CLINICAL RESEARCH

The development of transcatheter aortic valve replacement in the USA

Développement des valves aortiques percutanées aux États-Unis

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Summary The penetration rate of devices in general, and in transcatheter aortic valve replacement (TAVR) specifically, is significantly delayed in the United States of America (USA) compared with in Europe. This is mostly due to the mission statement of the regulatory agencies in the USA, which requires very rigorous clinical testing of a device prior to its approval. The USA had a major role in the development and evaluation of this technology and USA research has enabled clinicians inside and outside of the USA to conduct a concise scientifically based assessment of the performance of TAVR devices in terms of safety and efficacy. In the following review, we provide data on the development of TAVR in the USA, revealing the critical role the USA has played in this extraordinary process.

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Résumé La pénétration des dispositifs médicaux et des valves aortiques percutanées en particulier est retardée aux États-Unis comparé à l’Europe. Cela est essentiellement lié au processus réglementaires de régulation aux États-Unis qui requiert une évaluation clinique très rigoureuse avant approbation des dispositifs. Les États-Unis ont joué un rôle majeur dans le développement de cette technologie et l’évaluation scientifique a permis aux cliniciens à travers le monde d’obtenir une évaluation concise « basée sur les preuves » de la performance des valves percutanées en termes de sécurité et d’efficacité. Nous allons dans cette mise au point, décrire...

Abbreviations: AS, aortic stenosis; CE, conformité européenne; FDA, Food and Drug Administration; PAS, postapproval study; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; USA, United States of America.

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Background

It is now 10 years since the first human transcatheter aortic valve replacement (TAVR), a procedure performed in Rouen, France, in a patient with severe aortic stenosis (AS) [1]. Currently, a decade after this historic event, most TAVR procedures performed and the majority of innovations in the field of transcatheter valve technologies occur outside the United States of America (USA). Nevertheless, the USA played a major role in the development and evaluation of this technology (Fig. 1). It could be said that although TAVR was born in France, it matured in the USA. In the following review, we provide data on the development of TAVR in the USA, revealing the critical role the USA played in this extraordinary process.

The early days

In early 2004, almost 2 years after the first human TAVR procedure, when only a total of 17 patients had been treated by this technology, TAVR entered into the 'major league' of the industry with the purchase of a small privately held medical technology company, Percutaneous Valve Technologies, Inc. (PVT, Caesarea, Israel), by the American-born Edwards Lifesciences Corporation (Irvine, CA, USA). This transaction allowed Edwards to accelerate the development of this breakthrough technology while providing the needed expertise and resources to ensure successful commercialization (Fig. 2). Several months later, at the 2004 Transcatheter Cardiovascular Therapeutics (TCT) meeting held in Washington, DC, TAVR attracted major publicity as a widely discussed topic. One of the highlights was the live introduction of a patient 1-year post-TAVR.

Feasibility evaluation of the Edwards SAPIEN device

The USA Food and Drug Administration (FDA) had a major influence on the evaluation of TAVR devices. The FDA, an agency within the United States Department of Health and Human Services, is responsible for protecting and promoting public health through the regulation and supervision of numerous materials, including medical devices. The Center for Devices and Radiological Health is the branch of the FDA responsible for the premarket approval of all medical devices in the USA, as well as overseeing the manufacturing, performance and safety of these devices. In January 2005, the FDA conditionally approved the first feasibility trial of the Cribier-Edwards percutaneous aortic heart valve. Six months later, Edwards Lifesciences announced a delay in enrolment in its percutaneous aortic heart valve clinical feasibility trials in the USA using the antegrade transapical delivery, in order to incorporate the retrograde delivery system, which at that time had already been evaluated in several cases in Canada. The company took this action after some USA antegrade cases demonstrated a significant degree of clinical complexity and adverse outcomes. However, the 'loss' of the antegrade transapical approach was rapidly replaced that year by the antegrade transapical approach, performed using the Ascendra...
system. Later that year, the FDA approved the re-enrolment of 20 patients in a non-randomized feasibility trial of its Cribier-Edwards percutaneous aortic heart valve using the retrograde transfemoral approach. This pioneering trial took place at three clinical sites in the USA (William Beaumont Hospital, Royal Oak, MI; New York-Presbyterian/Columbia University Medical Center, New York, NY; and The Cleveland Clinic Foundation, Cleveland, OH). From January to May 2006, the three centres completed 20 cases. The FDA then approved the enrolment of an additional 35 patients.

The PARTNER (Placement of AoRTic traNscatheterER valves) trial

In March 2007, after submitting follow-up data from the original 55-patient feasibility study, Edwards Lifesciences received approval from the FDA to initiate a pivotal trial of its Edwards SAPIEN transcatheter aortic heart valve technology—the PARTNER trial (Placement of AoRTic traNscatheterER valves). This trial was a randomized controlled multicentre study that assigned patients into one of two arms: a 'non-surgical' arm (Cohort B), in which the Edwards SAPIEN valve was compared with medical therapy and balloon valvuloplasty at the operator’s discretion; and a 'surgical' arm (Cohort A), in which the device was compared with traditional surgical aortic valve replacement (SAVR). The trial began enrolment initially at two study sites that were part of the earlier transfemoral feasibility study. This rapidly expanded to another 15 study sites in the USA. One year later, Edwards Lifesciences received FDA approval to add the Ascendra transapical delivery system to the PARTNER trial and also received approval to increase the trial sample size from 600 to 1040 patients. During that period, positive experiences by the operators led to rapid enrolment. By March 2009, enrolment of patients in the non-surgical study arm was completed and by August 2009 enrolment in the operable arm was completed as well. Subsequently, Edwards Lifesciences has received FDA approval for non-randomized continued access to the Edwards SAPIEN valve for actively enrolling PARTNER sites.

One of the points of strength in the PARTNER trial methodology was the use of web-based conference calls, conducted by the executive committee, to further review and approve the selection of each patient before randomization. Every case was reviewed by executive committee members, including relevant imaging studies. A total of 3105 symptomatic severe AS patients were screened at the investigator sites for enrolment eligibility and 1094 were presented at those conference calls. A total of 145 cases (13.2%) were rejected during these presentations and 21 cases changed their cohort or access designation after review (1.8%). Overall, 34% of the total number of initially screened patients were ultimately randomized in the PARTNER trial (22% to the cohort A and 12% to cohort B). These presentations have added power to the study by enrolling a homogenous population, and the discussion during these meetings helped to disseminate knowledge and catheterization techniques between sites. It is now obvious that appropriate patient selection is one of the most difficult tasks in a TAVR programme and the presentation methodology used in the PARTNER trial allowed support for inexperienced sites to avoid beginners’ mistakes.

In September 2010, the results of PARTNER Cohort B were published [2]. This was a true milestone in the field of TAVR. For the first time, the cardiology community had solid scientific evidence based on a randomized trial showing the advantage of this technique in patients with severe AS who were not candidates for surgery. In 358 inoperable severe AS patients, TAVR, compared with standard therapy, significantly reduced the rates of death from any cause, the composite endpoint of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of major strokes and major vascular events. As a result, TAVR has become the new standard of care for patients with AS who are not suitable candidates for surgery.

Six months later, the results of PARTNER Cohort A were published [3]. That trial compared outcomes after treatment with either the Edwards SAPIEN valve or traditional open-heart surgery in high-risk operable patients. The study was a ‘non-inferiority’ trial designed to evaluate whether patient outcomes after TAVR with the Edwards SAPIEN valve are similar to surgical outcomes. The study achieved its primary endpoint at 1 year, concluding that survival of patients treated with the Edwards SAPIEN transcatheter aortic valve was equivalent to survival of those treated with SAVR. In patients with AS at high-risk for surgery, TAVR was non-inferior to SAVR for all-cause mortality at 1 year. In addition, mortality at 30 days was lower than expected in both arms of the trial. Even with this early-generation device and limited operator experience, the TAVR mortality rate was the lowest reported in any multiscience series of clinical data for the Edwards SAPIEN valve.

Food and Drug Administration (FDA) approval of the Edwards SAPIEN device

On 20 July 2011, the FDA Circulatory System Devices Panel reviewed the Edwards SAPIEN premarket approval application [4]. For the purpose of the application, only patients in the inoperable cohort (Cohort B), who were randomized
to standard therapy versus TAVR, were submitted and subsequently presented to the FDA for device approval. The FDA did not accept for evaluation any data from outside the USA. In their opinion, while various data had been accumulated from European registries, these data originated from non-randomized studies with endpoints that were less stringently monitored. An extensive discussion on the analysis and implications of neurological outcomes was undertaken due to the high stroke rates in the PARTNER trial. The Panel acknowledged that neurological adverse events had emerged as a major safety concern in the PARTNER trial, which was among the major concerns in approving the device.

The majority of Panel members agreed that the discussed device and procedure were effective in lowering mortality in the specific population studied. However, stroke rates among treated patients emerged as major issues, avoiding ‘indication drift’ in the device usage by tight postapproval monitoring. The Panel voted to recommend approval of the Edwards SAPIEN transcatheter heart valve for the treatment of certain inoperable patients based on data from the inoperable cohort of the PARTNER trial. The approved indication of use stated: ‘The Edwards SAPIEN transcatheter heart valve sizes 23 mm and 26 mm and RetroFlex 3 Delivery System are indicated for transfemoral delivery in patients with severe symptomatic native valve AS who have been determined by a cardiac surgeon to be inoperable for SAVR and in whom existing comorbidities would not preclude the expected benefit from correction of the AS’.

Two postapproval studies (PASs) were requested by the FDA, pending device approval, with the aim of assessing long-term safety and effectiveness, as well as adherence to indication of SAPIEN utilization. PAS-1 will continue clinical and echocardiographic follow-up on an annual basis and will monitor the incidence of clinical events for all previously enrolled patients in Cohort B of the PARTNER trial, as well as for the continuous access patients. PAS-2 will be an observational controlled prospective trial with a non-inferiority design and consecutive patient enrollment (n = 750) from a random sample (n = 75) of new sites previously selected by the Sponsor (n = 200). The proposed endpoints of this non-inferiority study will capture all neurological events, major vascular events, major bleeding, learning-curve assessment, valve durability to 5 years and quality of life measures to 5 years. In November 2011, Edwards Lifesciences received FDA approval for the Edwards SAPIEN device, which was the first USA commercial approval for a transcatheter device enabling TAVR. The criticism could be made that this FDA approval more than 4 years after the Conformité Européenne (CE) approval for European commercial sales of the Edwards SAPIEN transcatheter aortic heart valve technology (September 2007) was a result of the strict FDA regulations. Nevertheless, this method has created the PARTNER trial.

After approval of the Edwards SAPIEN device for commercial use, the American College of Cardiology and the Society of Thoracic Surgeons made a breakthrough decision to collaborate and initiated a postmarket Registry of all TAVR procedures performed in the USA. This will allow for continued outstanding scientific and regulatory data analysis, which will facilitate optimal utilization of TAVR in patients with AS. The FDA has mandated that all TAVR patients be enrolled in this Registry.

**The PARTNER (Placement of AoRTic traNscatheter valves) II trial**

During the last year, the FDA conditionally approved the first of two planned cohorts of the randomized controlled PARTNER II trial. The first cohort of the PARTNER II trial (Cohort B) will study the next-generation Edwards SAPIEN XT transcatheter heart valve. This trial includes the low-profile NovaFlex transfemoral delivery system, which broadens the number of eligible patients; the trial will study up to 450 patients. A second patient cohort (Cohort B) will compare traditional open-heart surgery with the Edwards SAPIEN XT valve delivered either transfemorally or transapically. This cohort is a non-inferiority study of up to 2000 patients with severe symptomatic AS who have an elevated risk for traditional open-heart surgery (Society of Thoracic Surgeons score > 4), which is a lower risk profile than that of those who were enrolled in the PARTNER trial. Patients will be evenly randomized to receive the Edwards SAPIEN XT valve or surgery. Those undergoing TAVR will be treated either transfemorally or transapically. The primary endpoint to be evaluated is a composite of death and major stroke at 2 years, with secondary endpoints that include valve performance and quality of life indicators.

**Evaluation of the CoreValve device in the United States of America (USA)**

In April 2009, Medtronic (Minneapolis, MN, USA) completed the acquisition of CoreValve Inc. This system, with self-expandable valve technology, received CE approval in March 2007. A year later, in October 2010, the FDA approved the evaluation of the CoreValve system with the AccuT rak™ stability layer in two independent studies. Together, the two studies will enrol more than 1300 patients at 40 clinical sites in the USA. Patients considered at high surgical risk are randomized one-to-one to either TAVR with CoreValve or SAVR. The primary endpoint for this trial is freedom from all-cause mortality at 12 months. Study participants deemed at extreme-risk (i.e. inoperable) for SAVR were at first randomized two-to-one to receive either TAVR with CoreValve or optimal medical management. Shortly thereafter, a conditional approval from the FDA to modify the CoreValve US Pivotal Clinical Trial was given. In the revised design, the trial will assess the CoreValve System in extreme-risk patients in a single-arm study with a primary endpoint of all-cause death or major stroke within 12 months. Patients deemed at extreme-risk will not be randomized to optimal medical management, where outcomes for these patients have been shown in the PARTNER trial to be significantly worse than for those treated with transcatheter valves. Rather, this patient group will be evaluated against a performance goal derived from contemporary studies. Furthermore, the revision included the evaluation of alternative implantation routes for delivering the transcatheter valve, such as the subclavian approach. This trial has coprimary
endpoints: all-cause death or major stroke occurring within a minimum of 12 months of follow-up and a composite of all-cause death, major stroke, days of hospitalization for aortic valve disease and number of hospitalizations for aortic valve disease occurring within a minimum of 12 months of follow-up. In December 2010, the Medtronic CoreValve US Pivotal Clinical Trial began. The first CoreValve procedure in the USA was performed by Dr. David H. Adams and Dr. Samin K. Sharma at the Mount Sinai Medical Center in New York, NY. In January 2012, enrolment for the extreme-risk arm of the CoreValve US Pivotal Clinical Trial was finalized.

Conclusion

In conclusion, it is clear that the penetration rate of devices in general, and in TAVR specifically, is significantly delayed in the USA compared with in Europe. This is mostly due to the mission statement of the regulatory agencies in the USA, which requires very rigorous clinical testing of a device prior to its approval. These requirements pose a heavy financial burden on companies and may delay expansion of the technology to all patients. This methodology, however, has enabled clinicians inside and outside the USA to form a concise scientifically-based assessment of the performance of TAVR devices in terms of safety and efficacy.

Disclosure of interest

Dr Pichard — “Proctor for Edwards Lifesciences”.

References