Transcatheter verus Surgical Aortic Valve Replacement – what does the latest evidence tell us?

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The ongoing uncertainty about the place of transcatheter aortic valve replacement (TAVR) was informed by emerging evidence presented in part at the American College of Cardiology meeting (16th to 18th March 2019 New Orleans) and in the New England Journal of Medicine. Edward Scientific's PARTNER 3,[1] and Medtronic's Evolut Low Risk Trial (LRT)[2] trials, were both simultaneously presented and published in NEJM.

Short term TAVR versus SAVR in low surgical risk patients – Is it the end of the road for SAVR?

PARTNER 3[1]

The 1 year results of the PARTNER 3 trial comparing TAVR and surgical aortic valve replacement (SAVR) in low surgical risk patients (STS PROM <4%) with severe aortic stenosis suitable for TAVR are now available.[1] The trial reports 1 year superiority in the composite of any stroke, hospitalisation related to the procedure, the valve or heart failure, or all cause mortality for TAVR (hazard ratio (HR) 0.54; 95% CI 0.37 to 0.79; p=.001). He also reported that follow up is planned out to 10 years; a welcome development for an area which has been challenged by short follow up in randomised trials. 503 patients were randomised to TAVR and 497 to SAVR, with 496 and 454 respectively included in an *as treated* analysis, a differential loss to follow up that is highly statistically significant (p<.0001). Many regulatory device trials continue to be analysed in a biased way (per protocol analysis undermines the protection of randomisation). It is a misconception that per protocol analyses are required for non-inferiority trials. ICH E9 (the relevant guidance in Good Clinical Practice for pharmaceutical trials) states of the use of the 'per protocol' analysis set that 'the bias, which may be severe, arises from the fact that adherence to the study protocol may be related to treatment and outcome'. [3]. A limited intention to treat population analysis was reported (for the primary analysis only) demonstrating a modest attenuation of effect. However the differential loss to follow up points to the recruitment of patients who are not actually considered suitable for either intervention and thus is a source of bias. Hospitalisation related to the procedure is not a helpful component of the primary outcome (particularly as it was not required that this hospitalisation was unplanned as would be normal practice in composite outcomes[4]). Fortunately, the data were presented enabling the analysis of components of the composite.

PARTNER 3[1] also randomised using a small block size (4 patients) stratified by site, which makes the next allocation quite predictable given knowledge of previous allocations within a site.[5] Where there are 71 sites, guidance is clear that such stratification is unhelpful [3]. There is evidence from the baseline characteristics that PARTNER 3 may have been subject to selection biases undermining the randomisation, with a significant difference in the proportion of patients with NYHA Class III / IV heart failure, (P=.01) with more severe patients in the TAVR group. PARTNER 3 broke with good methodological practice by asking an unblinded endpoints committee to adjudicate potential outcomes in the knowledge of the treatment assignment, although objective outcomes such as mortality will not be affected by this limitation.

Concomitant procedures were undertaken in 7.9% of subjects in the TAVR group, and 26.4% of subjects in the SAVR group, with revascularisation performed in 6.5% and 12.8% respectively. 6.6% of TAVR and 4.1% of SAVR patients with no pacemaker at baseline required a new permanent device. While similar at baseline, TAVR was associated with a significant -0.1cm^2 reduction in Aortic value area at 30 days and 1.5 mmHg increase in mean gradient which were both maintained at 1 year. TAVR was also associated with a statistically significant 7.4% higher ejection fraction at 30 days which was reduced but still significant at 1 year. The numbers with moderate or severe paravalvular

regurgitation at 30 days and 1 year were small for TAVR and SAVR (30 days: TAVR=0.82% SAVR=0.0% p = 0.08; 1 year: TAVR=0.64% SAVR 0.52% p = 0.85). However there was a substantially higher percent of subjects with mild or greater paravalvular regurgitation at 30 days and 1 year treated with TAVR (30 days: TAVR= 29.6% SAVR=2.9% p<0.0001; 1 year: TAVR= 30.0% SAVR=2.6% p<0.0001). By contrast there was substantially more new onset atrial fibrillation at 30 days and 1 year among SAVR patient (30 day: TAVR=5.0% SAVR=39.3% p<0.0001; 1 year: TAVR=7.0% SAVR=40.7% p<0.0001).

Evolut Low Risk Trial[2]

The short term results of the Evolut LRT which included patients with an expected mortality risk 30 days after surgery <3%, have been reported.[2] Evolut LRT[2] claims a 2 year follow-up, but in fact median follow up was only 12.2 months, and only 9.3% of randomised patients actually reached the 2 year follow-up. Evolut LRT appears to have avoided some of the pitfalls of PARTNER 3,[1] judging outcomes blind where possible, although the primary analysis was still undertaken '*as treated*'. The authors described the ITT results fully, enabling an appropriate analysis of these data. However although 734 patients were randomised to each treatment group there was again an imbalance with regards to differential drop out when forming the *as treated* population, with 9 not receiving TAVR and 56 not receiving SAVR (p<.0001). Such imbalances indicate that the selected population are strong candidates for TAVR but less strong for SAVR. Where the loss is due to patients withdrawing consent, strategies such as employing a second pre randomisation consent a few days after the first consent have been employed successfully [6], and it is unfortunate that regulatory trials in this space continue to experience largely avoidable biases. The primary outcome was the difference in the composite of disabling stroke and all-cause mortality, expressed on an absolute percentage scale, with an observed -1.4% rate in the TAVR group compared with the SAVR group (95% CL -4.9% to 2.1%) which firmly excluded the rather large non inferiority threshold of 6% and thus was declared non inferior. In Evolut LRT there was no apparent relationship between NYHA category and treatment group (p=0.13).

6.9% of TAVR patients received concomitant or staged percutaneous coronary intervention. 13.6% of SAVR patients received CABG. There was a significant imbalance in the proportion of patients having a permanent pacemaker fitted (19.4% versus 6.7%; p < 0.0001).

TAVR was associated with a statistically significant 0.2 cm^2 increase in Aortic valve area at 30 days which was maintained at 1 year, and among those for whom 2 year results were available. Similarly TAVR was associated with a statistically significant -1.9 mmHg change in Aortic Valve Gradient, which slightly increased at 1 year and among evaluable patients at 2 years. Treatment with TAVR was associated with a systematic increase in paravalvular leak across all classes at 30 days and 1 year (P<0.0001), illustrated by the increase in patients with mild or greater paravalvular leak (30 days: TAVR=39.4% SAVR=3.3%; 1 year: TAVR=37.6% SAVR=3.3%). There substantially higher atrial fibrillation among patients treated with SAVR compared to TAVR at 30 days and 1 year (30 days: TAVR=7.7% SAVR=35.4% p<0.0001; 1 year: TAVR=9.8% SAVR=38.3% p<0.0001).

Evolut LRT also plans to provide 10 year follow up.

What do these trials add?

PARTNER 3[1] and Evolut LRT[2] add important information on the short term effects of TAVR compared with SAVR with mean follow up in each of around a year. Both trials, and in particular PARTNER 3, should be congratulated in delivering TAVR with maximum efficiency.

As both trials provide short term evidence on mortality and disabling stroke, this can be combined with the findings from the two other recent trials of modern TAVR technology in intermediate surgical risk patients (SURTAVI[7] PARTNER 2[8]) for those outcomes, which are described in Figure 1.

For disabling stroke, there is a modestly significant reduction among patients randomised to TAVR in the low risk trials and in the combined analysis, but not in the intermediate risk trials. Event rates in both treatment groups are substantially reduced in the low risk patients as expected.

For all-cause mortality the low surgical risk trials add very little to the information from the intermediate risk studies, providing no convincing evidence of a difference in short term mortality for either approach but with considerable uncertainty remaining.

It is notable that incidence of permanent pacemakers in PARTNER 3[1] was only modestly raised, although this was substantially increased in Evolut LRT,[2] a finding which replicated those in SURTAVI[7] and PARTNER 2[8] (see Figure 2). PARTNERS 3[1] and Evolut LRT[2] demonstrate that, in highly skilled hands, TAVR can be delivered to carefully selected patients who experience a less invasive procedure with a shorter recovery time, and probably benefit from a modest reduction in the risk of disabling stroke compared to SAVR. There were differences in concomitant procedures in both trials among patients receiving SAVR and some modest and consistent echocardiographic differences between the groups. The major limitation for policy currently is the very short follow up; the regulatory requirement for a 10 year follow up is coherent, and reflects the outlook of a low risk population. So we should anticipate future updates on the progress of these cohorts of patients which can, in time, influence practice (a 5 year time frame for an interim update would be informative), but at this stage there is little evidence to support a switch to TAVR from patients who would otherwise have been selected for SAVR, with 6 year follow up available for just one small randomised trial of 274 patients.[9] It can be hoped that future updates will include an intention to treat analysis as this approach is what will best inform practice. That is a comparison of a strategy to utilise TAVR compared with a strategy to utilise SAVR. Further, given observations such as the variation in new pacemaker use between treatments and trials, and other differences in echo parameters between treatments, it will be important for practice to monitor carefully the outcomes among patients treated in real world practice including considering any effects of volumes on outcomes.

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