Transcatheter aortic valve implantation: What lies ahead?


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It is forecasted that by 2012 transcatheter valve (TCV) therapies will account for approximately 40% of the total heart valve procedures performed in Europe (fig. 1)[1,2]. The absolute number of surgical valve procedures, however, is projected to rise during this period. Thus, TCV therapies will expand the total pool of treatable patients with heart valve disease. Although transcatheter aortic valve implantation (TAVI) has become recognised as a viable alternative for high-risk or inoperable patients, many important questions remain unanswered. The goal of this opinion piece is to highlight areas where further research and advancement is needed in this burgeoning field. More specifically, we will address issues related to patient selection and risk scores, procedural complications and standardisation of the definition of clinical endpoints.

Patient selection and surgical risk scores

TAVI is currently reserved for high surgical risk or inoperable patients. Surgical risk scores (SRS), such as the Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM) and logistic EuroSCORE, are used commonly to identify such patients for clinical trials[3,4]. Furthermore, these SRS are used as benchmark performance measures for TAVI procedures. The application of SRS for transcatheter procedures can be associated with significant limitations. Firstly, it is important to appreciate the surgical population that was used to develop the risk score. For example, the logistic EuroSCORE was based on a general cardiac surgery population whereby 60% of patients had coronary artery bypass surgery, 30% had valve surgery and 10% had other cardiac-related

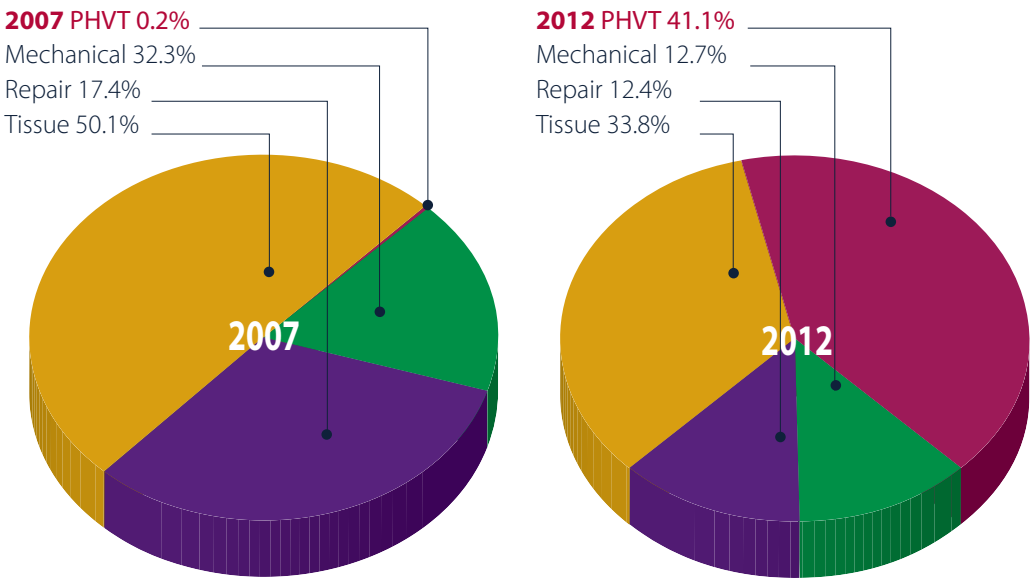


fig. 1

Heart valve market forecast... get ready for the storm!

Percentage of total heart valve procedures; expected to rise substantially from 2007–2012.

PHVT: percutaneous heart valve therapy. Adapted from [1,2].

surgeries. On the other hand, the STS risk score was based on patients undergoing valve surgery. Furthermore, 'inoperable patients' were obviously excluded during model development and high-risk patients likely accounted for a minority of those included in the analysis.

Although not particular to the STS or logistic EuroSCORE, several measurable and unmeasurable risk factors known to influence mortality are not factored into the equation[5,6]. For example, both models fail to include porcelain aorta and, more importantly, the frailty of the patient[7]. Also, using these surgical risk scores as benchmark performance measures for an unrelated procedure, such as TAVI, is not scientifically sound. This can lead to complacency on the part of the treating physician, especially when the SRS grossly overestimates the actual mortality risk of the TAVI procedure. In summary, two risk scores would be needed[8]:

- A SRS (developed using surgical patients) to help identify high-risk patients.
- A transcatheter risk score (developed using transcatheter patients) to act as a performance measure and improve patient-informed consent.

Procedural complications

The acute efficacy results are fostering the necessary enthusiasm and support for further development of the technology. What is perhaps of greater interest and importance is to understand the mechanisms behind the complications, to develop treatment strategies that either mitigate or prevent the complications and, finally, to appreciate the acute and long-term clinical implications of the complications. Conduction abnormalities and the need for permanent pacemaking, paravalvular aortic regurgitation, stroke and vascular complications have received particular attention and will be further discussed below.

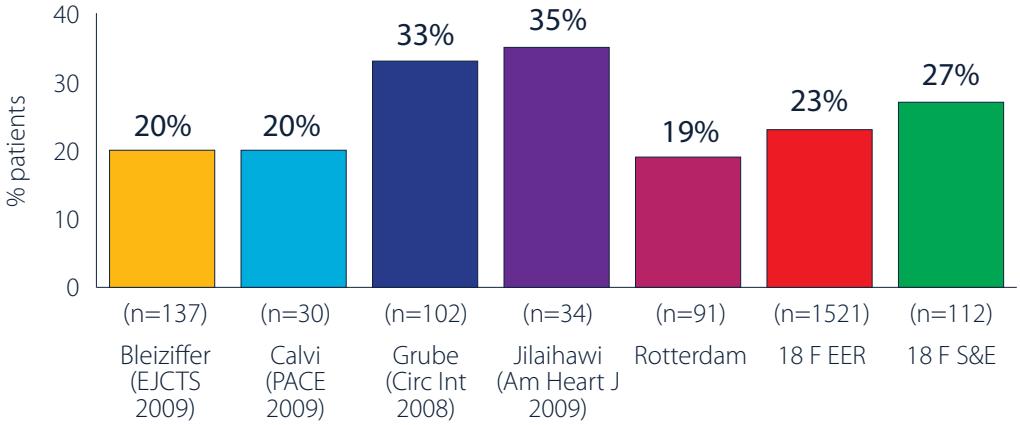
Conduction abnormalities and permanent pacemaker requirement

New-onset left bundle branch block (LBBB) has been reported in up to 40% of patients implanted with the CoreValve device (Medtronic, Inc, Minneapolis, MN, USA) and in 7% of patients implanted with the Edwards SAPIEN device (Edwards Lifesciences, Irvine, CA, USA)[9-11]. In parallel with these figures is the need for permanent pacemaking.

After implantation of the CoreValve device, the need for new permanent pacemaking has been reported to be in the range of 19–35% (fig. 2a)[9,10,12-15]. In contrast,

fig. 2a

Percentage of new permanent pacemaker implantations after CoreValve (Medtronic, Inc) implantation...



approximately 4–7% of patients are in need of permanent pacemaking after implantation of the Edwards device (fig. 2b)[16-19]. It must be highlighted that some centers implant permanent pacemakers on a 'prophylactic' basis (e.g. new-onset LBBB or asymptomatic bradycardia) or for administrative logistical purposes (e.g. promote earlier discharge). This may partly explain the wide range of observed permanent pacemaker implantation rates.

We have previously shown that the depth of implantation of the CoreValve device is associated with the development of LBBB (10.3 mm in those patients with new-onset LBBB vs. 5.3 mm in those without)[9]. Thus, we hypothesise that a more superior positioning of the CoreValve device within the left ventricular outflow tract may mitigate conduction abnormalities and reduce the need for permanent pacemaking. To put this into perspective, the Edwards SAPIEN device is implanted approximately 4–6 mm below the aortic valve annulus, whereas the CoreValve device, in our experience, is implanted a mean of 9–10 mm below the aortic valve annulus. Currently, it is being recommended to position the CoreValve device approximately 6 mm below the aortic annulus.

Paravalvular aortic regurgitation

Moderate-to-severe paravalvular aortic regurgitation is poorly tolerated after TAVI. In these cases, patients typically experience recurrent heart failure and longer lengths of stay in the intensive care units. According to the Expanded Evaluation Registry with the CoreValve device (n=1378) and the SOURCE registry with the Edwards SAPIEN device (n=1308), grade 3 or grade 4 paravalvular aortic regurgitation was observed in 3% and 5% of patients, respectively[17,20]. Of the remaining patients, approximately one-fifth had grade 0 paravalvular aortic regurgitation, two-thirds had grade 1 and one-fifth had grade 2. Anecdotal experience suggests that patients with grade 1 or 2 aortic regurgitation have a benign clinical course but this observation needs to be confirmed in larger clinical studies. The pericardial skirt of the Edwards and CoreValve device is 10–11 mm and 12 mm in height, respectively, and, together with the radial force of the device, functions to create a seal against the native aortic valve leaflets and left ventricular outflow tract, thereby mitigating paravalvular aortic regurgitation (fig. 3[21]).

Potential mechanisms of aortic regurgitation include:

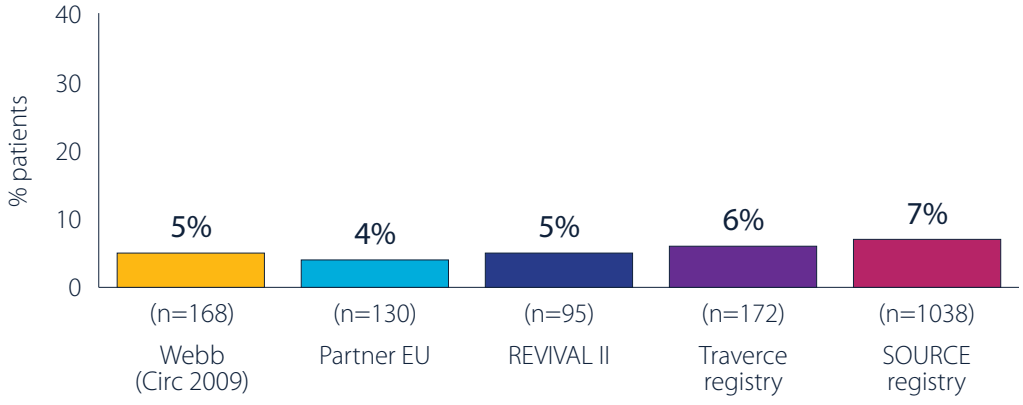


fig. 2b

...and after Edwards SAPIEN (Edwards Lifesciences) implantation.

- malpositioning of the device (too high or too low)
- incomplete expansion of the device or malapposition against the native aortic valve leaflets or left ventricular outflow tract due to bulky calcifications
- undersized prosthesis
- aggressive pre-implant balloon aortic valvuloplasty
- malcoaptation of prosthetic valve leaflets due to the guide wire or pigtail catheter across the valve
- prolapse of native aortic valve leaflets or calcific debris into the prosthetic valve impeding normal leaflet excursion (particular to Edwards SAPIEN device)
- diastolic hypotension resulting in insufficient closing pressure.

Corrective measures may include post-implant dilatation, valve-in-valve technique, and particular to the CoreValve device, the use of a goose-neck snare to reposition the device in a slightly higher position (typically 1–4 mm)[22]. Currently, there are no preprocedural screening methods to predict the occurrence or severity of paravalvular aortic regurgitation.

Stroke

Stroke can be a catastrophic complication even after a so-called 'uneventful' TAVI procedure. Stroke has been reported to occur in 2.9%–6.3% of patients undergoing transfemoral TAVI (with both the Edwards SAPIEN or CoreValve device)[12,13,15–18] and 1.8%–5% of patients undergoing transapical TAVI (Edwards SAPIEN)[17,18,23–25]. Some advocates suggest that the transapical approach is associated with lower stroke rates than the transfemoral approach. Data from prospective, multicenter, adjudicated, feasibility and postmarket trials, however, suggest comparable stroke rates between the two vascular approaches. The SOURCE registry, for example, reported a stroke rate of 2.4% and 2.6% for the transfemoral (n=463) and transapical approach (n=575), respectively[17]. Similar stroke rates were reported for the PARTNER EU trial (3.2% transfemoral [n=61] vs. 2.9% transapical [n=69])[18].

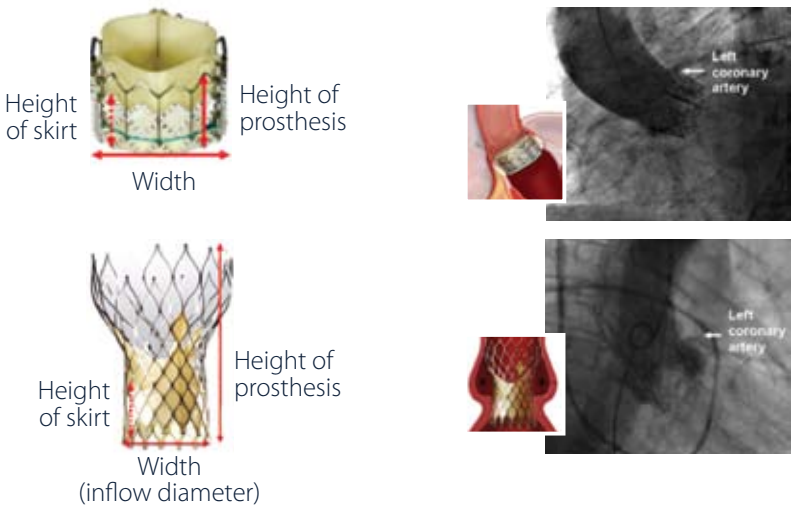
More recently, attention has focused toward the potential merits of using embolic protection devices. These devices are intended to divert embolic clots or debris away from the major neck vessels and

fig. 3

Edwards SAPIEN (Edwards Lifesciences) and CoreValve (Medtronic, Inc) devices

The pericardial skirt, in addition to the radial force of these devices, functions to create a seal against the native aortic valve leaflets and left ventricular outflow tract to mitigate paravalvular aortic regurgitation.

Adapted from [21].



towards the descending aorta. Clinical studies using the Aortic Embolic Protection Device (AEPD; SMT Research and Development, Ltd., Herzliya, Israel (figs. 4a+b) and the Embrella Embolic Deflector (Embrella Cardiovascular™, Inc., Malvern, PA, USA) will likely initiate by Q4 of 2009. In addition to these devices, it hoped that a more detailed assessment of the aorta, improved techniques and less traumatic catheters will decrease the occurrence of stroke.

Vascular complications

Given the large-bore catheters used for TAVI procedures, vascular complications are of particular concern. Imaging techniques such as fluoroscopic angiography, computed tomographic angiography and magnetic resonance angiography can provide objective information of the peripheral arterial system – salient features include vessel diameter, degree of calcification and atherosclerosis, obstruction, tortuousity and ulceration. The 18 F CoreValve Safety and Efficacy trial reported a vascular complication rate of 12%, whereas the Edwards PARTNER EU trial (22 F and 24 F devices) reported a rate of 27%[15,18,26]. Previous analyses have demonstrated that vascular complications are associated with increased in-hospital mortality (36% with vascular complications vs. 10.3% without)[27]. Cautious preprocedural screening (e.g. excluding patients with circumferential calcification of ilio-femoral vessels) is essential to reduce these complications. Edwards has recently introduced the 18 F Edwards SAPIEN XT device (associated with a cobalt-chromium alloy-stented valve and RetroFlex 4 delivery catheter) with the expectation that it will reduce vascular complications.

Standardisation of the definition of clinical endpoints

One complicating factor when trying to analyse and compare available TAVI data stems from the great heterogeneity involving the definition of clinical endpoints[28–30]. A number of organised societies have alluded to the need for standardised reporting practices[31–33]. Furthermore, any valid treatment comparisons between TAVI and surgical aortic valve replacement will require some common ground for clinical endpoint reporting. Thus, this endeavour should involve the mixed perspectives of interventional cardiologists, cardiac surgeons, clinical valve specialists, manufacturers and regulatory bodies located on both sides of the Atlantic. This framework was successfully adopted by the Academic

fig. 4a

The Aortic Embolic Protection Device (AEPD) from SMT Ltd.

This device is currently available in 8 F and is inserted via the transfemoral arterial route. The device spans the three major neck vessels.

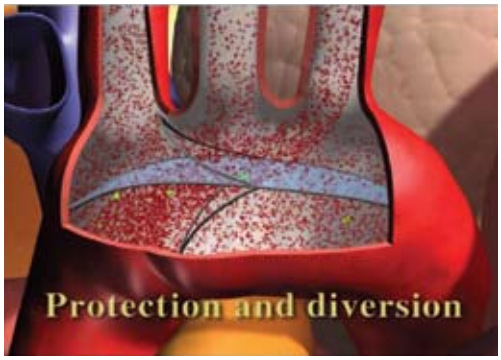


fig. 4b

Pictorial representation of the transverse aortic arch with major neck vessel

SMT filter device in situ functions to divert debris away from the major neck vessels.

Research Consortium (ARC) to standardise the definitions of clinical endpoints for stent trials[34]. Along these lines, the cardiology and cardiac surgery communities are currently working towards a Valvular Academic Research Consortium (VARC)[29].

The future

The future and widespread adoption of TAVI will rely on a number of inter-related factors, including long-term durability and safety data, randomised controlled trials comparing TAVI with surgical aortic valve replacement and reimbursement for the technology.

Given the obvious requirement for long-term follow-up data, the number of patients with ≥3 years' clinical follow-up is severely limited[35]. It is unlikely, given the age and multiple comorbidities of patients currently undergoing TAVI, that robust long-term follow-up data (i.e. >10 years) will become available. Furthermore, the long-term effects of either crimping the valve into a delivery catheter, performing a post-implant balloon dilatation or valve-in-valve procedure are currently unknown.

Undoubtedly, randomised controlled trials will be needed to establish the noninferiority or superiority of TAVI (versus surgical aortic valve replacement) and its eventual acceptance into medical practice as evidence-based medicine. At this time, a legitimate question may follow: "Has TAVI has reached an appropriate level of maturity to be subjected to a randomised, controlled clinical trial?" The pivotal randomised PARTNER US trial may shed light onto this important question – enrolment should be complete by Q4 2009 with the primary endpoint being all-cause mortality at 1-year.

As a result of its novelty, lack of comparative data (to surgical aortic valve replacement) and a lack of cost-effectiveness data, reimbursement policy makers may be skeptical about the potential merits of TAVI. The road to reimbursement can be summarised in the following points:

- CE mark approval is required from governmental regulatory bodies.
- Evidence-based medicine must prove the efficacy and safety of the technology.
- The risk/benefit ratio must be in favour of the individual patient.
- The cost-effectiveness must be established on a societal level.

Owing to limited financial resources, many TAVI programmes across Europe and Canada are restricted in the number of TAVI procedures they can perform. Despite these restraints, it is notable that approximately 8000 TAVI procedures have been performed since CE mark approval was obtained for the CoreValve (April 2007) and Edwards SAPIEN devices (June 2007).

In 2007, TAVI actually represented approximately 1.2% of all aortic valve procedures in Europe (including surgical aortic valve replacement); this percentage increased to 6.5% in 2008. With an expectation of ~9000 TAVI procedures to be performed in 2009, TAVI may represent nearly 13% of all aortic valve procedures (fig. 5).

It is unquestionable that refinements in the technique and technology (lower profile devices, ability to reposition and retrieve) will provide those patients with aortic valve disease with new hopes and aspiration in the future to come.

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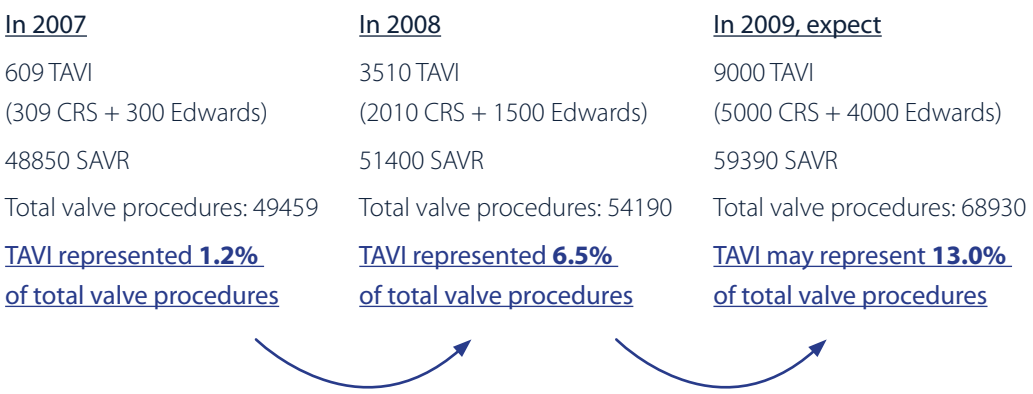

fig. 5

SAVR procedures continue to increase

This figure demonstrates that the number of surgical aortic valve replacement (SAVR) procedures continues to increase. Also, since CE mark approval, the percentage of total heart valve procedures represented by TAVI increased considerably from 2007 to 2008. A similar trend is expected for 2009.

DISCLOSURES: The opinions and factual claims herein are solely those of the authors and do not neccesarily reflect those of the publisher, editor-in-chief, editorial board and supporting company. NP is a consultant for Medtronic, Inc, PdJ is a proctor for Medtronic, Inc and AT and PWS have no relevant disclosures.

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