE [25] and FRANCE 2 registries, which included 3500 patients, offers the largest prospective and exhaustive overview of the state of the art in real life with the two models of valve. An increased number of TAVI centres in France is pending.

**Future prospects**

It has already been observed that lower-risk patients in Europe are receiving TAVI [25] and that clinical outcomes are better [26]. Extension of TAVI to intermediate-risk patients will be evaluated in European studies (the SURTAVI trial) as well as in the PARTNER 2 study in the USA. 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, and 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 to 30% of patients undergoing TAVI [27,28] and have a negative impact on the short-term clinical follow-up [22,29].

Neurological event rates, reported to range from 1.7 to 7% [22,25,30—32], remain an issue. The cause of stroke is multifactorial but most periprocedural and postprocedural strokes may be of embolic origin, as shown by post-TAVI magnetic resonance imaging: new cerebral lesions have been reported in 58 to 91% of patients undergoing TAVI [33], with no assessment of corresponding neurocognitive consequences. 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 postprocedural antiplatelet strategies.

Complete heart block is frequently reported after TAVI. It is apparent that the 9 to 36% rate of new pacemaker implantation with the CoreValve is much higher than the 3 to 12% rate reported with the Edwards device [25,34,35]. THVs implanted lower into the left ventricular outflow tract against the interventricular septum may increase the risk of heart block [30]. Better THV positioning with improved delivery systems might decrease the incidence of this complication.

Moderate to severe (> grade 2) paravalvular aortic regurgitation is infrequent, observed in less than 10% of cases and is typically due to bulky calcification, technical sizing or positioning errors [30,36]. Better determination of aortic valve anatomy and calcification, optimal valve size and positioning using advanced imaging techniques, as well as new prosthesis design, might decrease the rate of paravalvular aortic insufficiency in the future.

Importantly, it is unknown whether the favourable midterm durability of the currently used THV will be confirmed in the long term. Although clinical follow-up remains limited, structural THV failure has only been reported anecdotally. One report documents normal valve function 3 to 5 years after implantation of the SAPIEN precursor, the Cribier-Edwards valve [37], and the longest follow-up is 6.5 years in our series. Again, structural failure was not observed. The similar manufacturing of the Edwards THV and surgical bioprosthesis and the circumferential frame opening of the THV, avoiding inappropriate leaflet overlapping, are promising, but this has to be addressed in longer-term follow-up. Whether THV implantation 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 bioprosthesis. The first results are highly encouraging [38], 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 THVs are in early clinical evaluation. The aim was to incorporate features to reduce delivery catheter profile, facilitate accurate positioning, reduce paravalvular leaks and allow for retrieval, and they are generally self-expanding. Although these models of THV might represent the future of TAVI, minimal information is available to date on efficacy, procedural outcomes and durability.

**Conclusions**

The development of TAVI has been a 20-year odyssey from concept to real world, but it has been a fascinating adventure and the procedure is here to stay. TAVI already plays a major role in the management of patients with AS and can be considered the standard of care in non-operative patients, as well as a valuable alternative for patients at high surgical risk. An optimal multidisciplinary collaboration for patient screening and procedures and formally trained experienced physicians are the keys to success. Each indication for TAVI is a matter of clinical judgment and it should be reserved for the subset of patients in whom a good outcome is likely.

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, safe and successful with optimal patient outcome.

Within 5 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.
Disclosure of interest
Alain Cribier is a consultant for Edwards Lifesciences.

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