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Trans-femoral TAVI is superior to SAVR in elderly high risk patients with symptomatic severe aortic stenosis !

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Trans-femoral TAVI is superior to SAVR in elderly high risk patients with symptomatic severe aortic stenosis !

Neil Moat and Stephen Brecker

When transcatheter aortic valve implantation (TAVI) was first introduced, it was tested in clinical trials as a strategy against the gold-standard treatment for symptomatic severe aortic stenosis, namely surgical aortic valve replacement (SAVR)(1,2). Two first generation valves (the Edwards Sapien Valve and Medtronic CoreValve) were studied in high surgical risk patients. In Cohort A of the PARTNER Trial, that TAVI should be non-inferior to surgery was seen as a major achievement for a first generation valve (1). That TAVI might have superior outcomes to surgery, as suggested in the US PIVOTAL CoreValve Trial High Risk Cohort , was a surprise to many (2). Most commentators questioned "How did TAVI get so good?". The US Pivotal Trial was the first TAVI trial to mandate rigorous CT angiography pre-case planning, and changed practice as a result. It was carried out in the highest performing North American centres, with surgeons and interventionists of impeccable pedigree, and experienced proctors supervised many of the implants. Whilst it was clear that second generation valves would be even better, the question remained if other trials would have similar findings.

In this edition of the Journal, Siontis and colleagues present a meta-analysis of four trials comparing TAVI with SAVR, comprising over 3000 patients (3). They have added two further trials, the NOTION Trial (the only completed TAVI vs SAVR trial outside of North America), and the first TAVI Trial in a slightly less high risk patient population, PARTNER 2A in which patients were randomised to receive either the second generation SAPIEN XT valve or SAVR).. The PARTNER 2A Trial suggested that benefits were greatest in those receiving a transfemoral approach, and that there was little benefit of TAVI over surgery in those having transthoracic access. The Notion trial was very small and only contributes 7% of patients in this meta-analysis. PARTNER 2A included patients who fell within the highest decile of risk were they to undergo SAVR whilst the prior US trials recruited an even higher risk patient cohort. Thus this meta-analysis essentially relates to an elderly and relatively high risk patient population and must be interpreted as such.

One could be critical about a meta-analysis of only four trials in patients of varying risk categories, different valves, and with trials that were only powered to test non-inferiority.The findings are nevertheless compelling. The analysis demonstrates a consistency of benefit of TAVI over SAVR through two years of follow up, with benefits particularly marked in those undergoing a transfemoral as opposed to transthoracic approach, and, intriguingly, in females. This latter point is important for a number of reasons. TAVI is one of the only cardiac interventions where females enjoy greater benefits over their male counterparts, and this appears to be reflected in clinical decision making as well, as females are now the majority in many TAVI real-world registries. Interventional cardiologists are used to females representing a higher risk subset of patients, with small vessels and anatomy, higher frailty scores, and higher rates of vascular complications (4,5). It is clear that the differential risk of females undergoing cardiac surgery must be even greater.

That transfemoral access TAVI appears to show greater benefits over surgery compared to non-transfemoral access should come as no surprise as this has been suggested in all TAVI Registries. However the choice of access is non-random with the non-transfemoral cohort having higher risk scores, more frequent co-morbidities and a greater burden of vascular disease. It is not clear how much of the adverse outcomes in the trans-thoracic cohort are due to the above clinical risk factors and how much is due to the thoracic access per se. This study confirms the trend shown in PARTNER 2A that there is little benefit of transthoracic TAVI over SAVR in these patients. However, with newer delivery systems, over 95% of patients are likely to be suitable for trans-femoral access. It is not known what the outcomes will be in those patients who previously would have required a trans-thoracic approach when treated transfemorally.

This study, reassuringly, suggests that the benefit of TAVI is a class effect rather than device specific. Perhaps the point of greatest reflection however, is that paravalvar leaks and pacemaker implantation, neither completely benign, are higher in the TAVI group. These complications will also become much more relevant and of more clinical concern as TAVI moves into younger and less high risk patients. Given that this study only considered benefits out to two years, these potential disadvantages of TAVI cannot be ignored and may draw together survival curves together with longer follow up. Interestingly, the recently published 3 year data from

the US CoreValve trial showed a diminution in the delta between the TAVI and SAVR arms to a point where it did not reach significance (P=0.07 (6). However this may just be due to the reduced number of patients at risk by 3 years. The pattern of the survival curves seems constant across all the trials. That is to say that there is an excess mortality in the SAVR cohorts with increasing separation of the curves out to approximately 90 days following which the curves appear to match one another.

Another interesting observation in this analysis was a trend for endocarditis to be more common following TAVI. This is worthy of note and ongoing evaluation. Initial impressions were that TAVI would be associated with less prosthetic valve endocarditis due to the absence of a sewing ring. It might be that the crushed native valve tissue, or indeed the sealing skirts of latest generation transcatheter valves could be a potential nidus for infection.At this time, data on transcatheter valve durability is limited. Anecdotally there is no "fatal flaw" or early degeneration being detected. However some studies have suggested higher rates of subclinical degeneration in the medium term (five to six years post implant) than one would expect with contemporary surgical xenografts. It will be important to monitor these studies, and undertake meta-analysis of studies out to five years and beyond. It also demonstrates the need to have a follow up far beyond 5 years in future/ongoing trials comparing TAVI and SAVR in younger and lower risk patients.

In the discussion there are detailed descriptions of the on-going evolution of the TAVI procedure and trans catheter technologies which might be expected to further improve clinical outcomes in this cohort. It should be noted that surgical approaches are also evolving in ways that might improve patient outcomes. This includes the use of stentless and sutureless valves and the growth of minimal access SAVR. In all of the trials, SAVR was almost exclusively conducted with standard stented bioprostheses. Many of these (in the region of 40-50%) were of a small label size (19-21) which have an unfavourable haemodynamic performance and a significant incidence of patient-prosthesis mismatch. This is known to adversely effect long term outcomes ref. Thus an important message for surgeons undertaking SAVR in the contemporary (lower risk) trials is to adapt the initial implant to minimise the risk of patient prosthesis mismatch in the surgical arm so as to optomise and potentially improve the outcome of that cohort.

For high risk (e.g. STS score >5), elderly female patients eligible for a transfemoral approach, the pendulum has swung unequivocally in the TAVI direction. For a similar male patient, who is not suitable for a transfemoral approach, there would appear to be a degree of equipoise and the Heart Team should reconsider SAVR as an option. The results of this meta-analysis of elderly and high risk patients (in whom durability, pacemaker rates and paravalvar leak are of no great import) strongly favour TAVI. However these results cannot be applied, at the present time, to those patients who are younger and at a lower risk from SAVR. Currently over 90% of patients who undergo SAVR fall into this "lower risk" cohort. Thuse the results of other intermediate risk (SURTAVI), lower risk (UK TAVI) and low risk (NOTION2, and the US FDA low risk trials with both Sapien Sapien 3 and CoreValve EvolutR) will be neneded before therei is a clear evidenmce base to extend TAVI into these populations.

References

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010; 363:1597.
2. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014; 370:1790.
3. SIONTIS EHJ

4. Claessen BE[1], Chieffo A, Dangas GD, Godino C, Lee SW, Obunai K, Carlino M, Chantziara V, Apostolidou I, Henriques JP, Leon MB, Di Mario C, Park SJ, Stone GW, Moses JW, Colombo A, Mehran R; Multinational CTO Registry. Gender differences in long-term clinical outcomes after percutaneous coronary intervention of chronic total occlusions. J Invasive Cardiol. 2012 Oct;24(10):484-8.

5. Ahmed B, Dauerman HL.Women, Bleeding, and Coronary Intervention. *Circulation. 2013; 127: 641-649*

6. Deeb GM1, Reardon MJ Gleason TG 3 Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016 Jun 7;67(22):2565-74. doi: 10.1016/j.jacc.2016.03.506. Epub 2016 Apr 3.

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