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EDITORIAL

TAVI or Not TAVI—in Low Risk Patients? That Is the Question

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Q3 The evolution in the indication for transcatheter aortic valve implantation (TAVI) might be regarded as a model for the uptake of a new therapy, first meeting an unmet clinical need and then broadening its target population based on strong clinical trial evidence. There are interesting differences between the uptake of coronary angioplasty and that of TAVI. Following its inception by Gruentzig in 1978, coronary angioplasty gradually evolved from the treatment of simple single vessel lesions to now include the management of higher risk complex bifurcational and multi vessel disease and chronic total occlusions, sometimes with little clinical trial evidence. In contrast, since TAVI was first performed by Cribier in 2002 [1], it was proposed as a therapy for inoperable or very high risk patients and the clinical trial evidence for its use in this group is very strong [2–5]. The recent change to performing TAVI on younger lower risk persons with less comorbidities, and in whom there is less calcification of the aortic annulus and femoral arteries, is sure to be associated with lower complications and improved outcomes compared to the results obtained in the frail elderly. But is this appropriate and what is the evidence to perform this procedure in these patients? The early results of this procedure in lower risk patients is addressed in Q4 this issue of Heart, Lung and Circulation.

Along with this shift in target population, there has been a remarkable evolution in the procedure itself, including a reduction in delivery sheaths from 21F to 14F, the provision of sealing cuffs, improvements in deliverability, the ability to reposition and retrieve, and the move to a minimalist approach under local anaesthesia [6–8]. In addition, safety has been facilitated by developments in imaging and its analysis particularly using CT scanning, which has led to more accurate determination of device sizing and demonstrated potentially troublesome calcium nodules (which may interfere with device apposition or increase the risk of annular rupture). Computed tomographic scanning also accurately measures coronary height and coronary sinus size (which estimate the risk of coronary occlusion), and accurately evaluates the luminal size, tortuosity and calcification of the iliofemoral arteries. Sheath to iliofemoral artery ratio and presence of circumferential femoral calcification may predict adverse events with femoral access TAVI [9]. This facilitates the planning of vascular access, from the most commonly used transfemoral site to the transaortic, transapical, subclavian or even transcaval approaches.

International guidelines initially recommended TAVI in inoperable or high risk patients whose life expectancy is more than one year and the patient's quality of life is likely to improve with implantation, based on clinical trials which have demonstrated the safety and even superiority of this procedure over medical therapy or surgical aortic valve replacement (SAVR). High risk has been defined using a logistic EuroSCORE of over 20%, EuroSCORE II of over 10% or STS Score over 8%. Patient frailty is also utilised but is difficult to define, but ability to ambulate seems particularly important. Weight loss in the past year, low activity, exhaustion, low gait speed and reduced grip strength are predictive of surgical outcome [10]. Very excessive frailty (Charlton Index >5) may predict persons who have a poor short-term outcome regardless of how they are treated. The use of a multidisciplinary heart valve team for selection of patients is widely advocated where

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individualised risk assessment including frailty [4], functional assessment, comorbid conditions and social supports are evaluated, in addition to anatomic issues and traditional risk scores. Transcatheter aortic valve implantation is approved in over 50 countries for high risk patients.

A clinical trial of TAVI in intermediate risk patients (STS score 4–8% or lower with additional comorbidities) [11] demonstrated no difference in the two-year primary endpoint of death and stroke. There were differences in vascular injury (more common with TAVI) and life-threatening bleeding, acute kidney injury and new onset atrial fibrillation (more common with SAVR). Comparison of the results of the major clinical trials, demonstrates that the 30-day mortality benefit gap (MBG) from TAVI to SAVR, falls as the STS score falls (PARTNER 1A [2]: STS 11.75% with MBG 2.8%; CoreValve US Pivotal [4]: STS 7.4% with MBG 1.2%; Partner 2 [11]: STS 5.8% with MBG 0.2%) with equivalent mortality risk of TAVI and SAVR in the lower risk patients. As a result, in April 2016 TAVI received CE mark approval in Europe for those also at intermediate risk. After DRG-based funding was made available in Germany in 2007, the number of TAVI cases increased from 637 in 2008 to 13,264 in 2014 [12] and surpassed SAVR cases in 2013. During this period, with high volumes and increasing experience, German rates of overall complications, surgical conversion to sternotomy and hospital mortality have fallen dramatically. Germany currently performs about 164 cases per million inhabitants annually, whereas Australian TAVI rates in 2016, are similar to that of Germany eight years ago.

The goalposts have moved again and in this issue of Heart, Lung and Circulation Journal (HLC) the technique is now being performed with safety in Europe in even lower risk patients. In the meta-analysis reported in this issue [13], compared to surgical aortic valve replacement (SAVR), short-term follow-up of TAVI patients showed a trend to lower mortality and stroke, with significantly lower risk of bleeding and acute kidney injury, but an increased risk of vascular injury, paravalvular regurgitation and pacemaker implantation. In the only randomised control trial [14] included in the meta-analysis, the mean STS score was only 3.0%, and the TAVI patients also had a larger improvement in effective orifice area and a higher NYHA class at one year compared to patients undergoing SAVR.

The awaited results of three large trials which have included low risk patients (STS score <4%), PARTNER 3, SURTAVI and UK TAVI will be pivotal in confirming the broadened indication.

Although there is increasing evidence for the short-term clinical safety of TAVI in lower risk patients, extension of the procedure to these patients also requires consideration of the following issues:

- Cost effectiveness.
- Long-term valve durability.
- Paravalvular regurgitation and permanent pacemaker requirement.
- Local/Geographical/Political.

Cost-Effectiveness

Despite higher procedural costs with TAVI than SAVR, overall costs with TAVI are offset by reduced ICU and hospital stays and post-discharge residential care. Both balloon expandable and self-deploying TAVI valves have been shown to be cost-effective in high risk populations [3,15–17]. Further improvements in TAVI technology, higher volumes and increased experience, lower complications [18], improved care [19], and reduced costs [20] are all likely to improve cost-effectiveness in the future.

Durability

Extension of TAVI to low risk patients, especially those under 75 years, raises the issue of durability. Long-term results of the first generation balloon expandable Edwards valve from two centres demonstrated almost 50% degeneration (gradient >20 mmHg or AR worsened to at least moderate) at eight years of follow-up, with reduced GFR as the strongest predictor of degeneration [21]. The five-year results of the PARTNER study, however, did not show any significant degeneration. The five- year results of the Italian CoreValve Registry showed only 1.4% device failure, but deterioration beyond five years has been demonstrated with the balloon expandable Edwards valve [22]. Reduced valve mobility has also been reported with the PORTICO valve with the suggestion that this may be secondary to subclinical thrombosis and may be prevented with anticoagulant therapy [23]. This is being investigated in a number of ongoing trials utilising follow-up CT scanning. Deteriorated bioprosthetic valves as small as 21 mm however, have been treated with valve-in-valve TAVI [21,24] and this use has been approved by both US and European regulators.

Paravalvular Regurgitation and Permanent Pacemaker Requirement

A better understanding of the causes of paravalvular aortic regurgitation, a previous major limitation of TAVI, has led to improvements in outcome. Predictors of paravalvular aortic regurgitation include incomplete prosthesis apposition, undersizing or malpositioning. Poor apposition is more frequent in larger and eccentric annuli and calcium nodules in the commissures or TAVI landing zone. Recently developed sealing skirt technology has dramatically reduced this problem. The pacemaker implantation rate is lower with balloon expandable devices and is falling with newer generation valves and higher implant positioning which reduces pressure on the left ventricular outflow tract, but will never be eliminated completely and imposes long-term costs and comorbidities in younger patients.

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