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The development of transcatheter aortic valve replacement (TAVR)

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INTRODUCTION

The development of transcatheter aortic valve replacement (TAVR) can certainly be considered one of the most fascinating examples of successful translational research in medicine. Thanks to an outstanding partnership between multidisciplinary clinicians and engineers, we could move from concept to bench, bench to bedside, bedside to clinical feasibility trials, then on to larger clinical registries and evidence based trials, leading ultimately to a breakthrough technology with durable impact on the pattern of medical practice.

This disruptive technology evoked scepticism and criticism in the beginning, but thanks to innumerable clinical trials and evidence based investigations, it is now widely accepted by the medical community and its acceptance is continuing to grow. In the last fourteen years, TAVR has been performed in around 300,000 patients in 65 countries and adoption is increasing by 40% year on year.

The field of TAVR is rapidly evolving, with major refinements in technology, procedural techniques, patient selection and biomedical engineering. With the development of better devices, new approaches and new implantation strategies, TAVI has become much simpler and safer. The indications were initially limited to elderly aortic stenosis patients with multiple co-morbidities. The same are now cautiously and appropriately growing to include a broader population of patients with lower surgical risk, degenerated surgical bioprosthesis, and even patients with other valvular diseases such as pure aortic or even mitral insufficiency. There are few examples of clinical fields in medicine that match the rapid and careful evolution of TAVI.

BACKGROUND

Calcific aortic stenosis (AS) is the most frequently acquired valvular heart disease in developed countries, and its prevalence increases with an ageing population.[1] The natural history of symptomatic aortic stenosis carries a poor prognosis[2] with a survival rate of 60% and 32% at one and five years respectively.[3] The only effective treatment for decades was surgical aortic valve replacement (SAVR) with remarkable results in ideal candidates, but which required invasive heart surgery with extracorporeal circulation. Operative mortality of SAVR is low, <5%[4] and alleviation of symptoms and a return to normal life expectancy are observed. However, the operative risks, including post-operative complications and mortality, significantly increase in very old patients and/or

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in the presence of associated cardiac or non-cardiac comorbidities.[5,6] These factors are considered one of the main reason for which at least one-third of patients with symptomatic AS are not referred for SAVR[7] (Fig. 1).

In the 1980s, age of over 75 years was considered a contraindication of SAVR, and this stimulated our group to develop a less invasive therapy, balloon aortic valvuloplasty (BAV), consisting of enlarging the calcified native valve with a balloon catheter using standard catheterization techniques.[8] This technology was adopted with enthusiasm by the medical community, as highlighted by the thousands of patients included in broad European and US registries and the 1,300 indexed articles dedicated to the procedure.

However, the enthusiasm progressively declined following the recognition of important limitations, headed by early valve restenosis. BAV appeared to provide only temporary relief of symptoms with a modest survival benefit[9,10], its role remaining controversial in US guidelines.[11] Interest in BAV resurged with the development of TAVR and its frequent integration in the procedure. BAV is also used today as a palliative option in patients with contra-indication to TAVR or SAVR, as a bridge to those procedures in severely depressed left ventricular function, or when urgent non-cardiac surgery is indicated. Even though age is no longer considered a surgical contraindication, large numbers of severe AS patients are not offered valve replacement in Europe or the United States.[12,13]

FROM BALLOON VALVULOPLASTY TO THE CONCEPT OF PERCUTANEOUS AORTIC VALVE

For those of us who had been pioneering BAV, addressing the issue of post-BAV valvular restenosis became an obsession in the early 1990s. Placing a balloon expandable stent frame containing a valvular structure (stented-valve) within the calcified native valve appeared a possible option (Fig. 2). The project had the advantage of requiring similar approaches and techniques to those used for BAV. Among several visions of endovascular valve implantation, with initial animal investigation performed by Davies,[14] H. R. Andersen's project was the most elaborated. In 1992 he developed and patented[15] a hand-made "stented valve" for the treatment of various cardiovascular diseases,

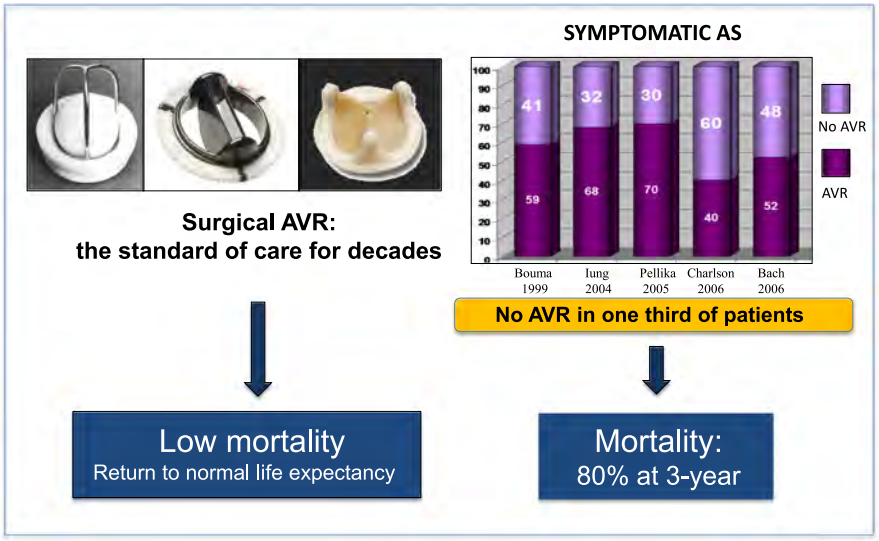


Figure 1. Rational for developing interventional technologies for severe AS: An Unmet Clinical Need

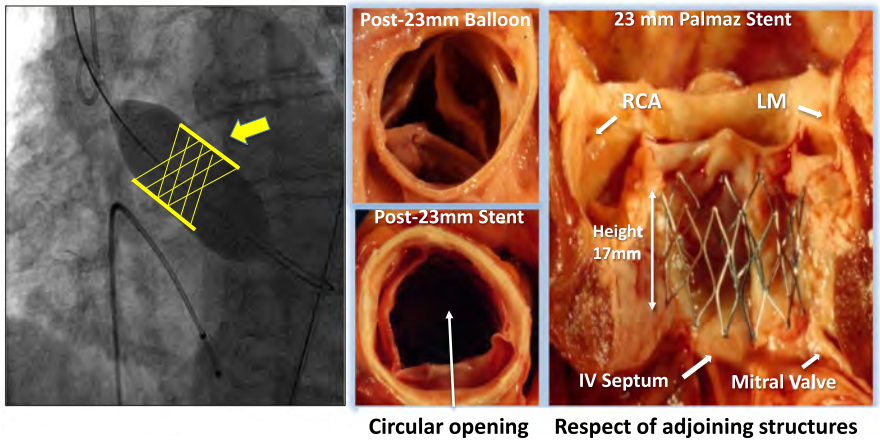


Figure 2. Birth of the idea of "stented-valve" in AS. *Left panel*: A stent crimped over a high-pressure valvuloplasty balloon might keep the valve open and prevent restenosis. A valve structure should be added within the stent. *Right panel*: Validation of the concept of intra-valvular stenting and optimal height of the frame to respect adjoining structures.

but the project remained at the experimental stage. In 2000, Bonhoeffer first used a stented-valve in a human, a bovine jugular vein in a metallic stent to treat degenerative ventriculo-pulmonary conduits in children.[16]

Our goal to implant a stented valve in calcific AS, on the beating heart, was very original but posed specific, difficult and at first sight insurmountable issues. These issues came from the calcified nature of the diseased native valve, and the immediate proximity of essential anatomical structures: coronary ostia, mitral valve, and interventricular septum (seat of the conduction system).

VALIDATION OF INTRA-AORTIC VALVE STENTING AND FEEDBACK OF EXPERTS

To validate the concept of intravalvular stenting in aortic stenosis, an autopsy study was conducted in Rouen in 1994 on 12 cases of calcific AS (Fig. 2). The study demonstrated that a balloon-expandable peripheral artery stent of 23 mm in diameter (Palmaz stent) was able to maintain a circular opening in all calcified aortic valves. The study also made it possible to establish the optimal dimensions of the stent height, avoiding any contact with the neighboring structures. Furthermore, the stent required a high traction force to be dislodged from the annulus, thus lowering the potential risk of device embolization.

This study was a fundamental milestone and validated the concept of aortic valvular stenting in a model of human calcific AS. At that stage, the type of valve prosthesis and its physical properties were still limited to drawings, however they were still used to file a European patent (Fig. 3).

Getting biomedical companies interested in this concept was a total failure with unanimously unfavorable opinions from all experts with regard to the design of the prosthesis, the potential risks of the procedure and the medical indication itself. Major clinical issues were constantly brought up: coronary occlusion, mitral valve injury, stroke, aortic regurgitation, prosthesis migration, permanent auriculo-ventricular block, bleeding, endocarditis, and non-lasting results. The project was looking like the "most stupid ever proposed".

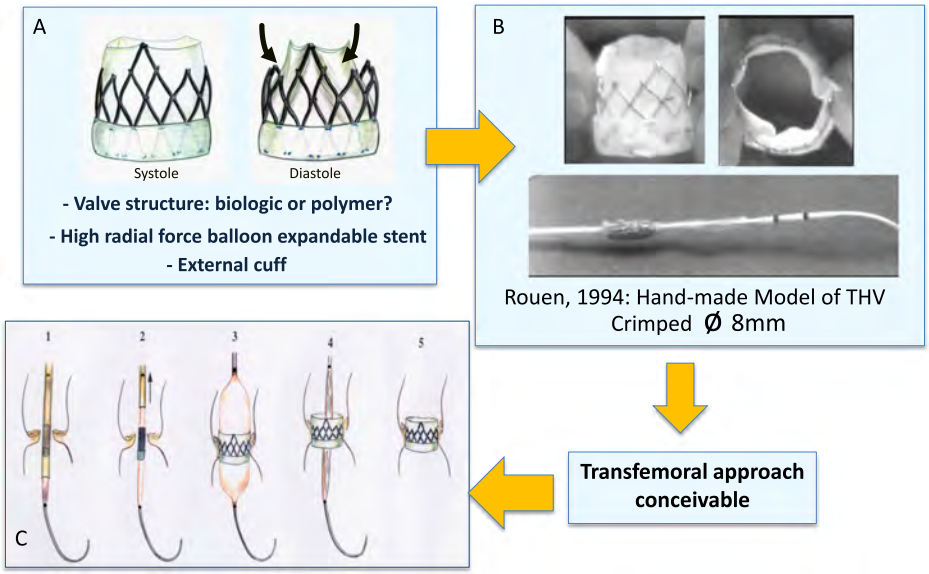


Figure 3. 1994: Drawings and model prefiguring a balloon expandable transcatheter bioprosthesis. A: specific stent frame design allowing to attach a tricuspid valvular structure. Partial external coverage would limit the risk of aortic regurgitation through the struts. B: Hand made model of stented-valve before and after crimping over a balloon catheter (external diameter: 8 mm). C: Drawing of the different phases of transcatheter aortic valve implantation.

FROM CONCEPT TO PROTOTYPES: PRE-CLINICAL EVALUATION

Creation of the start-up: Percutaneous Valve Technologies

To accomplish this venture, a start-up company, 'Percutaneous Valve Technologies' (PVT, NJ, USA) was finally formed in 1999 (Alain Cribier, MD, Martin Leon, MD, Stan Rabinovich and Stanton Rowe, PhDs). A development and first investment partner was found in Israel (ARAN, R&D, Ltd, Caesarea) a small biomedical company with great engineers which became our long-lasting partner in this venture. This was the start of a strong, durable and successful collaboration between engineers and clinicians. The translational pathway to TAVR, set by PVT and ARAN, would remain unchanged in the future for all companies working on the development of such a procedure (Fig. 4).

Preclinical engineering output: From concept to finalized prototype

Indications given to the engineers for the development of a transcatheter heart valve (THV) were particularly challenging. They had to integrate many innovative technologies: a balloon-expandable stent, a high-pressure balloon for stent expansion, a valvular structure and a delivery system. According to the "philosophy" of the THV, they had to create a prosthesis made of a highly resistant frame containing a valve structure, able to be homogeneously compressed to 7-9 mm over a high pressure balloon (trans-femoral artery insertion) and expanded to a diameter of 23 mm by balloon inflation, without damaging the frame and leaflets. Selection of the valve material, conceiving its attachment to the frame, and the valve design to provide sufficient strength, low profile and durability were other issues. The question of how to deliver the valve accurately, within the calcified valve, on the beating heart, would come later.

Many different valve configurations were investigated. Valve design was dependent on:

1. Frame material and design (profile, dimensions, skirt, crimping process and

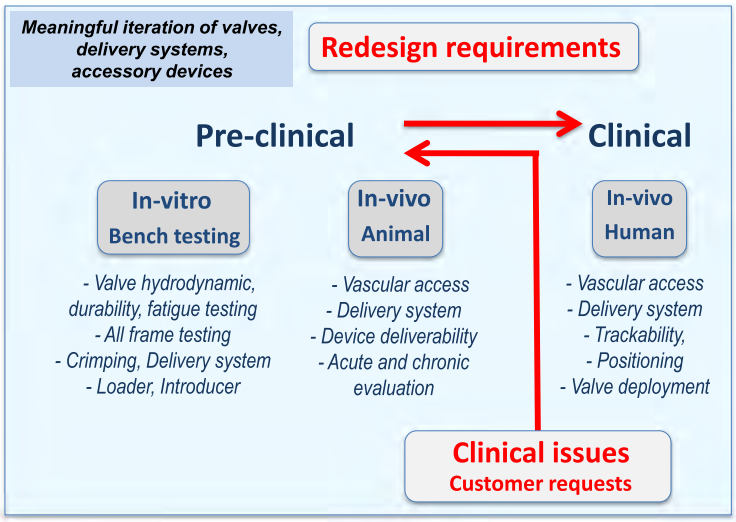
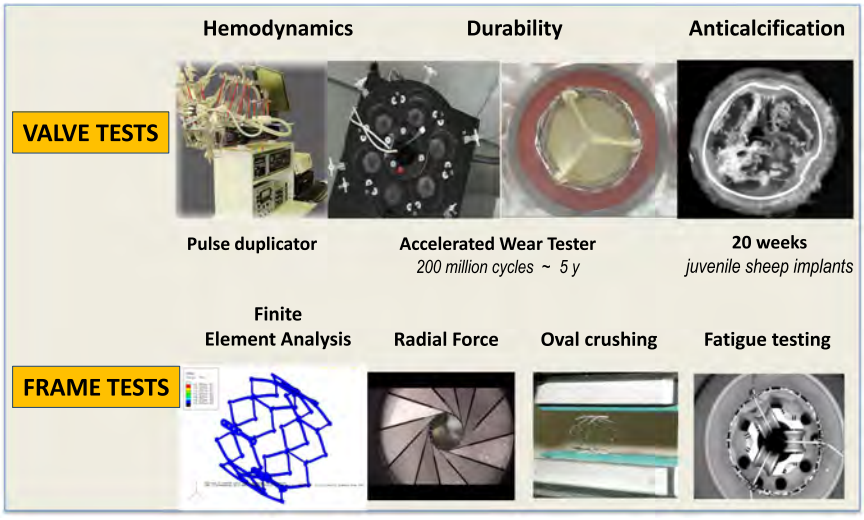


Figure 4. The translational pathway of transcatheter aortic valve replacement: driving for superior outcomes.

2. Leaflets design (material, attachments, cooptation, stress distribution, leak, hemodynamics, fatigue and durability, calcification).
3. Loading and delivery catheter system.

Each of these elements required specific work on design-geometry, material selection, manufacturing and processing. Geometry optimization used the Finite Element Analysis (FEA) method. The goal was to maintain the durability constraints while reducing the crimping profile. For laboratory testing (Fig. 5), the company had to design its own equipment for a new technology: crimping tools, pulse duplicators, accelerated wear and durability testers, various frame testers, hydrodynamic testers, and a leaflet calcification tester.

The first "finalized" device (Fig. 6) consisted of a stainless steel stent, 23 mm in diameter, 17 mm in height, containing a tri-leaflet valve initially made of polyurethane (later changed to a bovine pericardium valve), which had been proven for more than 25



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