TRANSCATHETER AORTIC VALVE IMPLANTATION: FROM THE BIRTH OF A DREAM TO WORLDWIDE EXPANSION

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The year 2022 was very special for interventional cardiology as it marked the 20th anniversary of the first percutaneous transcatheter aortic valve implantation (TAVI) performed in Rouen (France) on April 16, 2002. The moving celebration of this anniversary in Rouen in May 2022 brought together hundreds of participants from all over the world, underlining the enormous interest in this breakthrough technique and the importance it has assumed in medical practice.

If it is recognized that innovation in medicine is a difficult task, attempting to innovate in a field exclusively reserved for cardiac surgery has made the adventure even more challenging. The road has been long and full of pitfalls, but the results have far exceeded expectations. If the innumerable obstacles could be finally overcome, it is thanks to the cohesion and constant support of our admirable team of interventional cardiologists in Rouen, headed by my collaborator Hélène Eltchaninoff, but also to a remarkable and rare partnership with our cardiac surgery team.

For the newer generation of interventional cardiologists, it is hard to imagine what it was like treating cardiovascular disease less than 50 years ago. For those of us who bore witness to that period and the development that followed, it was another world.

Degenerative calcific aortic stenosis (AS) is the most common acquired valve disease in developed countries. It is formidable because of its long and quiet evolution and its catastrophic prognosis as soon as the first symptoms appear, with mortality reaching around 80% within 3 years. It is typically a disease of the elderly and its prevalence increases with age, on the order of 7% per year beyond the age of 75 years, which is considerable, a prevalence practically equivalent to Alzheimer's disease. The number of patients affected is expected to double by 2050 as the population ages. For a long time, the only possible and life-saving treatment was surgical aortic valve replacement (AVR) by mechanical valves and then increasingly by bioprostheses. This surgery, which started in the 1960s, provides remarkable results in patients without risk factors, with low mortality, few complications, and the restoration of a normal lifespan for age. However, it is a complex open-heart operation, with sternotomy, extracorporeal circulation, prolonged hospitalization, and functional rehabilitation necessary for several weeks. For these reasons, until the 1990s, more than half of the patients were turned down for the operation because of

comorbidities as well as age (>70/75 years), which was in itself, at that time, considered a surgical contraindication. These inoperable patients were, in the short term, simply condemned. For example, at the University Hospital of Rouen in the 1980s, only 10% of patients operated o for AS were over 70 years old. This was the context – a glaring and unmet clinical need – that we faced in 1985. Thus, finding a less invasive alternative to cardiac surgery for these patients became our priority.

The first step: balloon aortic valvuloplasty

It is with this objective that balloon aortic valvuloplasty (BAV) was first developed in Rouen, modeled on the technique of dilation of congenital pulmonary stenosis of which the team had experience, while being aware of the limitation that valvular calcifications would create on the quality of the results. Dilating a calcified aortic valve with a balloon was at the time unanimously considered unthinkable, unrealistic, and dangerous. Nevertheless, the first case of BAV was performed in Rouen in September 1985 on a very symptomatic 72-year-old patient, who had been totally invalidated by multiple daily syncopal attacks and had been rejected several times for AVR because of her age and associated coronary insufficiency. The result of BAV, performed percutaneously *via* the femoral artery under local anesthesia, was spectacular. Despite a moderate decrease in the transvalvular pressure gradient, the symptoms disappeared, and she was able to immediately resume a normal life. Faced with this impressive result, several patients rejected for AVR were in turn treated with BAV in Rouen with a comparable effect on symptom improvement. The publication of the results of our first series in The Lancet in 1986[1] had a bombshell effect on the medical community. Clinicians perceived this technique to be an unexpected rescue solution for the many patients rejected for AVR. The enthusiasm was remarkable, with hundreds of cardiologists from all over the world coming to Rouen to learn the technique, on-site training provided by the team all over the world, and tens of thousands of patients dilated in the 5 years that followed. Enthusiasm then gradually waned due to numerous recurrences, especially after the publication in 1992 of European and American registries confirming an unacceptable rate of early valve restenosis – 80% at 1 year – and the lack of demonstrated effect on mortality. At the same time, cardiac surgeons were pushed to demonstrate their ability to operate on the oldest patients, octogenarians and nonagenarians without comorbidities, with very favorable results. The abandonment of BAV then became inexorable, apart from a few selective indications validated by the Food and Drug Administration (FDA) in the USA. As there is always something good to remember from a failure, we are happy to see that this technique still exists, that its practice is required before certification of TAVI centers, and that it is used daily all over the world as a procedure associated with TAVI, for valve predilatation, or post-dilation of prosthesis.

This failure did not bring us down. On the contrary, it pushed us to find a solution against valve restenosis. We focused on the concept of a percutaneous aortic valve, implantable by cardiac catheterization, under local anesthesia, as first announced at a seminar in Rouen in 1987 where we were already alarmed by the number of recurrences. The clinical need persisted despite surgical progress, because a third of symptomatic patients could still not be operated on, as shown by several surveys including the Euro Heart Survey conducted by Alec Vahanian and his team in 2003.[2]

The early stages of transcatheter aortic valve implantation development

The idea of non-surgical valve replacement had been around since the 1970s, with the goal being essentially to treat aortic insufficiency or non-cardiac diseases, but certainly not degenerative AS, which could only be entrusted to surgeons due to the peculiarities of the disease, including severe valve calcifications. Several models of artificial valves had been tested on animals without any clinical application. With the same objectives, a Danish cardiologist, Rud Andersen, carried out in 1991[3] an experimental study in pigs with implantation *via* the abdominal aorta of a valve model made of an artisanal stent including a porcine aortic valve, but this study also remained without clinical application. The idea we developed in Rouen was, on the contrary, focused solely on the treatment of AS, which appeared at the very least audacious and above all foolish.

We had observed that in BAV, balloons 23 or 26 mm in diameter could always be totally inflated, cylindrically, pushing the valve calcifications aside. It was then possible to imagine that a highly compressive-resistant balloon-expandable stent could keep the valve fully open, and the calcified native valve would allow solid anchoring of the prosthesis. A sutured valve structure inside the stent should be able to restore normal valve function.

Despite the opinion of all medical colleagues and especially surgeons who rejected the technique as absolutely impossible and dangerous, we were able to validate the concept of intravalvular stenting in AS by performing a landmark autopsy study without which we would not be where we are today. The study was conducted in 1994 on fresh specimens of patients who died of the disease. It demonstrated that, contrary to the predictions of all cardiac surgeons, a stent, 23 mm in diameter and 17 mm high (a Palmaz stent that had recently been launched to treat peripheral arteries), could be implanted within the valve calcifications, opening the valve orifice completely, without interfering with the surrounding structures, the coronary ostia, the mitral valve, the upper part of the intraventricular septum, and the seat of the His bundle. An equivalent confirmatory study was carried out later, in 2002, just before the first case, by Dr. Renu Virmani, a renowned American pathologist, who admits to having been stunned by the results. A traction force of 2 kg was required to extract the stent after implantation, which greatly limited the risk of secondary embolization of the prosthesis, an inevitable complication according to experts.

Balloon-expandable aortic prosthesis schemes and the retrograde femoral implantation technique were developed for a European patent. A prosthesis model was built manually: it had a 23 mm diameter, reduced to 8 mm after compression on an aortic dilation balloon, which made its insertion through many human femoral arteries conceivable, likely allowing the ability to implant the stented valve using a transfemoral retrograde approach (Figure 1.1).

Figure 1.1. The team during the first case.
From left to right: Christophe Tron, Hélène Eltchaninoff and Alain Cribier.

For over 5 years, we failed to convince biomedical manufacturers (including Edwards Lifesciences and Medtronic!) to develop a prototype. The project appearing absolutely unrealistic to all experts ("the most stupid project ever heard...").

Creation of percutaneous valve technologies and preclinical evaluation

It is in this context that we created a start-up in 1999: Percutaneous Valve Technologies (PVT, Fort Lee, NJ, USA) with two engineers from Johnson and Johnson (J&J), Stan Rabinovich and Stanton Rowe (who had previously participated in the creation of the Palmaz-Schatz coronary stent), and a renowned American cardiologist, Martin Leon, who was at that time the Medical Director of J&J. All three showed great interest in this project despite the limited hope, Martin Leon said, of carrying it out successfully. Luckily, a small biomedical company in Israel (ARAN R&D) was interested in the project. They not only secured the initial financing, but, above all, their engineers succeeded in creating prototypes corresponding to our indications in record time. They included an expanding 23 mm steel stent, containing a tricuspid valve initially made of polymer and then equine pericardium. The prototypes were tested extensively in the laboratory in Israel and regularly improved.

At the same time, a major preclinical study on the sheep model was carried out in Paris in 2000 at the Centre de Recherches Appliquées (CERA) of the Institut Mutualiste Montsouris. With my colleague Hélène Eltchaninoff, more than a hundred implantations were performed at various cardiac and vascular sites, an endeavor that made it possible to develop and refine, session after session, all the technical aspects of transcatheter valve implantation. The first preclinical case of orthotopic valve implantation presented at the international Transcatheter Cardiovascular Therapeutics (TCT) congress in the USA in 2000 opened the door to invaluable private investments that allowed the project to be carried out. An original protocol to evaluate the functioning of the valve prosthesis in the midterm in animals was created,[4] which confirmed the integrity of the valve function as well as the absence of anatomical and histological alterations of the valve after 5 months of functioning in the descending aorta. This information was essential for future hypothetical FDA approval. Nevertheless, the different anatomy and the absence of aortic valve calcification in animals did not in any way ensure the feasibility and safety of implantation in humans in the intra-aortic valve position. Therefore, the decision to switch to humans was particularly difficult to make.

The first case of transcatheter aortic valve implantation in humans: moving from dream to reality

The decision to perform the first human implantation was taken in Rouen on April 16, 2002, in a very particular context, as a last resort, on an unusually young 57-year-old patient with severe AS on a bicuspid aortic valve, referred from Lille for emergent BAV. This patient was dying: He was in cardiogenic shock with a left ventricular ejection fraction of 12%. Surgery had been rejected because of multiple comorbidities including past lung cancer, chronic pancreatitis, and severe arteritis with subacute leg ischemia by occlusion of aortoiliac bypasses. He also had a left intraventricular floating thrombus. BAV could

only be attempted transeptally in the absence of patent femoral arteries, an approach for which our very experienced center was frequently solicited. It had to be cut short due to repeated episodes of ventricular fibrillation and the patient was in cardiogenic shock again 24 hours later. TAVI then appeared as a single and unlikely rescue solution, with a small chance of success given the dramatic clinical situation and the need for a transeptal approach, making the procedure even more challenging.

With the full agreement of the patient and his relatives, the indication for a first TAVI was retained despite the low chance of success and the considerable risks. Performed 48 hours after BAV, under local anesthesia, without transesophageal echocardiography (TEE) guidance, and against all expectations, the procedure was carried out without complications, in just 2 hours. The disappearance of the transvalvular aortic pressure gradient was accompanied by an immediate clinical improvement, a real and unforgettable resuscitation on the table (Figures 1.1, 1.2). The emotion of the entire team was just incredible.

Two hours later, the patient was able to sit up in his bed and drink champagne with the team. One day later he was able to give multiple interviews to the press and TV channels. Unfortunately, 4 months later, he did not survive a leg amputation imposed by the progressive worsening of preprocedural leg ischemia. The publication of this case in

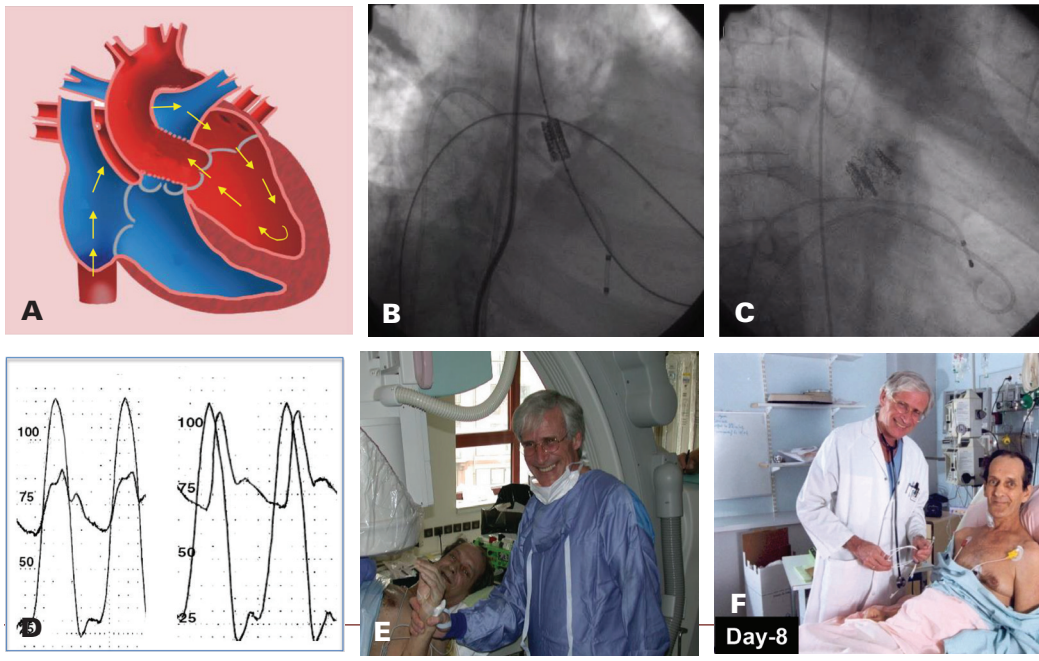

Figure 1.2. First case of TAVI: A) pathway for transeptal implantation; B) TAVI valve positioning before delivery; C) TAVI valve in place within the calcified native valve; D) hemodynamic result with elevated aortic pressure and disappearance of ventriculo-aortic pressure gradient; E) the patient after completion of the procedure; and F) the patient 8 days later.

Circulation[5] was a resounding success in the medical community.

The first series of transcatheter aortic valve implantation in Rouen, and the take-off of the technique beyond France

The first series of TAVI was conducted in Rouen a year later after long and difficult talks with the French High Authority of Health given the skepticism of the experts (cardiac surgeons). Drastic conditions were imposed. The technique had to be reserved for extreme situations, purely compassionate (estimated spontaneous survival of <2 weeks) and had to be attempted using the transseptal route as in the first case. Nevertheless, a series of 38 patients could be constituted, with 85% procedural success. The published results made headlines.[6, 7] This series confirmed the feasibility of TAVI, the reliability of the implantation, and the absence of most major complications announced, apart from paravalvular leaks due to the unique 23 mm prosthesis size available. Despite the early or midterm death of several patients from non-cardiac causes related to severe comorbidities, the dramatic clinical improvement of many other patients was observed with emotion, some of whom survived for several years without any symptoms and returned to normal life. For example, an 83-year-old patient in cardiogenic shock was implanted as a last resort at the request of her family, after cardiologists at a major Parisian hospital gave up all treatment and sent the patient home. She was able to travel to the USA 1 year later at the invitation of Martin Leon, to celebrate her first post-TAVI year and to talk about her TAVI experience at the 2004 TCT meeting. She lived normally for nearly 7 years without any prosthetic dysfunction. Another 85-year-old patient had to be implanted for the first time by the femoral retrograde percutaneous route (the direct route we had always considered) because of an associated mitral stenosis contraindicating the transeptal approach. This much simpler and faster procedure was followed by a total improvement for more than 5 years. This case made it possible to realize what the future of TAVI might look like. The publication of the results of this study was decisive for the acceptance of the procedure and the take-off of TAVI throughout the world with the first cases carried out in France, Europe, and the USA. In 2005, there were 100 global TAVI cases.

Acquisition of PVT by Edwards Lifesciences and technological and scientific advances: the explosion of transcatheter aortic valve implantation throughout the world

In 2004, the acquisition of PVT by Edwards Lifesciences (Irvine, CA, USA) accelerated the evolution of the technique with the creation of the Edward-SAPIEN valve (a modification of the Cribier-Edwards valve with an additional size of 26 mm, made essential by the frequency of paravalvular leaks) and new delivery systems allowing its implantation by the retrograde transfemoral route,[8] and a year later by the transapical route.[9] This last route required minimally invasive surgery on the beating heart through a small latero-thoracic incision under general anesthesia. With these two routes, all TAVI candidates could be treated: If the femoral artery proved too small for the caliber of the introducers, then the transapical route could be used as an alternative. The same year, a competing valve appeared, the self-expanding CoreValve, later acquired by Medtronic (Minneapolis, MN, USA).[10] The transfemoral route was still the first-line

approach, while a minimally invasive surgical subclavian route was offered as an alternative. It is indisputable that this competition between the two valve models has considerably accelerated the expansion of the technique.

Technological advances

Over the past 10 years, there have been constant – and still ongoing – technological advances with both valve models. They consisted mainly of the creation of additional valve sizes for optimal coverage of the aortic rings, and a reduction in the size of the arterial introducers, allowing for a considerable simplification of the implantation procedures, nearly all performed retrogradely from the femoral artery. Today, nearly 95% of TAVI are performed worldwide by using a so-called "minimalist" technique: a smaller team in the room, simple local anesthesia and sedation, no peri-procedural TEE, limitation of the arteriovenous pathways, and very short hospitalization with a return home in 2 or 3 days (perhaps even the same day in some centers). This implantation strategy was initiated by the Rouen team in 2012[11] with Edwards Lifesciences' second generation valve, the SAPIEN XT, despite the opposition of most centers, especially Anglo-Saxon, who insisted on general anesthesia and ETO to position the prosthesis. Currently, 94% of TAVI is performed in the USA *via* the femoral route, with the minimalist strategy used in 85% of cases. When necessary, other routes are used: transapical, subclavian, carotid, direct transaortic, and vena cava to aorta. The success rate of TAVI now exceeds 95%, and complications continue to decrease – in particular, perivalvular aortic insufficiency by adding an external skirt to the stent frame. Strokes occur in less than 2% of cases and can be the subject of preventive measures with brain protection catheters. Complete atrioventricular blocks have also significantly decreased to around 10%. In the past 20 years, many medical companies, stimulated by the success of TAVI, have created other valve models that have been the subject of preclinical investigation, and some have crossed the bar of human implantation. There are currently two other self-expandable models on the market in Europe from Boston Scientific (Marlborough, MA, USA) and Abbott (Abbott Park, IL, USA). The latest generation of these valves are promising and makes them attractive in many centers. Others from Asia (more particularly India) or South America are currently under clinical investigation.

Today, a patient with symptomatic AS can be treated in half an hour, under local anesthesia, and go home within 1-3 days without scarring and without the need for rehabilitation. The resumption of normal activities is almost immediate. There is no indication for anticoagulant treatment, contrary to what had been required for mechanical surgical prostheses, but only antiplatelet therapy. Follow-up is provided by consultation and ultrasound in the first month and then every year, and physical training is encouraged. The difference with AVR is striking and the enthusiasm of patients for TAVI can be easily understood.

Outstanding scientific evaluation: the key factor for the expansion of transcatheter aortic valve implantation

A scientific evaluation of TAVI was clearly needed to better understand the place of this procedure in relation to cardiac surgery. Few medical techniques have been the subject of such extensive and challenging scientific evaluations, starting from the most severely ill subgroups of patients, and then evolving, step by step, to subjects with lower surgical risk.

In 2007, both prostheses received the CE marking (European conformity), an event quickly followed by multiple European national and international registries (SOURCE Registry) on inoperable patients or those at very high surgical risk. These developments led to the first expansion of TAVI worldwide.[12-19] In this respect, the French registries – FRANCE, then FRANCE 2 and FRANCE TAVI – have been and remain among the most important and most documented.[17-19] However, the crucial step came from the pivotal randomized Placement of Aortic Transcatheter Valve Trial (PARTNER, Edwards Lifesciences) comparing TAVI with medical treatment (PARTNER IB) in inoperable patients and with AVR (PARTNER IA) in high-risk patients. The results of these large randomized studies published in *The New England Journal of Medicine* in 2010,[20, 21] marked a turning point in the history of TAVI. There was broad superiority over medical treatment in inoperable patients, as well as non-inferiority of TAVI compared with surgery in high-risk patients in terms of all-cause mortality and re-hospitalization at 1 year. This "evidence-based medicine" evaluation has allowed TAVI to travel a long way in 10 years from the first case in humans and to appear in European recommendations (2012) in the USA (2014) with level IA evidence in inoperable patients and level IIA evidence in patients at high surgical risk. The key role of a multidisciplinary discussion of each case (the heart team) for the selection of patients was therefore essential and profoundly marked the medical culture. The Medtronic CoreValve performed the same type of study with comparable results.[22]

The expansion of TAVI to lower-risk patients was expected. This change has benefited greatly from the growing experience of the teams, numerous technological and procedural improvements, and the essential support of the industry for patient selection and procedural safety. Over the past decade, several registries with propensity scores[23, 24] have shown the absence of inferiority of TAVI compared to surgery in subgroups of patients at surgical risk called "intermediate," with the risk being assessed by using different scores that consider many clinical parameters. The result of two major randomized studies – PARTNER 2 in 2016 with the SAPIEN XT valve (Edwards Lifesciences)[25] and SURTAVI in 2017 with CoreValve (Medtronic)[26] – confirmed these favorable results on mortality and stroke at 2 years in intermediate-risk patients. PARTNER 2 also demonstrated the superiority of TAVI in the case of transfemoral implantation based on these same criteria. Since 2017, the American and European recommendations have validated this indication (grade IIA) while lowering the recommendation level for high-risk patients to IA. These studies have led to a very significant growth in TAVI indications worldwide.

The essential step came from the publication in 2019 of the results of the new randomized studies PARTNER 3 (SAPIEN 3 valve) at 1 year[27] and Evolut Low-Risk (CoreValve Evolut) at 2 years[28] in low-risk patients (mean age 73 years, 10 years younger than in previous studies), a subgroup that constitutes 80% of surgical indications. The two studies targeting non-inferiority of TAVI were positive, and in PARTNER 3, TAVI was revealed to be superior to AVR on the main endpoints: death, stroke, re-hospitalization at 1 year (8.2% *vs.* 15.1%). At 1 year, mortality was 1% after TAVI against 2.9% after surgery. The lower stroke rate is particularly noticeable in these two studies (at 30 days: 0.6% *vs.* 2.4%). In the USA, the FDA shortly thereafter validated TAVI with the two models of valves in this indication for all patients over 65 years of age. This indication has also appeared in the European recommendations for patients over 75 years of age, while for an age between