

Transcatheter aortic valve implantation in the elderly: current state of play

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Abstract

Aortic stenosis is the most common acquired valvular abnormality in the Western world, with ever-increasing disease prevalence due to an aging population. Surgical aortic valve replacement remains the first-line standard of care, however, over one-third of potential patients are not candidates because of the prohibitive nature of their comorbidities and consequent peri-operative risk. In the last few years, transcatheter aortic valve implantation has emerged as a less invasive treatment strategy in high-risk patients. Recent randomized trials have shown that this is non-inferior to surgery in high-risk patients; and vastly superior to medical therapy in patients deemed unsuitable for surgical intervention. Since the “first in man” procedure was performed in 2002, there have been major advances in implantation techniques and device technology, together with a growing evidence base. It is highly likely that transcatheter aortic valve implantation will be used in an increasing number of patients in the aortic stenosis population, but its exact role alongside surgery will need to be defined in a judicious and evidence-based manner.

Keywords: TAVI; aortic stenosis; transfemoral; transapical; stroke; surgical AVR

■ Heart Metab. (2011) 52:20–27

Introduction

Acquired, degenerative calcific aortic stenosis (AS) is the most common valvular lesion in the Western world [1, 2], affecting almost 1 in 12 patients by 85 years of age [1]. It is expected to become increasingly relevant to healthcare economics given our aging population. Once symptoms (dyspnea, syncope, chest pain) have developed, the prognosis for untreated severe AS is dire—mortalities at 1 year and 5 years are 40% and 68% respectively [1]. The benefits of surgical aortic valve replacement (sAVR), incorporating cardiopulmonary bypass, sternotomy (or mini-sternotomy), cross-clamping of the aorta and cardioplegic arrest, are well documented. It remains a class I indication and the standard of care in symptomatic AS patients [3, 4]. However the multiple co-morbidities and age of potential recipients can often deter surgeons and over one-third of patients who could potentially benefit are not offered sAVR [2]. These patients with prohibitive peri-operative risk, as judged by the Logistic EuroScore (in the United Kingdom and Europe) or the STS Score (in the United States), are the target cohort for transcatheter aortic valve implantation (TAVI) (Table 1 [5]). The evidence for its role in the management of AS is growing with short- and long-term registry data providing encouraging safety

Selection Criteria

- Synchronized multi-disciplinary “heart team” approach to patient selection comprising interventional and non-interventional cardiologists, cardiac surgeons, cardiac imaging specialists, cardiac anesthetists and cardiac nurses alongside the input of geriatricians.
- Confirmation of the severity of AS by standard transthoracic echocardiography (note the use of low-dose dobutamine stress echocardiography to differentiate between severe AS and “pseudo-severe AS” in those patients with a low gradient and low left ventricular ejection fraction).
- Patients must have symptoms that can be directly attributed to severe AS.
- Currently, patients with an expected mortality >20% with the Logistic EuroScore and >10% with the STS score are amenable to treatment with TAVI.

It is important to note that these scoring systems are an imperfect science, particularly because these high-risk patients form only a small proportion of the populations from which the scoring systems have been gleaned.

Ultimately sound clinical judgement within a multidisciplinary framework is key.

- An appropriately sized aortic valve annulus:
 - 19–25 mm annulus recommended for a 23 mm or 26 mm SAPIEN™ transcatheter heart valve
 - 20–27 mm annulus requires a 26 mm or 29 mm CoreValve®

N.B. A 28-mm annulus will also be treatable once the 29 mm SAPIEN XT™ THV is widely available.

Exclusion Criteria

- LVEF ≤20% contraindicates all TAVI procedures.
- Bicuspid aortic valves, due to a risk of incomplete deployment of the prosthesis (N.B. this position is likely to change in the near future).
- Apical thrombus.
- Significant asymmetric valvular calcification, which may lead to compression of the coronary arteries during valve-stent deployment.
- Not recommended for those patients who have declined sAVR merely on the basis of personal preference.
- Patients with a life expectancy of <1 year should not be recommended for TAVI.

Table 1 A summary of inclusion and exclusion criteria for TAVI. Adapted from [5]. (N.B. Revised ESC guidelines, in collaboration with the EACTS, on the management of valvular heart disease will be published in early 2012).

and efficacy outcomes in a real world setting [6–8], evidence of functional improvement [9], prognostic benefit [10,11] and most recently truly landmark results from both arms of a multicenter randomized controlled trial.

The evolution of TAVI

Today’s exponential rise in the uptake of TAVI can be traced to the efforts of one man, Henning Rud Andersen. On May 1, 1989, he performed the “first in animal” implantation of a rudimentary aortic valve-stent prosthesis constructed from metal wire and native porcine valves obtained from a local butcher. The technique was refined in the proceeding two years with a further 40 implantations in anaesthetized pigs. Despite the potential for a paradigm shift in the management of severe AS, it was not until 1992 that the *European Heart Journal* published his findings [12]. There was also a degree of ambivalence shown by the device

companies in taking up this new technology until the notion of TAVI was championed by several opinion leaders and the “first in man” percutaneous pulmonic valve implant, performed by Bonhoeffer et al, was published in 2002 [13]. Shortly thereafter the “first in man” TAVI procedure conducted by Cribier et al was published in 2002 using an antegrade trans-septal approach through a femoral vein [14]. Subsequent developments have yielded standardized techniques via retrograde trans-femoral (TF) [15] and trans-subclavian [16] approaches, the antegrade trans-apical (TA) route [6], and now a novel retrograde trans-aortic approach via a mini-sternotomy [17] (Table 2). Currently, no available randomized data compares the TF and TA routes, and therefore there is no robust evidence of which is superior.

There are currently two CE-marked prostheses in use: the Edwards SAPIEN™ transcatheter heart valve (THV) (Edwards LifeSciences, USA) and the

| Implantation Approach | Advantages | Disadvantages |
|-------------------------|---|--|
| Trans-femoral | Potentially allows for a fully percutaneous procedure in a conscious patient if the peripheral artery (usually femoral, rarely iliac) has an adequate caliber | Contraindicated in the presence of: <ul style="list-style-type: none"> • Peripheral vascular disease (PVD) • Previous aorto-femoral bypass • Tortuous vessels • Small-caliber vessels • Previous aortic surgery <p>Associated with major, minor and critical vascular complications such as:</p> <ul style="list-style-type: none"> • Vessel dissection • Vessel rupture • Vessel avulsion |
| Trans-apical | Potentially reduces the risk of calcium dislodgement (compared to a relatively rigid TF catheter in a diseased aorta) | Apical bleeding (very rare) |
| | Can be performed in the presence of PVD | Contraindicated in the presence of: <ul style="list-style-type: none"> • Apical thrombus • Calcified pericardium • Severe chest deformity • Poor lung function • Previous chest irradiation • Recent myocardial infarction • Inaccessible LV apex |
| | Can be conducted in those patients with a history of aortic surgery | |
| | A more “direct”, “steady” and “straightforward” technique | |
| Trans-subclavian | A more direct and steadier pathway due to the short distance from insertion site to the aortic valve | Currently an “off label” technique |
| | An alternative to the TA route when there is PVD or a diseased aorta | Potential complications: <ul style="list-style-type: none"> • Postoperative bleeding • Vertebral/internal mammary ischaemia • Vessel rupture • Vessel dissection |
| | Does not require a thoracotomy (compare to TA) | |
| Trans-aortic | Is a novel option when both TF and TA approaches are contraindicated or not feasible | Risk of massive postoperative bleeding |
| | | Contraindicated in the presence of a “porcelain” aorta |

Table 2 A comparison of TAVI implantation approaches.

CoreValve[®] ReValving system (Medtronic Inc USA). The former is a balloon-expandable tubular system, cobalt-chromium frame with bovine pericardial valve leaflets. It is currently available in 23-, 26- and 29-mm sizes and is suitable for aortic annulus sizes 18 to 27 mm in diameter (Fig. 1). The CoreValve[®] device consists of a porcine pericardial valve mounted within a longer, self-expanding nitinol frame. It has an hourglass shape with a central waist to accommodate the coronary ostia, and wider portions providing fixa-

tion within the left-ventricular outflow tract and the ascending aorta. It is available in 26- and 29-mm sizes and requires an annulus diameter of 20–27 mm (Fig. 2). The advantage of the latter is its stability and potential retrievability, however this is countered by disadvantages such as a higher rate of conduction disturbance requiring permanent pacing in a third of patients [18] compared with 7% with the Edwards bioprosthesis [7]. The CoreValve[®] device was at one point the sole device available in smaller 18 French



Fig. 1 Edwards SAPIEN™ transcatheter heart valve (printed with permission. ©2011 Edwards)



Fig. 3 Edwards SAPIEN™ XT transcatheter heart valve (printed with permission. ©2011 Edwards)

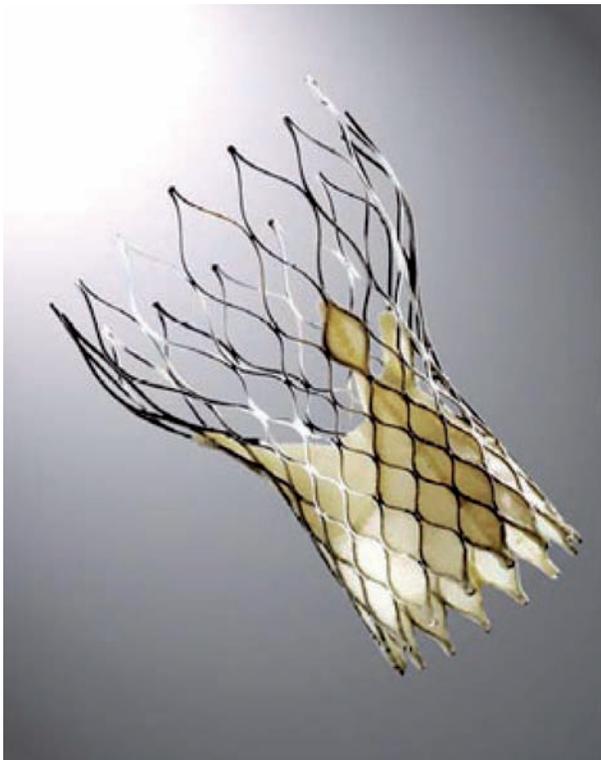


Fig. 2 CoreValve® transcatheter heart valve (printed with permission. ©2011 Medtronic)

gauge delivery systems allowing arterial access in vessels of only 6 mm in diameter. Through successive iterations culminating in the SAPIEN™ XT THV (Fig. 3), delivered via the NovaFlex platform, the Edwards device now has similar ease of access. Both devices require preparation of the valvular apparatus using balloon aortic valvuloplasty (BAV). The NovaFlex+ delivery system, which has also just received a CE Mark (May 2011), has further facilitated valve delivery and can now be delivered through an expandable 16F sheath system making access even less traumatic.

The inability to excise native calcified valve tissue and the resultant “gaps” between the circular device and the irregular annulus commonly result in paravalvular regurgitation, but this is trivial to mild in the majority of cases [19, 20] and does not significantly deteriorate at one year, with 46% actually improving [21]. The valves themselves appear durable as manifested during follow-up of up to five years [22, 23].

The PARTNER trial

Prior to the completion and reporting of results from the Placement of AoRtic TraNscathTER Valves (PARTNER) trial, there had been no robust multicenter randomized controlled trial data available comparing TAVI with conservative medical management or sAVR. The

PARTNER Trial incorporated two individually powered patient cohorts:

- PARTNER A was a non-inferiority trial comparing the safety and effectiveness of the Edwards SAPIEN™ THV with sAVR in high-risk patients with severe symptomatic AS [24].
- PARTNER B was a superiority trial comparing the safety and effectiveness of the Edwards SAPIEN™ THV against best medical management in patients with severe AS deemed too risky for surgery [10].

From the 26 centers (22 in the United States, three in Canada and one in Germany) participating in the trial a total of 3,105 high-risk AVR candidates were identified and initially screened between May 2007 and March 2009. Of these 1,057 patients were enrolled in two parallel trials. Those patients (n=699) enrolled in PARTNER A were deemed operable, but at high risk as defined by an STS score $\geq 10\%$ or assigned a predicted risk of operative mortality $\geq 15\%$ at 30 days by a site surgeon and cardiologist. Those patients (n=358) enrolled in PARTNER B were deemed inoperable due to co-existing conditions that would give rise to an operative mortality of $\geq 50\%$ at 30 days. Two cardiac surgeons had to agree that this was the case.

Severe AS was defined by echocardiographic criteria as a mean gradient >40 mmHg or jet velocity >4.0 m/s or an aortic valve area of <0.8 cm². Patients had to be symptomatic as judged by a New York Heart Association (NYHA) functional class of II or worse. Key exclusion criteria for both arms of the study included: a bicuspid or non-calcified aortic valve, an aortic annulus measurement <18 mm or >25 mm, acute myocardial infarction within the preceding month, severe LV dysfunction (EF $<20\%$), significant coronary artery disease requiring revascularization, pre-existing severe AR or MR or a prosthetic valve already in situ, severe renal dysfunction, and a transient ischemic attack (TIA) or stroke within the last 6 months.

Of the 699 patients in Cohort A, 492 were deemed suitable for TAVI via the TF approach. The remaining 207 were deemed unsuitable for a TF procedure, and were enrolled into the TA arm of the study. Following this initial assessment, patients were then randomized in a 1:1 fashion to receive sAVR or TF TAVI or sAVR or TA TAVI. Following randomization, the aim was to treat the patient within a 2-week timeframe. Results were analyzed on an intention-to-treat (at time of randomization) and as-treated (at time of anesthesia induction)

basis depending on the endpoints studied. Of note 28 patients in the surgical arm of the study either refused treatment or withdrew from the study compared with only one patient from the TAVI arm. Patients were very evenly matched in terms of age, STS score and NYHA functional status at baseline.

The primary endpoint of all-cause mortality was numerically lower in the TAVI group at 30 days (3.4% TAVI versus 6.5% sAVR, $P=0.07$), but not statistically so. Out to one year both treatment arms were nearly identical (24.2% TAVI versus 26.8% sAVR, $P=0.44$), therefore fulfilling the predefined criteria for non-inferiority. Observed rates of mortality were lower than expected in the surgical arm at both time points suggesting that sAVR remains a safe and effective treatment modality for this group of patients (30-day mortality rates: expected—11.8%, observed—8.0% in the as-treated population). There was no statistical difference between the TA or TF arms in terms of 30-day or 1-year mortality, although numerically TA patients did suffer more fatalities. This is in keeping with patients assigned to the TA route being at slightly higher risk.

In terms of secondary safety endpoints, all strokes combined with TIAs were statistically higher in the TAVI arm at both 30 days (5.5% TAVI versus 2.4% sAVR, $P=0.04$) and 1 year (8.3% TAVI versus 4.3% sAVR, $P=0.04$). Further analysis of the neurological injury subset presented at the American Association for Thoracic Surgery Annual Meeting in May 2011 demonstrated an increased frequency of events in the first two weeks post-TAVI. Those eligible for a TF approach appeared to suffer significantly more neurological events at 30 days and 1 year compared with sAVR although proportionately TA patients suffered more events overall in the TAVI group, again confirming the higher baseline arteriosclerotic burden of TF-ineligible patients, as manifested by significantly higher rates of previous coronary artery bypass graft surgery and pre-existing cerebrovascular and peripheral vascular disease compared to the TF cohort. Major bleeding was statistically higher in the surgery arm (9.3% TAVI versus 19.5% sAVR, $P<0.001$), but major vascular complications were higher in patients treated by TAVI (11.0% TAVI vs. 3.2% sAVR, $P<0.001$). In terms of secondary efficacy endpoints, NYHA class and 6-minute-walk test were better for TAVI at 30 days but by one-year results had converged between the two treatment modalities.

It should be remembered that the PARTNER Trial was conducted at a time when TAVI was in its infancy. Clinicians, who may well have had experience of only implanting one or two valves prior to study participation, were also using large first-generation transcatheter-valve systems. We are now using fourth-generation systems. They were being compared to a surgical technique that had been honed over many years and conducted by the best cardiac surgeons at each of the participating centers. As operators gain more experience and newer, less bulky transcatheter devices with improved profiles come to the market we should expect to see rates of stroke, TIA and vascular complications fall. Further studies will determine whether new-generation, smaller-caliber delivery systems with adjunctive embolic protection devices on a background of increased operator experience will help attenuate the incidence of cerebrovascular insults caused by transcatheter manipulation. Nevertheless the trial confirms that both sAVR and TAVI are viable, safe and effective methods of managing high-risk patients with symptomatic severe AS. Dichotomous peri-procedural hazards should, however, be borne in mind when making individual case-based management decisions.

Results from PARTNER B were no less remarkable. In total 358 patients with severe AS deemed unsuitable for surgery were randomized in a 1:1 fashion to conservative management or TF TAVI. Crossover from the standard-therapy group to the TAVI group was not permitted. Patients were followed up for at least one year. The standard-care group had an unusually high frequency of BAV use (63.7% within 30 days of randomization plus an additional 20.1% thereafter) albeit with its limitations and propensity for restenosis. Despite this, the rate of death from any cause at one year was 30.7% with TAVI compared with 50.7% with medical management, indicating a staggering absolute 20% difference in mortality between the two treatment modalities. It not only confirmed that TAVI improved survival and quality of life in this particular cohort of patients but also served to reaffirm the severe natural history of untreated symptomatic AS. The rate of the composite endpoint of death from any cause or repeat hospitalization at one year was 42.5% with TAVI and 71.6% with conservative therapy ($P < 0.001$). As with PARTNER A, the rate of major strokes was more frequent in the TAVI group and vascular complications significantly more so.

In contrast, secondary efficacy endpoints like NYHA class significantly improved in the TAVI group alongside improvements in echocardiographic parameters such as aortic valve area and mean gradient, which were maintained at one year. Although these very positive results in respect of TAVI can only be directly applied to implantation via the TF route, industry and national registry data suggest that the profound difference in outcomes in PARTNER B are not likely to be adversely affected by the slightly higher procedural mortality associated with the TA approach.

The future

With the prognostic benefits of TAVI established, further improvements in outcome are to be gained through better patient selection and honing of techniques. The question of how to optimally tackle coexisting coronary artery disease (CAD) in these patients remains a challenge. Patients receiving TAVI must undergo assessment of their coronary vasculature. For our surgical colleagues, the presence of significant CAD is a Class I indication for combined revascularisation by coronary artery bypass surgery (CABG) with sAVR [4]. CAD is highly prevalent in this group of patients [25] and has similar risk factors [26]. It has been suggested that prior revascularisation by either CABG or percutaneous coronary intervention (PCI) (used as a marker for CAD) raises the 30-day mortality risk in TAVI patients by a factor of ten [27]. The effects of PCI to treat significant coronary lesions prior to TAVI are unknown. The manufacturers' guidance for both the commercially available bioprostheses suggests treatment of significant CAD at least 30 days prior to procedure, but this is not standard practice in many centers. PCI post-TAVI has been successfully performed [28, 29].

The success of these two devices has prompted the development of newer prostheses incorporating and improving many of their features. Deliverability and retrieval of the devices to promote accurate positioning are the ultimate aims. These include the Direct Flow device (Direct Flow Medical Inc., USA), for which there is the greatest literature [30, 31], the Lotus (Boston Scientific Inc., USA), the JenaClip (JenaValve inc., Germany) and the HLT (Heart Leaflet Technologies Inc., USA). Some, such as the Ventrator Embracer Valve (Ventrator Technologies Inc., Israel) provide more "anatomic" positioning in the aortic root [32].

The treatment of failing sAVR bioprostheses is another area into which TAVI is expanding. Promising results with both the CoreValve® [33] and the Edwards [34] systems reflect enthusiasm among operators to reduce the enhanced risk of re-do surgery [35]. TAVI-in-TAVI procedures have successfully been performed, mostly for sub-optimal results in the initial implant [36]. This has led some to discuss the replacement of sAVR with TAVI in low-risk patients. However given the current results of sAVR, with low mortality in appropriate patients [37], and the high cost of current transcatheter devices, it would be very difficult to make TAVI cost-effective in lower-risk patients. In addition, there is a paucity of data currently available on the durability of the trans-catheter valves. There has, however, been no reported structural failure of the valves to date, with the longest implant remaining in situ for over five years. Ultimately, it is highly likely that TAVI will be used in an increasing proportion of the AS population, but this must be conducted in a prudent, carefully judged way, and in an evidence-based manner. TAVI will also no doubt stimulate our surgical colleagues to streamline and perfect the sAVR procedure, and therefore all members of the heart team will be happy: surgeons will perform more interventions, cardiologists have a new focus for their skills and, most importantly, patients will receive the most safe and effective treatment available. •

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