Transcatheter aortic valve implantation: changing patient populations and novel indications

Michael J Mack

INTRODUCTION
As the experience with transcatheter aortic valve implantation (TAVI) grows, expanded use in new patient populations and for novel indications can be anticipated. There are however, many as yet unsolved clinical issues that need to be addressed before unbriddled, expanded application into lower risk patients is warranted. For example, paravalvular leak occurs to some degree in the majority of patients receiving a transcatheter aortic valve. There is increasing evidence that even mild paravalvular leak is associated with increased mortality at 2 years. As indicators for TAVI expand to younger and lower risk patients with a longer life expectancy, this issue will carry greater importance. Similarly, valve durability has hitherto not been an issue of significant clinical consequence. The long term durability of catheter delivered valves is as yet unknown. With TAVI use in populations with longer life expectancy post implant, this issue will also carry greater importance.

In this article, we will first discuss some of the unsolved technical and clinical issues with TAVI and update the progress that has been made in addressing them. We will then discuss expanded and novel indications including TAVI in lower risk patients, patients with previously implanted surgical bioprostheses and in those patients with concomitant coronary artery disease. Lastly, we will survey the landscape of next generation valves and the novel ancillary technology that is being developed to both facilitate the procedure as well as address some of the current shortcomings. This technology includes access devices for both transfemoral and transapical approaches, cerebral protection devices, and measures to minimise paravalvular leak.

UNSOLVED TECHNICAL AND CLINICAL ISSUES
TAVI-in-TAVI
Placement of a second or on rare occasions even a third transcatheter valve at the time of initial implant is a relatively unusual event, occurring in 58 of 2208 (1.8%) of patients in a recently reported meta-analysis. The usual indications for TAVI-in-TAVI include excessive paravalvular leak due to malposition of the initial implant, or transvalvular leak due to leaflet malfunction from incomplete stent expansion or calcified leaflet overhang from low placement. In the PARTNER II trial, multiple transcatheter valves (≥2) were implanted in 7/548 (2%) patients because of valve embolisation (in two patients) or residual aortic regurgitation (in five patients in whom a second valve was placed within the first valve). Three of these seven patients died. Greater experience leads to more facile and accurate placement of the initial valve, minimising the need for a second valve. However, leaving significant residual aortic regurgitation is so consequential that placement of a second valve inside the first valve, when repeat balloon dilation is not successful, is appropriate and indicated.

TAVI and concomitant coronary artery disease
Approximately one half of patients undergoing surgical aortic valve replacement (AVR) have concomitant coronary artery disease (CAD) and hence undergo bypass surgery at time of AVR. The mortality in these patients is twice as high as in patients undergoing isolated AVR, reflecting both the added complexity of the procedure as well as the additional comorbidities of the patient population being treated. The clinical management of CAD in patients undergoing TAVI has evolved without strong evidential basis. Since most patients undergoing TAVI are elderly and debilitated, a treatment philosophy of ‘less is more’ has evolved. CAD which previously would have been bypassed at the time of surgical valve replacement is frequently now approached as ‘bystander disease’ and the culprit pathology aortic stenosis (AS) alone is treated. From our experience and that of others, this appears to be an appropriate strategy at least in the short term. However, more experience is necessary before it can be determined whether this is the correct long term strategy.

The other approach has been to treat compelling CAD with percutaneous coronary intervention (PCI) before TAVI, since treatment of concomitant disease simultaneously was not allowed in the various TAVI trials. Whereas this approach seems to work out well on an ongoing clinical basis, evidentiary support for this approach is similarly lacking. The current PARTNER II trial is enrolling AS patients with CAD requiring treatment. AS plus CAD patients will be substratified but not powered to show differences, but strategies will be compared (TAVI+PCI vs AVR +CABG). Complex CAD (unprotected left main stem lesions, multivessel disease with SYNTAX score ≥33) will be excluded and less aggressive complete revascularisation has been deemed acceptable for both TAVI and AVR.

Postprocedural aortic regurgitation and its implications
The majority of patients undergoing TAVI develop varying degrees of aortic regurgitation (AR), both paravalvular and transvalvular. The aetiology of postprocedural regurgitation is multifactorial and occurs with all TAVI devices (box 1). These include device malposition (both too high and too low...
relative to the aortic annulus), undersizing of the device relative to the size of the annulus, or incomplete expansion of the stent due to technique or the presence of eccentric, bulky calcification. There is an increasing body of evidence that residual aortic regurgitation post-TAVI is associated with intermediate term mortality. An Italian Registry of the CoreValve device showed a hazard ratio for late mortality of 5.75 for a paravalvular leak ≥2+. The two year results of the PARTNER trial demonstrated that even mild degrees of paravalvular leak were associated with increased mortality (HR 1.75, 95% CI 1.17 to 2.61).

There are many efforts directed at both determining the causes as well as solving the issue of paravalvular leak. First and foremost is ‘right-sizing’ the valve to the annulus. Device and aortic annular ‘discongruence’ has been shown to be a common cause of paravalvular leak. It is becoming increasingly apparent that the traditional methods of annular sizing using transthoracic or transoesophageal echocardiography in fact underestimate true annulus size. Using CT reconstruction to measure the minimum and maximum diameter of an aortic annulus, which is actually oval, or measuring the perimeter or area of the aortic valve, seems to be more accurate and result in less paravalvular leak. The results of the recent PREVAIL TA (Placement of Aortic Balloon Expandable Transcatheter Valves Trial – TransApical) Registry showed that one third of patients enrolled received the largest 29 mm Sapien XT (Edwards Lifesciences, Irvine, California, USA) valve and had only minimal paravalvular leak, suggesting previous undersizing.

There is also evidence that the amount and pattern of leaflet calcification can lead to greater degrees of paravalvular regurgitation. Bulky, eccentric calcification, as is seen with bicuspid aortic valves, can prevent complete circular deployment of the stent with the resultant oval shape leading to both paravalvular leak and leaflet malcoaptation.

With the increased focus on the management of paravalvular leak, there is an increased use of repeat postimplant balloon dilatation, with some centres performing this in approximately 40% of patients (Leon M, March, 2012, personal communication). Careful measurement of paravalvular regurgitant volumes using three dimensional transoesophageal echocardiography during the procedure and diligent use of accurate sizing measurements, more aggressive postdilatation when a leak is present, and broader availability of larger size TAVI devices may eventually reduce the incidence of this procedure related phenomenon.

**Long term durability of devices**

Early structural valve deterioration is a theoretical concern with TAVI. Whereas the current generation of surgical tissue valves have a freedom from structural deterioration of >90% at 15 years, the long term durability of transcatheter valves is as yet unknown. The Edwards Sapien valve is constructed of the same bovine pericardial tissue that has been treated with the same fixation and decalcification processes as the surgical valves, and has the same durability performance by accelerated wear testing on the bench. However, one cannot assume that the durability of transcatheter valves will be the same as surgical valves for a number of reasons. First, the mounting of the tissue within the stent is not identical with resultant differing shear forces on the tissue; second is the use of thinner pericardial tissue, which may have less durability, and finally the crimping process necessary for valve delivery may inadvertently cause tissue damage.

To date there has been no substantive reports of early structural valve deterioration with transcatheter valves. No cases of operation for structural valve deterioration or changes in aortic valve area and mean transvalvular gradients were reported in the PARTNER trial at 2 years. Bleiziffer et al reported 2-year results in 227 patients. The postprocedural mean transprosthetic gradient was 12±4 mm Hg and the effective orifice area was 1.5±0.4 cm² with no change over 2 years of follow-up. Gurvitch reported valve haemodynamics in 70 patients with a minimum of 3 years follow-up and a mean of 3.7 years. There was a small but significant increase in transaortic pressure gradients from 10.0 mm Hg immediately after the procedure to 12.1 mm Hg after 3 years (p<0.05). Likewise, bioprosthetic valve area decreased from a mean of 1.7±0.4 cm² after the procedure to 1.4±0.3 cm² after 3 years (p<0.01). Although there were no cases of structural valve deterioration, stent fracture, deformation, or valve migration, it is too early to tell whether these changes are meaningful.

Obviously experience is too limited to date, with only a small number of patients having intermediate term follow-up, to make statements with any degree of assurance regarding long term durability. However, it is reassuring that until now structural valve deterioration has not been an issue. This issue will assume greater importance though as TAVI experience expands into lower risk and younger patients with longer life expectancy. Whereas the mean life expectancy in the current TAVI treated population is 5–7 years, some greater assurance of long term durability is necessary before significant further expansion occurs. It should also be remembered that with surgically implanted valves, there is decreased valve durability in younger ages and one can assume that transcatheter valves will follow the same pattern.

**Novel indications for TAVI**

**Low to intermediate risk patient populations**

As the outcomes of TAVI improve, it is appropriate to consider expansion into lower risk and younger patient populations. The group from Munich recently reported their experience in 420 patients by quartiles of enrolment. They determined that over a 3-year period, the mean age decreased from 81 to 79 years and that the STS (Society of Thoracic Surgeons) predicted risk of mortality decreased from 7.1% to 4.3%. Also the observed 30-day mortality decreased from 11.4% to 3.8% and the 6-month mortality from 23.5% to 12.4%.

Although these results are encouraging, a number of concerns need to be addressed before significant downward ‘age and risk
Box 2 Major issues with expansion of transcatheter aortic valve implantation into low and intermediate risk populations

- Procedure mortality relative to surgical aortic valve replacement
- Neurologic events
- Postprocedure aortic regurgitation
- Valve durability

Creep occurs. Three factors that need to be taken into consideration include the increased stroke risk with TAVI, the intermediate term consequences of paravalvular leak, and the unknown durability of transcatheter valves (box 2). Although the incidence of stroke was lowest in the most recent quartile from the Munich cohort, more evidence of a lower stroke risk with accrued experience and in lower risk patients needs to be forthcoming. The issues of both valve durability and paravalvular leak have been addressed above. It should also be remembered that there is a greater incidence of bicuspid aortic valves with associated bulky and eccentric calcification leading to greater paravalvular leak and device malposition in younger patient populations.

To address these and other outcome issues with TAVI in lower risk populations, two clinical trials have been designed. The PARTNER II trial is currently randomising the Sapien XT valve versus surgical AVR in intermediate risk patients with an STS Predicted Risk of Mortality (STS PROM) ≥4, which is the upper tertile of risk. The primary trial end point is non-inferiority compared with surgery of all cause mortality and major stroke at a minimum of 2 years. A similar trial with the Medtronic CoreValve device, the SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trial, has just started in Europe and the USA.

TAVI for aortic regurgitation

There is minimal experience with TAVI in patients with AR that is largely a disease of the aortic root and ascending aorta. Very few patients with AR have intrinsic leaflet or cusp pathology as a cause of the insufficiency. Hence, aortic regurgitation has been an exclusion from all TAVI trials and a relative contraindication outside of trials. In addition, the balloon expandable valves are dependent on leaflet calcification, which is uniformly absent in patients with AR to aid radial strength for valve fixation. Anecdotal experience with self-expanding valves exists, but without enough evidence to reach any conclusions. A new valve, Centera SE (Edwards Lifesciences), has been designed specifically for patients with AR. If transcatheter valves are used in patients with AR, continued expansion of the untreated aortic root and ascending aorta will be an ongoing concern in these patients.

TAVI for redo surgical aortic valve replacement: valve-in-valve

TAVI presents an attractive alternative for the management of patients with degenerated, surgically implanted bioprostheses. Patients with degenerated tissue valves are typically quite elderly and frequently have patent saphenous vein grafts that increase the risk of reoperative surgical valve replacement. The stent frame of the previously placed bioprosthesis presents an ideal landing zone for TAVI with clearly defined markers, albeit different for the various valves, and a stable fixation platform. Each surgical bioprosthesis has its own details which need to be ascertained before implantation, including inner diameter of the particular prosthesis, valve design, and whether the tissue is mounted internal to or external to the stent. Valve models in which the tissue is mounted external to the stent, including the Mitroflow (Sorin Inc, Milan, Italy) and Trifecta (St Jude Medical Inc, St Paul, Minnesota, USA) (figure 1), may present particular hazards for coronary obstruction by tissue when the TAVI device is deployed, so details regarding prosthesis height relative to the coronary orifices also need to be ascertained.

Another concern regarding ‘valve-in-valve’ is the creation of patient prosthesis mismatch (PPM) by placing a TAVI device inside a small surgical prosthesis. More than 50% of surgically implanted valves are 19 mm or 21 mm in size, and creation of too small a valve orifice by placing a transcatheter valve inside these smaller sized valves is a real concern.

---

Figure 1 The Mitroflow (A) and Trifecta (B) valves.
should be avoided in any patient with a 19 mm valve in place and in most patients with a 21 mm valve, unless the patient body surface area allows an effective orifice area index \(>0.8 \text{ cm}^2/\text{m}^2\) to be achieved.

Seiffert et al reported on a series of valve-in-valve procedures in 11 patients.18 Severe patient–prosthesis mismatch was evident in five patients and absent in six. Mean transvalvular gradients only decreased from 29.2±15.4 mm Hg before implantation to 21.2±9.7 mm Hg at discharge in patients with PPM and from 28.2±9.0 mm Hg before implantation to 15.2±6.5 mm Hg at discharge in patients without PPM. Indexed effective orifice area only increased from 0.5±0.1 cm²/m² to 0.6±0.1 cm²/m² and from 0.6±0.3 cm²/m² to 0.8±0.3 cm²/m². No differences in New York Heart Association functional class improvement or survival during follow-up were observed. One patient required reoperation for symptomatic PPM 426 days after implantation. The authors concluded that although valve-in-valve implantation can be performed in high risk surgical patients to avoid reoperation, PPM frequently occurs, making adequate patient selection crucial. They recommended that small bioprostheses (<23 mm) should be avoided and that implantation into 23 mm xenografts could only be recommended for patients with a body surface area <1.8 m² and that larger prostheses seemed to carry a lower risk for PPM. Although no delay in clinical improvement was seen at short term, one PPM related surgical intervention raises concern regarding long term performance. It can be anticipated that on longer term follow up, more issues including increased mortality will be seen in TAVI patients with PPM similar to that seen in surgical patients with PPM.19

TAVI for redo surgical AVR: valve in other valves

Valve-in-valve has been performed in all other valve positions besides the aortic, including mitral prostheses, pulmonary and tricuspid valves and right ventricular conduits.17 The Sapien XT valve has been used in mitral prostheses while both the Sapien XT and the Melody valve (Medtronic Inc, Minneapolis, Minnesota, USA) have been used in the pulmonary and tricuspid positions. Experience is small and remains anecdotal at the current time.

THE NEXT GENERATION OF DEVICES AND CATHETER DELIVERY SYSTEMS

Valves

Among the first generation TAVI devices, the Edwards Sapien valve has undergone changes from its first iteration. The original stainless steel stent has been replaced by a cobalt chromium stent which facilitates delivery through smaller sized sheaths (19 mm internal diameter for the 26 mm valve and 18 mm internal diameter for the 23 mm valve). In addition, a 29 mm valve has been introduced with a 20 mm valve planned. A first-in-man implant with a new 14 mm self-expanding valve...
Two other valves, both developed for the transapical approach, have also received commercial approval (CE Mark) in Europe, in 2011. The JenaValve (JenaValve Inc, Munich, Germany) consists of a porcine root valve sewn onto a nitinol self-expanding stent. The root valve is fitted with an outer porcine pericardial patch to minimise paravalvular leak and is available in 23 mm, 25 mm and 27 mm sizes. A multicentre experience in 73 patients has been reported, with an 89.6% procedural success and 30-day mortality of 7.6%.20

The Symetis Acurate TA Transapical Aortic Bioprosthesis (Symetis SA, Lausanne, Switzerland) is composed of a porcine biologic valve attached to a self-expandable nitinol stent, and is designed for anatomical orientation of the commissures and for subcoronary implantation. Ninety patients have undergone implantation with this valve with a 95% success rate and a 30-day mortality of 7.8%.21

There are a number of other valves that have undergone first-in-man implantations and are in early clinical trials. Among those are the St Jude Portico Valve (St Jude Medical), the Medtronic Embracer Valve (Medtronic Inc), the Direct Flow Medical Valve (Direct Flow Medical Inc, Santa Rosa, California, USA), and the Sadra Valve (Boston Scientific Inc, Natick, Massachusetts, USA). Additional design features of some or all of these valves include repositionability, retrievability and coverings to address paravalvular leak (figure 2).

Vascular access sheaths

Vascular complications continue to be a significant cause of mortality and morbidity with TAVI. In the PARTNER trial, major vascular complications occurred in 11% of TAVI cases and were an independent predictor of mortality.5 In a recent meta-analysis, vascular complications also occurred in 11.9% of TAVI procedures in 16 reported series. In the current clinical experience of many physicians it appears, however, that these complications have become less frequent and less life threatening.22 This is due to better patient selection, more liberal use of alternative approaches, including transapical and direct aortic approaches in patients with marginal vascular access for the transfemoral approach, and broader application of endovascular repair techniques. Smaller vascular access delivery systems may also be a factor in decreasing vascular complications.

The SoloPath vascular access system (Onset Medical, Irvine, California, USA) (figure 3) is an 18 French (Fr) balloon expandable sheath for device delivery which, when placed in a small vessel, can be expanded for valve delivery and then retracted again for removal. The E Sheath (Edwards Lifesciences) is also a 14Fr sheath that allows delivery of an 18Fr valve and is being used in the current PARTNER II A trial.

Apical access and closure devices

The transapical approach for TAVI is attractive due to the direct axis of approach to the aortic valve, short delivery distance, and antegrade crossing of the valve. However, the requirement for even a small thoracotomy is a significant source of morbidity and invasiveness, which is poorly tolerated in elderly and debilitated patients. Although the early experience of access related complications from the occasional ‘hostile apex’ have largely diminished, a less invasive (even percutaneous) and secure access and closure system for the transapical approach remains attractive. There are a number of unique suture based and device based transapical access and closure systems in development. The APICA transapical device (APICA Cardiovascular Inc, Atlanta, Georgia, USA) (figure 4) incorporates a corkscrew type device on the end of a conventional delivery sheath, offering secure access, and then upon removal a closure plug is screwed into the corkscrew access platform. The CardioClose device (Entourage Medical Inc, Menlo Park, California, USA) (figure 5) is also in development and places a suture based double helix through the myocardium through which a delivery sheath is placed. Suture closure is then accomplished upon sheath removal. Other suture and device based concepts for transapical access and closure are being developed by Micro Interventional Devices (Bethlehem, Pennsylvania, USA), Novogate Medical Ltd (Haifa, Israel), SpirX Closure LLC, Whitmore, California, USA), and Cardiapex Ltd (Akiva, Israel).

Cerebral protection devices

Stoke is a devastating complication of AVR, whether it be performed by a surgical or transcatheter approach. Results from the PARTNER trial demonstrate that the neurologic event rate (major stroke, minor stroke, transient ischaemic attack) is approximately twice as high in patients undergoing TAVI compared with surgical intervention (4.6% vs 2.4%).23 The majority of neurologic events occur periprocedurally and therefore may be amenable to prevention by cerebral protection. However, a fair number occur outside of the immediate periprocedural period and may be due to other causes, including atrial fibrillation. Many series of surveillance brain imaging with diffusion weighted MRI have been performed in patients receiving TAVI and demonstrate embolic debris in the brain in the large majority of patients.24–25 Although correlation with neurocognitive impairment has not been demonstrated in patients undergoing TAVI, adverse impact on cognitive function has been demonstrated in other patient populations and it therefore makes

Figure 3  The SoloPath balloon expandable sheath.
intuitive sense that adjunctive measures to reduce the potential emboli burden to the brain would be desirable.

There are three different devices that have been developed and are undergoing clinical testing in humans. Two devices, the Embrella Embolic Deflector (Edwards Lifesciences) (figure 6) and the Shimon Embolic Filter (SHEF – SMT Medical, Herzliya Pitauch, Israel) (figure 7) are ‘deflection’ devices that shield the great vessels from embolic debris, while the third device, the Montage dual filter system (Claret Medical Inc, Santa Rosa, California, USA) (figure 8), is a ‘capture’ device that is deployed in the innominate and left carotid artery during the procedure.

Although embolic protection of the brain is desirable, there are many issues yet to be overcome before use of these devices becomes routine. First, ease of use with proper deployment of these devices has been an early issue. Second, it has not been demonstrated that use of the devices leads to fewer emboli in the brain. Third, the ability to prove a clinical benefit, even if it were to be demonstrated that there are fewer cerebral emboli, is challenging from the standpoint of trial design. Fourth, the source of the debris is unknown when using the capture device and conceivably some could have been induced by the device itself. Lastly, with the deflection devices it is unknown where the deflected debris goes and whether other organ systems, including the renal bed and the gastrointestinal tract, could be damaged while the brain is spared.

SUMMARY

TAVI is clearly a disruptive technology that is in the midst of causing a significant paradigm shift in the management of patients with AS. Although it has been only a decade since the first clinical case was performed, worldwide experience now exists in excess of 50 000 patients and we are now experiencing the maturing of that disruptive technology. As with the
experience gleaned from the introduction of any new technology into any field, medicine or otherwise, the true value to a disruptive technology is ultimately determined by the incremental improvements that occur after the initial introduction. In the decade since TAVI was first performed in man, there have been a myriad of incremental improvements in not only the technology itself, but also the deployment techniques, patient selection and postprocedure care. There remain many challenges as discussed above. However, with continued iterative improvement in technology and techniques, expansion into lower risk and more diverse populations and improved outcomes in existing patient populations can be anticipated. These iterative improvements in all aspects of TAVI will ultimately enhance the value of the original disruptive technology of transcatheter valves and allow expanded treatment with TAVI in more patients with AS.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES