

Can we still learn from single center experience after PARTNER?

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Abstract

With the publication of the Placement of Aortic Transcatheter Valves (PARTNER) trial, transcatheter aortic valve replacement (TAVR) has undoubtedly become the gold standard for severe aortic stenosis in patients that are not suitable candidate for surgical aortic valve replacement (AVR). The PARTNER trial also showed that TAVR is non-inferior to AVR in high-risk patients. A recent publication by Ben-Dor *et al* evaluated the outcome of high-risk patients with severe aortic stenosis who were referred to their institution for participation to the PARTNER trial. Only a minority of patients made it in the trial and the majority of patient ended being treated medically. Some patients were also treated with AVR outside the trial. The outcomes of all these patients were stratified by the treatment they received (AVR, TAVR or medical therapy with or without balloon aortic valvuloplasty). The 3 groups were different in their baseline characteristics. Ben-Dor *et al* found that patients treated medically had greater mortality than patients treated with TAVR or AVR. The survival of patients treated with TAVR was similar to those treated with AVR. Independent predictors of mortality were also found from their analysis. In this commentary, we discuss the finding of this study and compare it with

COMMENTARY ON HOT TOPICS

We have read with great interest the recent manuscript by Ben-Dor *et al*^[1] evaluating the outcome of high-risk patients with severe aortic stenosis (AS) referred to their institution for a trial of transcatheter aortic valve replacement (TAVR) stratified by the treatment they received, and believe it is worth discussion. Symptomatic severe AS is a deadly and incapacitating disease when left untreated. For many decades, surgical aortic valve replacement (AVR) has been considered the treatment of choice because of its ability to improve survival and symptoms. It was however shown that approximately one third of patients with severe symptomatic AS do not benefit from AVR because of multiple of reasons^[2]. Balloon aortic valvuloplasty (BAV), although less invasive than AVR is only palliative. More recently, TAVR has been shown to be superior to medical therapy (including BAV) in patients that are not candidate for AVR^[3] and to be non-inferior to AVR in high-risk patients^[4].

Ben-Dor *et al*^[1] reviewed 900 patients who were referred for TAVR evaluation (PARTNER trial) between April 2007 and May 2011. These patients had severe AS defined by a mean gradient ≥ 40 mmHg or valvular area < 1 cm². Only 13% ($n = 19$) of AVR and 4.9% ($n = 29$)

of medically treated patients were enrolled in the PARTNER trial. The PARTNER trial as been described in details^[3,4] but in summary consisted of two parallel studies. The cohort A consisted of patients at high-risk for AVR (risk of 30-d mortality $\geq 15\%$) that were randomized to TAVR (from a trans-femoral or trans-apical approach) *vs* AVR. The cohort B included patients that were deemed non-operative based on an estimated risk of mortality or major irreversible morbidity of $\geq 50\%$; which were randomized to TAVR *vs* medical therapy (including possible BAV). Ben-Dor *et al*^[1] evaluated the outcomes of patients treated in their institution stratified by the treatment they received. Medical treatment was adopted in 66.1% of patients ($n = 595$), among whom 345 patients also had BAV, 17.6% ($n = 159$) had TAVR and 16.3% ($n = 146$) had AVR. Groups were significantly different in their baseline characteristics with younger and healthier patients undergoing AVR and sicker patients with lower ejection fraction and higher BNP value in the medical treatment group. The STS score was significantly different across groups with values of 8.5%, 11.8% and 12.1% for AVR, TAVR and medical treatment respectively ($P < 0.001$). The transcatheter heart valve (THV) used for TAVR was the Edwards SAPIEN THV (Edwards Life Sciences, Irvine, CA, United States). A trans-femoral (TF) approach was used in 69.1% ($n = 110$) of cases and a trans-apical (TA) approach in 30.9% ($n = 49$).

In their study, Ben-Dor *et al* found a 1-year mortality of 21.2%, 21.3% and 36.4% for patients treated with TAVR, AVR and medical therapy respectively ($P < 0.001$). In the medical therapy group, patient who had a BAV performed had higher mortality (55% *vs* 34%, $P < 0.01$). Thirty-day mortality was 11.7%, 12.8% and 10.1% for TAVR, AVR and medical therapy respectively. The STS score predicted 30-d mortality was 11.8%, 8.4% and 12.3% while the logistic Euroscore predicted 41.2%, 25.6% and 43.1% for TAVR, AVR and medical therapy respectively. Patients with STS score ≥ 15 had a significantly greater mortality (59.2%) compared with those with STS score < 15 (35.2%). In the entire cohort, atrial fibrillation and renal failure were found to be independent predictor of mortality. When stratified by the treatment received, independent predictor of mortality were STS score and renal failure for patients undergoing TAVR, renal failure and NYHA class IV for patients undergoing AVR and renal failure, pulmonary artery pressure and aortic systolic pressure for patient treated medically.

This is a retrospective, non-randomized single center study evaluating outcomes of patients referred for TAVR, stratified by the treatment received. Multiple limitations from the trial should be discussed. Because of the absence of randomization, the 3 groups compared in this study represent very different populations. The medical therapy group consisted mainly of patients that were not randomized in the PARTNER trial, most likely representing patients that are just too sick to benefit from TAVR (often referred as the cohort C patients). In fact, 30-d mortality was higher (10.1%) in these pa-

tients compared to the medically treated patients from the PARTNER trial (2.8%). What is surprising is that the 1-year mortality of medically treated patients in this study is lower (36.4%) than the 49.7% observed in PARTNER. These findings are hard to explain and should raise questions about the clinical follow-up of this study, which is not detailed in the manuscript. An alternative is that some patients received medical therapy because they had asymptomatic aortic stenosis, hence no indication for valve replacement. TAVR and AVR patients were also different. Non-operable patients received TAVR and lower risk patients that would not qualify for the PARTNER trial based on their risk were included in the AVR group. Despite these differences, the 1-year mortality was similar between both groups. Interestingly, the STS predicted 30-d mortality for AVR was lower than what was observed, a finding that is in contradiction with the observations from the PARTNER trial. TAVR patients, despite all being part of the PARTNER trial had a 30-d mortality (11.7%) that was worse than in the trial (5.0% for non operative and 3.4% for high-risk patients). Given the absence of randomization between the AVR and TAVR groups in this study, it would be unadvisable to conclude to the equivalence of these two approach solely based on this study. In a recent meta-analysis of 16 TAVR studies using VARC criteria and regrouping 3519 patients^[5], the 1-year mortality was 22.1%, similar to what observed by Ben-Dor *et al*^[1]. Significant outcomes such as vascular complications, stroke, acute kidney injury are absent from this present trial and could put some light on the early mortality.

Medically treated patients are driving the results of their multivariable analysis. Also, their multivariable analysis for TAVR and AVR patients are over fitted in relation to the number of events. Renal failure was found to be a predictor of mortality for all patients and is consistent with the current literature^[6,7]. They however did not define was they considered as renal failure and did not report on acute kidney injury which has been described as an independent predictor of mortality after TAVR and AVR^[8]. The proportion of patient on dialysis was also not reported in this study. The PARTNER trial excluded patients on chronic dialysis and patients with a serum creatinine ≥ 3 mg/dL. It would have been interesting to know the proportion of these patients represented in the AVR and in the medically treated groups. No data on frailty was presented in this study. Frailty is known to be an independent predictor of mortality after open-heart surgeries^[9], is often a cause of non-operability and has now been characterize in the VARC-2 consensus document^[10]. Frailty could be an unmeasured confounder that could alter the results of this multivariable analysis.

In conclusion, this single center, non-randomized study is globally consistent with the PARTNER trial^[3,4] and larger multicenter registries^[11-13]. TAVR is already recognized as the gold standard therapy for non-operative patients that cannot benefit from aortic valve replacement. The biggest challenge remaining will be to identify

patients that are dying with severe AS and not from AS and that would not improve after TAVR. New trials (PARTNER 2, SURTAVI)^[14] are already randomizing moderate-risk patients to AVR *vs* TAVR, searching for potential benefits of TAVR in these patients.

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