



## PARTNER 3 - the death knell for surgical aortic valve replacement?

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### Introduction

Aortic stenosis (AS) is the commonest valvular abnormality in the western world.[1] Untreated severe aortic stenosis has one-year mortality rates approaching 50%.[2] Historically, the only definitive treatment for aortic stenosis was surgical aortic valve replacement (SAVR) with a mechanical or bio-prosthetic valve.

The first transcatheter aortic valve implantation (TAVI) in humans was performed via an antegrade trans-septal approach on 16<sup>th</sup> April 2002 by Prof Alain Cribier in Rouen, France. This was a "last resort case" in a 57-year-old man with calcific AS and cardiogenic shock who was turned down for surgery. Implantation of a percutaneous heart valve consisting of 3 bovine pericardial leaflets mounted on a balloon implantable stent resulted in significant clinical and echocardiographic improvement.[3] The first transfemoral and transapical procedures followed shortly afterwards in 2005 by Dr John Webb in Vancouver.[4,5]

Since then, a series of landmark trials have established TAVI as a viable and, some would argue, superior alternative to SAVR. Rates of TAVI in the UK have increased significantly year on year, with 3250 procedures performed in the UK in 2016 (up from 2516 the previous year).[6] Major access site complications have fallen to 2% and in hospital mortality has fallen to 1.8%.[6] With same day discharge after TAVI a possibility in some circumstances[7], has the time come for TAVI to be the first line treatment for AS regardless of surgical risk?

### The story so far

Since 2011, the PARTNER investigators have published a series of landmark studies examining the role of TAVI in cohorts of patients with differing surgical risk. The original PARTNER trials compared TAVI against SAVR (PARTNER A) and TAVI against medical therapy (PARTNER B) in high risk surgical patients. TAVI was non-inferior to SAVR with regards to all-cause mortality, albeit with higher rates of stroke and TIA. In patients deemed too high risk for surgery, TAVI was associated with a significant mortality benefit compared with medical therapy.[8,9]

### Take Home Messages

- Aortic stenosis is the commonest valvular abnormality in the Western world.
- TAVI is well established for the management of high surgical risk patients.
- The evidence for TAVI in low risk patients is less clear
- PARTNER 3 suggests that TAVI is a safe and viable treatment for low risk patients with severe aortic stenosis.
- However, there still remains a role for surgical aortic valve replacement.



Thus, the evidence is clear that TAVI is a safe and effective treatment for severe AS in patients with high surgical risk. However, 75% of patients with severe AS fall in the low-intermediate risk categories and it is clear from registry data that implantation of transcatheter devices does occur in this patient population, despite the relative paucity of data.[10]

The PARTNER 2A trial was published in 2016 and compared TAVI with SAVR in patients with intermediate surgical risk [mostly patients with Society of Thoracic Surgeons (STS) risk 4-8%]. The primary endpoint was a composite of death from any cause or disabling stroke at 2 years and the trial showed no difference in the primary endpoint (19.3% for TAVI vs 20.1% for SAVR,  $p=0.33$ ), thus confirming non-inferiority.[11] Similar findings were demonstrated in the SURTAVI trial which also showed non-inferiority of TAVI compared with SAVR. Surgery was associated with higher rates of atrial fibrillation, acute kidney injury and transfusion, while TAVI was associated with higher rates of pacemaker implantation and residual aortic regurgitation.[12]

### **PARTNER 3**

The PARTNER 3 trial was designed to address the issue of whether TAVI was a viable alternative to SAVR in patients with severe symptomatic AS and low surgical risk (defined as STS <4%). This randomised multicentre open label trial enrolled 1000 patients between March 2016 and October 2017. Eligible patients were randomised 1:1 to TAVI with a Sapien 3 system (Edwards Lifesciences, Irvine, CA) ( $n=503$ ) or SAVR ( $n=497$ ). The primary endpoint was a composite endpoint of death from any cause, stroke or rehospitalisation at 12 months. All TAVI procedures were performed through a transfemoral approach.

PARTNER 3 showed a significant reduction in the primary endpoint in favour of TAVI (HR 0.54, CI 0.37-0.79,  $p=0.001$ ), demonstrating superiority against SAVR in this low risk group. On analysis of key prespecified secondary endpoints, there was a significant reduction in new onset atrial fibrillation, length of hospitalisation and death or stroke at 30 days. Rates of moderate or severe paravalvular regurgitation were similar in both groups although rates of mild paravalvular regurgitation were higher in the TAVI arm (29.4% vs 2.1%) [13]

The findings were met with a standing ovation when they were presented at the American College of Cardiology 68th Annual Scientific Session[14], highlighting the potentially game changing nature of this trial.

The results of PARTNER 3 were further strengthened by the publication of the Evolut trial. This randomised 1468 patients in a 1:1 fashion to TAVI with a self-expanding bio-prosthesis (Corevalve, Evolut R, Evolut PRO, Medtronic, Fridley, Minnesota) or SAVR. TAVI was non-inferior to SAVR for the primary composite endpoint of death from any cause or disabling stroke at 24 months.[15]

### **The end of the road for surgical aortic valve replacement?**

Despite PARTNER 3's undoubtedly exciting message, there are a number of limitations with the trial design that need to be considered. Firstly, it is important to consider the choice of composite endpoint. Previous PARTNER trials and other trials of TAVI such as SURTAVI have used harder composite endpoints of death or stroke.[8,11,12] In PARTNER 3, the significance of the primary endpoint was driven primarily by a reduction in rehospitalisation in the TAVI arm (7.5% vs 11%, HR 0.65 CI 0.42 to 1).



Rehospitalisation was lower with TAVI at both 30 days and 12 months. The choice of rehospitalisation potentially biases against SAVR, given that rehospitalisation is more likely to occur after surgery due to the increased risk of short-term complications. However, rehospitalisation represents an important source of morbidity, and one that most patients are likely to want to avoid.

Secondly, only one-year outcomes are reported here. With low risk patients, TAVI valves are implanted in generally younger patients who have a longer life expectancy. In this population, valve durability is an important consideration. Data are limited on valve durability post-TAVI, which is understandable given the relative novelty of the technique. 5 year data from the original PARTNER study showed that moderate or severe aortic regurgitation was more common in the TAVI arm, and was associated with lower survival.[16] However, more recent data from the UK TAVI registry showed that 91% of patients were free from structural valve dysfunction (SVD) at 5 years.[17] This compares with rates of SVD for SAVR as low as 1.3% reported in a single centre series of 1000 patients using the Carpentier-Edwards bio-prosthesis.[18] Longer term follow-up is needed to assess the prevalence and significance of TAVI SVD in the younger population studied in PARTNER 3. Continued clinical and echocardiographic follow-up out to 10 years is planned to address this question.

Thirdly, patients with bicuspid aortic valves (BAV) were excluded from the PARTNER 3 trial.[13] However, patients with BAV are disproportionately represented among younger low risk patients with AS.[19] Although some studies have reported reasonable success rates with TAVI for bicuspid valves, it is recognised that intervention is technically more challenging than on a tricuspid valve.[20] Until techniques for TAVI are refined for the BAV population, its utility in low risk patients is somewhat limited.

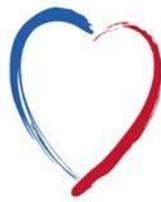
## **Conclusion**

TAVI is rapidly asserting itself as the optimal treatment for severe aortic stenosis. Despite the undoubtedly positive results of PARTNER 3, further evidence addressing the safety and long-term durability of TAVI prostheses in low risk patients is required before it becomes the default treatment for this condition. In addition, SAVR will continue to play a key role in patients with complex aortic valve anatomy or those who need concomitant coronary revascularisation by means of coronary artery bypass grafting.



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