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Transcatheter valves and interventional cardiology

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Transcatheter valve treatment: another innovation in interventional cardiology born in Europe which had to emigrate to get recognition

Europe has played a major role in the development of transcatheter valve treatment, spearheaded by the experimental work of H.R. Andersen in Denmark[1], the pioneering clinical applications in the pulmonary position by Philipp Bonhoeffer in the UK[2], and in the aortic position by Alan Cribier in France[3]. This year, the European Society of Cardiology Board has kindly followed the nomination of our Association and awarded Professor Cribier the most prestigious recognition in this field: the Gruentzig lecture, delivered in Stockholm to an overcrowded room and followed by a prolonged standing ovation. The first valve implanted in man, now commercialised in an improved and miniaturised version by Edwards Lifesciences, returned to Europe after John Webb, a Canadian, successfully demonstrated in a large series that the retrograde implantation is feasible[4] and a German cardiac surgeon, Fredrich Mohr, popularised the transapical approach[5]. Also, the second of the two transcatheter aortic valves in current clinical practice, the Medtronic CoreValve self-expanding valve, was designed by the French cardiac surgeon Jacques Seguin, and was tested clinically mainly in Europe, with Eberhard Grube and the group of Siegburg as the main proponents[6]. The same story repeated itself for the mitral valve: Alain Carpentier, gold medal of the European Society of Cardiology, has made reconstructive surgery with valvuloplasty and annuloplasty the standard for treatment of severe mitral insufficiency. Ottavio Alfieri from Italy has described a simplified method of valvuloplasty (edge-to-edge repair) suitable for percutaneous application[7]. The message is clear: in old Europe there are bright inventors and skilled clinicians but nobody is able to take advantage of these ideas and transform them into a viable product able to benefit patients. Listen to Cribier and Bonhoeffer when they recall their failures and frustration of many years dealing with the Industry and the regulators in Europe. Look at the millions of Euro's spent by the European Union, national governments and respected Charities on "scientific" projects that do not always have an impact on patients' lives and well-being...while biomedical technology and clinical research are completely neglected to the advantage of US, and probably soon, of Chinese and Indian companies.

From scepticism to enthusiasm

Yes, we confess, we were also somewhat sceptical at the start. We remembered the short-lasting results and frequent complications of aortic balloon valvuloplasty, introduced in the late 80s also by Alain Cribier[8-11]. We recalled the large degenerated nodules of the post-mortem valves which we studied with computed tomography to understand the mechanism of balloon valvuloplasty[12]. It is still hard to believe you can deploy a valve in a stable safe position using a balloon or relying on the sturdiness of the nitinol memory without breaking the annulus, without pushing the cusps against the coronary ostia (rarely a problem), without large perivalvular gaps. Yes, grade 2 aortic insufficiency is much more frequent[13] than after a prosthetic valve has been carefully sutured by a capable surgeon, but this normally requires us to open the chest and start extracorporeal circulation, with tightrope walking alternatives via minimally invasive or robotic surgery still unable to pick-up years after their introduction. It is a small miracle of modern technology that a 23-29 mm valve able to withstand the heavy prolonged tests of duration simulating millions of cardiac cycles can be squeezed around a catheter to the diameter of 6 mm without permanent damage. Both balloon expandable and self-expanding aortic valves consistently deliver excellent immediate results to the point that the haemodynamic measurement of transvalvular gradient after valve implantation has been abandoned in many active centres because it

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is consistently non-existent (but measurements of left ventricular end-diastolic pressure and diastolic aortic pressure are still helpful to grade aortic insufficiency). The valves have been around for too short a time to ensure they can match the results of biological surgical valves, but relatively large series of up to five years and more appear very reassuring. More than 12,000 aortic valves are expected to be implanted in Europe in 2010, still a small proportion of the more than 60,000 procedures of aortic valve replacements likely to be performed in Europe during this same period. The difference is much more pronounced for transcatheter mitral valve repair, with surgical procedures of mitral valve repair of around 1,300 percutaneous implantations of the only clinically approved devices (MitralClip, Evalve; Abbott Vascular, Redwood City, CA, USA) with a few more cinch devices in the coronary sinus still implanted under strict research protocols.

Cooperation and team work: the secret of a success beyond expectations

The development of factual cooperation among all the doctors involved was required by the general agreement that this practice requires the combination of surgical and interventional skills as well as expert interpretation of multimodality imaging – too much to be mastered by a single individual. This general acceptance and involvement boosted the clinical application of TAVI, avoiding the bitter controversies which still surrounds coronary angioplasty 33 years after its introduction. Surgeons have learned the mistake they made at the time dismissing this new technology with ironical comments and leaving it to cardiologists in the expectation coronary angioplasty was going to be a niche application. This "niche" has now become 3-6 times bigger than all the procedures of coronary bypass surgery, with emergency surgery required in far less than 1/1000 procedures[14]. Having learned from this experience, and having observed widespread acceptance of "keyhole" surgery and shrinkage of conventional surgery in many other fields, from thoracic to abdominal, cardiovascular surgeons were quick to jump into this possibility. They understand that they had to maintain an active role in procedures due to replace some of their surgical operations, but also with the potential to expand indications beyond the current boundaries of valve replacement and repair. They brought to the table the experience of their surgical/anaesthesiological teams in handling these patients, their connections with referring centres, their ability to secure alternative access routes in old patients with diffuse atherosclerotic disease. Their presence prevented potentially deadly nightmares via prompt interventions to repair the femoral and iliac arteries or, very rarely, via true surgical conversions. Besides the appreciation of this important cooperation, interventional cardiologists also learned lessons from the past. Controversies with surgeons have undermined the expansion of PCI indications and jeopardised the credibility of all forms of myocardial revascularisation in the medical community. Similar discrepancies over the role of an expensive new technology to be applied to high risk patients with 5-8% mortality in the most recent registries could have killed TAVI before birth. Learning to work together and to assist another specialist in key parts of the procedures might have been difficult for both cardiac surgeons and interventional cardiologists, but the experience has made them grow tremendously and have greatly benefited their patients. There are exceptions and centres where transcatheter valves are only implanted by surgeons or where surgeons are only offering standby in case of unexpected complications of purely percutaneous procedures only performed by cardiologists. At present, however, the European registries show that the recommendations of the ESC/EAPCI/EACTS Task Force of two years ago[15,16] are still closely followed and, in the vast majority of cases, both a surgeon and an interventional cardiologist are physically scrubbed for these procedures, still performed in most cases under general anaesthesia.

How far will the revolution go?

In the world of evidence based medicine it is easy to answer "as far as the evidence goes". I am old enough to have seen many approved devices and drugs seldom used, and many others with insufficient or even negative evidence from trials becoming standard of practice. Cost and complexity of use are two elements difficult to be caught in randomised trials conducted in highly selected high volume centres. The driving force of every innovation is the perception that the new technology offers a gain over existing techniques. In a way, the difference in clinical application of the MitralClip and the aortic valve is proof of this statement, and reflects the results of their key respective randomised trials. The results of the EVEREST 2 trial were released in March at the ACC in Atlanta 2010[17]. The trial showed non-inferiority of the Mitralclip to conventional surgical repair in reaching the combined efficacy endpoint of death, need of mitral surgery or presence of mitral regurgitation > grade 2 at 12 months. By trial design, all patients had to be surgical candidates. Mitral repair is a very effective operation, leading to excellent immediate results and long lasting reduction of mitral regurgitation with no need of implantation of a new prosthesis. The demonstration that there was a potential non-surgical alternative had a small impact in the slowly growing adoption of the MitralClip implantation. PARTNER has been the great shock of the TCT in Washington, with a 20% higher mortality at one year in the group of inoperable patients randomised to medical treatment vs. TAVI[18]. The advantage was so obvious, and the result so predictable, that the medical community did not wait for these results to move to a general adoption of the technique in patients inoperable or at very high risk for surgery.

New directions of research

TAVI has addressed from the start patients with an incredibly poor prognosis and limited alternatives. The remaining question is at which level of surgical risk it becomes beneficial over surgery, and this question will be addressed by the second randomised arm of PARTNER as well as by new trials due to start soon taking advantage of the more deliverable new transcatheter valves (SURTAVI). There are still potential technical improvements expected in the coming years, but with the two existing valves and the various established implantation routes (transfemoral, percutaneous or surgical, transubclavian or transaxillary, direct aortic and transapical) the vast majority of patients can already be treated, and sufficient experience has been developed in a large number of European centres.

The situation is completely different for the MitralClip. The pressing need here is to investigate its efficacy in the severe MR of patients with advanced heart failure. It occurs in up to 30% of these patients, is associated with worsening symptoms, a high hospitalisation rate, a much poorer prognosis under medical treatment and a prohibitive mortality with conventional surgery. In EVEREST II, functional MR was a small subgroup, but they appeared to benefit symptomatically as much as the patients with degenerative MR. With 55 centres in Europe actively practising this technique, but still many of them far from having acquired enough experience to achieve the maximal benefit at the minimal risk in these demanding frail patients, a large randomised trial will probably require time to start as well as years to be completed to finally reach the long term follow-up expected to detect a difference.

What to do while waiting for randomised trials? The importance of independent registries

Nothing can replace randomised trials, but decisions cannot wait the years required. A partial answer can be given by properly conducted registries enrolling consecutive patients and with sufficient information on clinical, echocardiographic and procedural data to establish the mortality and complication rate and identify the predictors of failure. Complete tracking of adverse events and uniformity of definition and adjudication is essential to demonstrate that the results of TAVI or transcatheter mitral repair are comparable with results expected with contemporary surgery and better than the results of medical therapy[19]. Numerous TAVI and MitralClip registries have been conducted, most of them fully sponsored by the valve or device manufacturers, an obvious problem for their credibility. These limitations were in part overcome by country-wide registries with promotion or involvement of national health authorities or scientific societies, but these registries still lack a European-wide approach to make results widely applicable. The recent presentations of six national TAVI registries with more than 3,000 patients included at the EuroPCR 2010, EAPCI's annual congress, illustrate well the strengths and weaknesses of these endeavours. Despite the best efforts, the absence of control and auditing, and the differences in definitions were responsible for large variations in the percentages of complications; from vascular access to cerebrovascular complications. Even an easily controllable endpoint such as the rate of PM implantation ranged from more than 43% to 18% with the same self-expanding valve system. The report of the ALKK German Registry in 900 patients has been published in the European Heart Journal because it represents one of the largest series reported; but no endpoint definitions are listed, clearly showing that these were left to the assessment of the individual investigators with no central monitoring or audit[20]. The European experience with the MitralClip (1,031 patients in 55 centres, end of August 2010) is also impressive and complementary to the trial results as it addresses more complex patients with mainly functional insufficiency, and includes patients excluded by the original EVEREST II criteria[21]. Still, the results are provided by industry, and the evaluation of success or complications entirely left to the goodwill of the investigators to report. See the "EuroObservational ESC Sentinel registry of transcatheter valve treatment".

The European Society of Cardiology has launched a sentinel registry of transcatheter valve implantation for 2011-12 adopting the new VARC definitions and following the stringent policy of the ESC to document conflicts of interests of the investigators. All the Interventional Cardiology, Imaging, Acute Cardiac Care, Cardiovascular Surgery Working groups and Associations have been involved in the development of the registry protocol and database. It will be up to the individual national societies and investigators to ensure the success of an initiative essential to ensure a good understanding of the advantages and risks of these new procedures. From this registry we will reliably know results and complications using the same definitions across Europe, with a CEC reviewing events. Its design, presented at the London Valve Course to the 840 delegates present in the main arena, takes advantage of national initiatives, with IT facilitating the work of busy interventionalists to transfer data avoiding double entry[22]. The ESC gave an enormous opportunity to interventional cardiology offering this independent registry to understand how the lessons from trials are applied in Europe, and to learn how new trials can take advantage of technical developments and increased centre experience. We should not miss this opportunity, blinded by local conflicts and petty jealousies. Transcatheter valves are associated with cooperation and teamwork, let's keep it this way also in our research.

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