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TAVR in low risk severe AS has landed: what remains uncertain?

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Take Home Messages

- The first randomized controlled trials of transcatheter aortic valve replacement (TAVR) versus surgical AVR (SAVR) in 'low risk' severe AS are here.
- PARTNER 3 (n = 950) showed superiority for the primary endpoint (all-cause mortality, stroke or rehospitalization at 1 year) with transfemoral TAVR.
- Evolut LR (n = 1403) showed noninferiority for the primary endpoint (all-cause mortality or disabling stroke at 24 months) in the TAVR group, but median follow-up was 12.2 months.
- Both trials found reduced 1-year rates of new-onset atrial fibrillation with TAVR.
- Remaining areas of uncertainty include: the long term impact of paravalvular regurgitation and PPM implantation, optimal strategies for pre-procedure risk assessment, cerebral embolic protection, antithrombotic therapy, screening for valve thrombosis, and peri-procedural coronary revascularization.

Introduction

Since the first human transcatheter aortic valve replacement (TAVR) case (Cribier *et al.*, 2002), the pool of patients with severe symptomatic aortic stenosis (AS) eligible to benefit from TAVR has expanded, with successive trials indicating benefit initially versus conservative management in prohibitive (extreme) surgical risk patients (Leon *et al.*, 2010; Popma *et al.*, 2014; Kapadia *et al.*, 2015), and then noninferiority versus surgical aortic valve replacement (SAVR) in high risk (Smith *et al.*, 2011; Adams *et al.*, 2014; Mack *et al.*, 2015; Deeb *et al.*, 2016; Gleason *et al.*, 2018), intermediate risk (Leon *et al.*, 2016; Reardon *et al.*, 2017), and intermediate-low risk (Thyregod *et al.*, 2015; Søndergaard *et al.*, 2019) patients. These findings were supported by the SAPIEN 3 observational study of intermediate-risk patients (Thourani *et al.*, 2016). In the last two weeks, two independent randomized trials reported non-inferior or superior two-year outcomes in low risk patients receiving TAVR when compared to SAVR (Mack *et al.*, 2019; Popma *et al.*, 2019). As 80% of patients who underwent isolated SAVR between 2002-2010 were at low risk (Thourani *et al.*, 2015), their implications will likely be seen as historic. It is therefore a good time to take stock of where this leaves us.

First, a note on interpreting the terminology of risk. 'Prohibitive', 'high', 'intermediate' and 'low' surgical risk are terms that reference conventional surgical risk scores such as Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) (O'Brien *et al.*, 2009, 2018) and Euroscore II (Nashef *et al.*, 2012) (Table). These categories have been used to guide eligibility for trials of SAVR versus TAVR in severe symptomatic AS. Very high, high, intermediate and low risk refer to STS risk scores of operative mortality

(defined as in-hospital mortality regardless of timing or 30-day mortality regardless of venue) of >15%, >10%, 4-10% and <4% respectively (Kappetein *et al.*, 2012), although trials have not observed these cutpoints strictly. Importantly, these scores were designed for SAVR, not TAVR, and do not incorporate factors relevant to TAVR case selection such as favourable transfemoral access, porcelain aorta, frailty, and functional disability (Hermiller *et al.*, 2016). Nor do they incorporate operator or hospital experience. Second, improvements in surgical technique, anaesthesia and critical care have resulted in improved outcomes post SAVR such that subjects judged high risk in 2009 would be reclassified as intermediate risk in 2015 (Rogers *et al.*, 2017). Third, these risk scores set left ventricular ejection fractions (LVEFs) >0.50 to 0.50 (Table 3 in O'Brien *et al.*, 2009). As pressure overload may result in concentric remodelling, which mandates higher LVEFs to preserve LV stroke volume (Aurigemma *et al.*, 1995), these risk scores are blind to the risk incurred by borderline LVEFs (0.50-0.59) in severe AS (Ito *et al.*, 2018; Lancellotti *et al.*, 2018; Bohbot *et al.*, 2019). (For the relevance of borderline LVEF to risk assessment in AS, see my editorial of 31 Jan 2019).

Risk category	STS estimated operative mortality
Prohibitive	> 50%
Very high	> 15%
High	> 10%
Intermediate	4-10%
Low	<4%

Table 1. *Surgical risk categories referencing conventional surgical risk scores such as Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), defined as in-hospital mortality regardless of timing or 30-day mortality regardless of venue* (O'Brien *et al.*, 2009, 2018; Kappetein *et al.*, 2012).

Low Risk TAVR Trial

Besides the NOTION trial, which accepted patients with a range of risk levels, of whom 82% were low risk (Thyregod *et al.*, 2015), the first prospective evaluation of TAVR in low risk patients with symptomatic severe AS was the Low Risk TAVR trial (Waksman *et al.*, 2018). This was a single-arm, unblinded, multicentre feasibility trial of 200 low risk patients with severe symptomatic AS (age (mean ± SD) 74 ± 6, STS-PROM score 1.8 ± 0.5%, LVEF 64 ± 8%) compared with 719 historical controls (age 70 ± 8, STS-PROM score 1.6 ± 0.6%, LVEF 59 ± 9%) who underwent SAVR at the same institutions. The **primary endpoint** was all-cause mortality at 30 days. TAVR procedures were transfemoral and used either the balloon-expandable Sapien 3 (Edwards, 88%) or the self-expanding CoreValve, Evolut R or Evolut PRO (Medtronic, 12%). 59.4% of SAVR patients received valves sized ≥ 23 mm, compared with 95.5% of TAVR patients. TAVR was safe, with zero mortality and disabling stroke at 30 days, compared with 1.7% 30-day mortality in the SAVR group. Rates of new PPM implantation (6.5%) and > mild

paravalvular leak (0.5%) at 30 days were lower than all other major TAVR studies. However, subclinical leaflet thrombosis (by CT or TOE), i.e. hypo-attenuating leaflet thickening, was observed in 14.0% at 30 days.

PARTNER 3 trial

This was a multicentre randomized controlled trial comparing transfemoral TAVR with a third generation balloon-expandable SAPIEN 3 valve (Edwards) with SAVR in low risk patients (STS PROM < 4%) with severe AS and conventional indications for intervention (Mack *et al.*, 2019). There were multiple **exclusion criteria**, the most salient of which were: unicuspid or bicuspid aortic valves, native aortic annulus unfavourable for valve sizes 20, 23, 26, or 29 mm, unfavourable iliofemoral access, unsuitable aortic anatomy, myocardial infarction within 30 days, severe aortic or mitral regurgitation, prior valve prosthesis, complex coronary disease, LVEF < 30%, haemodynamic instability, stroke/TIA within 90 days, significant frailty, and life expectancy < 24 months. Patients received aspirin and clopidogrel before TAVR and continued these for at least one month post procedure. The **primary endpoint** was a composite of all-cause mortality, stroke or rehospitalization (for the procedure, valve or heart failure) at 1 year. The primary analysis was performed in the 496 of 503 patients assigned to TAVR and 454 of 497 assigned to SAVR who received the assigned procedure and comprised the as-treated population.

TAVR patients had similar ages (73.3 ± 5.8 vs 73.6 ± 6.1% in SAVR patients), STS scores (1.9 ± 0.7% versus 1.vs ± 0.6%), aortic valve areas (AVAs) and LVEFs (65.7 ± 9.0 vs 66.2 ± 8.6%), but were more likely to be in NYHA III-IV (31 vs 24%). TAVR patients were more likely to receive valves sized ≥ 23 mm (97.8 vs 79.9%) and less likely to receive concomitant coronary revascularization (6.5 vs 12.8%). The primary endpoint (TAVR vs SAVR) was met in 8.5 vs 15.1% (hazard ratio 0.54, 95% CI 0.37-0.79, p = .001 for superiority). Sensitivity analyses and subgroup analyses were consistent with this finding. All components of the primary endpoint saw a reduction in the point-estimate: all-cause mortality (HR 0.41, 95% CI 0.14-1.17), stroke (HR 0.38, 95% CI 0.15-1.00), and rehospitalization (HR 0.65, 95% CI 0.42-1.00). TAVR also was associated with lower rates at 30 days of stroke (HR 0.25, 95% 0.07-0.88), death or stroke (HR 0.30, 95% CI 0.11-0.83), new-onset atrial fibrillation (HR 0.10, 95% CI 0.06-0.16), and life-threatening or major bleeding (HR 0.12, 95% CI 0.07-0.21) and shorter index hospitalisation (3 vs 7 days). Aortic valve orifice area (mean ± SE) at 1 year was similar between groups (1.7 ± 0.02 vs 1.8 ± 0.02 cm^2). Unlike in previous major trials, there were similar rates at 1 year of major vascular complications (2.8 vs 1.5%), coronary artery obstruction (0.2 vs 0.7%), more than mild paravalvular regurgitation (0.6 vs 0.5%), and PPM implantation (7.5 vs 5.5%). TAVR patients were more likely to have LBBB at 1 year (23.7 vs 8.0%) and less likely to have new-onset atrial fibrillation (7.0 vs 40.9%).

The superiority of TAVR was not related to worse-than-expected performance in the SAVR group: 30-day mortality was lower than predicted in both groups (0.4 vs 1.1%). The findings depended on the use of experienced operators and centres; the relative excess of stroke, major vascular complications, more than mild paravalvular leak and pacemaker implantation versus SAVR in the early trials was not observed. The authors

noted limitations including unblinded adjudication of endpoints and no reporting of rates of asymptomatic valve thrombosis, although a subset of each group underwent serial CT angiography as part of a subtrial (to be reported).

Evolut Low Risk Trial

This was a multicentre randomized controlled trial comparing TAVR with a self-expanding CoreValve (3.6%), Evolut R (74.1%) or Evolut PRO (22.3%) valve (Medtronic) with SAVR in low risk patients (STS PROM < 3%) with severe AS and conventional indications for intervention (Popma *et al.*, 2019). **Exclusion criteria** were similar to those in PARTNER 3 and included bicuspid aortic valve and aortopathy, SYNTAX score > 22, and need for a mechanical valve. Randomization was stratified by need for coronary revascularization. The **primary outcome** was all-cause mortality or disabling stroke at 24 months. The analysis was performed in 725 of 734 patients assigned to TAVR and 678 of 734 assigned to SAVR on an as-treated basis. Patients not completing 24 months of follow-up for this publication had their outcome imputed based on their last known clinical status; for this first publication, median follow-up was 12.2 months; 12 and 24 month follow-up were available in 432 vs 352 (TAVR vs SAVR) and 72 vs 65 patients respectively.

TAVR patients had similar ages (74.1 ± 5.8 vs 73.6 ± 5.9), STS-PROM (1.9 ± 0.7 vs 1.9 vs 0.7%), AVAs, LVEFs (61.7 ± 7.9 vs 61.9 ± 7.7%) and comorbidities compared with SAVR patients. 22% of SAVR patients received 19 or 21 mm valves; TAVR valve sizes are not directly comparable as the self-expanding valves are supra-annular. The primary endpoint was met in 5.3 vs 6.7%, meeting the prespecified criteria for noninferiority but not superiority. Similar results were found on intention-to-treat analysis and sensitivity analyses. There were no significant between-group differences in components of the primary endpoint estimated at 24 months (all-cause mortality (4.5 vs 4.5%) and disabling stroke (1.1 vs 3.5%)). 30-day all-cause mortality was similar between groups (0.5 vs 1.3%). The 30-day composite safety end point (death, disabling stroke, life-threatening bleeding, major vascular complication, stage 2 or 3 acute kidney injury) was reduced in the TAVR group (5.3 vs 10.7%). At 1 year, TAVR was associated with larger effective orifice areas (2.3 ± 0.7 vs 2.0 ± 0.6 cm^2), less patient-prosthesis mismatch (1.8 vs 8.2%), reduced new-onset atrial fibrillation (9.8 vs 38.3%) and rehospitalization for heart failure (3.2 vs 6.5%), increased rates of PPM implantation (19.4 vs 6.7%) and more than mild paravalvular regurgitation (3.6 vs 0.6%), and similar rates of major vascular complication (3.8 vs 3.5%), coronary artery obstruction (0.9 vs 0.4%) and valve thrombosis (0.2 vs 0.3%). The most notable limitation was that the median follow-up was only 12.2 months, so that 24 month outcomes in most patients were estimated rather than observed.

Ongoing TAVR trials and areas of uncertainty

An ongoing trial in low risk patients is NOTION-2 (NCT02825134), whose primary endpoint is a composite of all-cause mortality, myocardial infarction and stroke within 1 year. This trial excludes patients age >75 and bicuspid valve with aorta ≥ 45 mm. Other trials are testing unconventional indications for AVR: moderate AS with impaired LV function (TAVR UNLOAD (NCT02661451)), asymptomatic severe AS with a negative

treadmill stress test (EarlyTAVR (NCT03042104)), and asymptomatic severe AS with mid-wall fibrosis on MRI (EvoLVeD (NCT03094143)).

Several caveats remain before recommending TAVR whole-heartedly in low risk populations. In younger, more active, populations, longer term outcomes assume greater priority: valve efficacy, durability, freedom from infection, valve thrombosis and PPM implantation, and cardiac prognosis. Both PARTNER 3 and Evolut Low Risk Trials have prespecified 10 year follow-up, yet only 2- and 1- year follow-up has been reached in most patients to date. The significance over longer term follow-up durations of more than mild paravalvular regurgitation (which increased 2-year mortality in PARTNER 2 (Leon *et al.*, 2016)) or of increased LBBB (which would be expected to impair LV functional recovery) is not yet fully appreciated, and rates of TAVR thrombosis still unknown. If the procedure is to become more widespread in low risk patients, operators should also be more experienced, with one author recommending at least 100 TAVR procedures per operator before starting low risk patient programmes (Sousa Uva, 2019). Furthermore, the optimal strategies for pre-procedure risk assessment, cerebral embolic protection, antithrombotic therapy, screening for valve thrombosis, and peri-procedural coronary revascularization are still under investigation. Younger patients with bicuspid aortic valves with or without concomitant aortopathy are notably excluded from TAVR trials and are less likely to benefit from TAVR, as they experience higher rates of aortic regurgitation and vascular complications. Although rates of bioprosthetic valve dysfunction were comparable (56 vs 67% in TAVR and SAVR respectively) at 6-year follow-up of NOTION-1 (mean entry age 79.4 vs 78.8), these rates will not be reassuring to patients in their early 70s, and while TAVR is a good solution in failing surgical bioprotheses, far less data is available for the feasibility and safety of TAVR in failing TAVR.

These three studies therefore do not close the chapter on managing low risk severe AS: they increase both the options available and the uncertainties.

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