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In pursuit of perfection: "alive and better" as the measure of procedural success

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Ultimately, the goal of any medical therapy is the extension of life and the relief of suffering. For the majority of inoperable patients with symptomatic aortic stenosis (AS), transcatheter aortic valve replacement (TAVR) achieves both when compared with standard medical therapy –with a substantial reduction in 2-year mortality among all but the sickest patients (STS PROM ≥15%) and at least a "moderately large" improvement in quality of life in more than 75% of survivors[1,2]. As a result, TAVR is quickly becoming the standard of care for the treatment of appropriately selected individuals with inoperable AS.

While the benefits of TAVR have been established for the treatment of inoperable patients, the benefits (versus surgical aortic valve replacement [SAVR]) in "high-risk operable" patients are less clear. Although TAVR has been associated with a lower perioperative risk of mortality, no difference in one- or two-year mortality was observed in the high-risk operable arm (Cohort A) of the PARTNER trial[3,4]. Likewise, while TAVR patients experienced a more rapid reduction in symptoms (NYHA classification) and improvement in functional status (6-minute walk test) than SAVR patients, no difference in symptom relief existed between survivors in the two treatment groups at either the one- or two-year post-operative follow-up.

Although available data suggests that quality of life will be similar at one year in a cohort of high-risk operable survivors treated with TAVR versus SAVR, no randomised data exists to address this question. Concerns remain about the long-term effects of residual aortic insufficiency, and recent data suggests that the functional improvement achieved early after TAVR may be degraded by one year[5]. As a result, an evaluation of long-term trends in quality of life is particularly salient. Additionally, with an estimated 30% of 30-day TAVR survivors either dying or remaining highly symptomatic by one year[1], identification of patient and procedural characteristics associated with optimal outcomes may help guide patient selection. In this edition of EuroIntervention, two analyses are reported that address these question in moderate to high-risk TAVR cohorts.

Long-term functional recovery following TAVR

In their manuscript, Taramasso and colleagues provide the first-ever evaluation of QOL to two years after TAVR using a cohort of 100 consecutive high-risk individuals (mean age, 80±6 years)[6]. In this cohort, the median logistic EuroSCORE (27.9±16) was slightly lower than that observed in Cohort A of the PARTNER Trial (logistic EuroSCORE, 29.3±16.5), and the 2-year survival was slightly higher (72.6% vs. 66.1%). By one year post-TAVR, a large and clinically significant improvement in functional status was observed. Importantly, this result was maintained to two years, with a 20-point increase in the SF-36 Physical Component Summary (PCS) score and a 34-point decrease in the Minnesota Living with Heart Failure Questionnaire (MLHFQ). In total, more than 70% of survivors achieved a SF-36 PCS greater than or equal to that observed in a similarly-aged Italian population.

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The sustained functional improvement observed in the Taramasso cohort stands in contrast to one-year results reported in two prior studies. In an equally high-risk cohort (n=99), Fairbairn et al observed an early improvement in the SF-12 PCS that was sustained to six post-operative months (SF-12 PCS Δ, +7 points)[5]; however, unlike the Taramasso cohort, a subsequent decline in functional status was observed between six months and one year (PCS Δ, –4 points; p<0.001). Likewise, in an analysis by Krane et al, early improvements in functional status (SF-36 PCS Δ, +6 points) were followed by a slight but statistically significant decline to one

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year (PCS Δ, –1 point; p<0.05)[7]. Similar trends in long-term quality of life have been observed following SAVR. For example, in one cohort of 96 isolated SAVR survivors, an initial increase in functional status at 6 post-operative months (SF-36 PCS Δ, +5 points) was followed by a slight deterioration at two and three years (SF-36 PCS Δ, –1 point and –2 points versus the 6-month peak)[8]. As in the TAVR cohorts; however, the baseline PCS remained above that of the age-normalised general population throughout the study interval.

The results reported in each of these studies raise an important question, '"What is a clinically meaningful change in QOL metrics?" Does a 4-point (or 1-point) decrement in the SF-36 PCS translate to a meaningful clinical decline; or, from another perspective, does a 7-point increase in SF-36 PCS indicate a meaningful increase in functional capacity? Prior literature provides some perspective, here. For example, in two widely referenced studies, a clinically meaningful change in the SF PCS was identified as one-half of one standard deviation of the mean composite score (i.e., roughly 4 to 7 points)[9,10]. Standards indicating a "clinically-relevant response" have also been developed for other metrics, including the Kansas City Cardiomyopathy Questionnaire (KCCQ) (5 points indicates a small clinical change; 10 points, a moderate change; 15 points, a large change)[11] and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (≥5 points indicates a clinically meaningful change)[12]. Using these prior examples as a reference, the 7-point increase in the SF-36 PCS observed in the Taramasso cohort is considered a clinically meaningful change, while the 4-point decrement reported between six months and one year by Fairbairn et al[5] may also be relevant; however, the 1-point decrement reported by Kane et al[7] would not be considered clinically-relevant, despite statistical significance. Although the results of Taramasso and colleagues need further validation, the available literature can be interpreted with a reasonably unified message: on average, in high risk patients, TAVR [like SAVR] is associated with an early, clinically-relevant increase in quality of life (particularly, functional status), followed by clinical stabilisation (with the possibility of a slight decline) to two years.

Predictors of functional improvement following TAVR

While long-term data among "responders" appears promising, our ability to accurately identify patients who will receive a functional benefit from TAVR is limited, with roughly one-third of treated patients experiencing no measurable increase in quality of life following TAVR[1]. With TAVR, as with other medical interventions, our capacity to predict functional recovery is dependent on our ability to identify patients in whom 1) symptoms are primarily due to the targeted disease process (i.e., aortic valve obstruction), and 2) the deleterious effects of the targeted disease process are expected to be reversible. It follows that optimisation of outcomes among patients with AS will depend on our ability to identify both 1) the estimated 20% of patients with severe AS who are thought to have symptoms from other causes[13], and 2) the roughly 50% of low-output patients in whom left ventricle negative remodelling has not become irreversible[14]. Finally, even in appropriately selected patients, procedural complications (e.g., vascular or neurologic complications and residual paravalvular insufficiency) may limit functional recovery. The extent to which functional recovery following TAVR is related to patient versus procedural characteristics remains poorly understood. What, if any, data exists to aid in this assessment?

Based on limited published data, both patient characteristics and procedural complications seem to affect the likelihood of post-TAVR functional recovery. For example, TAVR patients with oxygen-dependent lung disease in Cohort B of the PARTNER Trial did not experience a QOL improvement versus medical therapy[2]. Likewise, a comparatively less robust QOL improvement has been reported among patients with baseline moderate to severe mitral regurgitation and among those with a higher baseline STS perioperative risk of mortality[7]. Additionally, decreased operator experience and increased vascular complications have been associated with a less significant improvement[5].

In contrast to previous findings, Taramasso et al observed no association between either patient demographics or baseline comorbidities and the degree of post-TAVR functional improvement. In their analysis, functional improvement was more closely associated with operative complications. For example, residual moderate to severe paravalvular leak (n=5) and periprocedural stroke (n=4) were each associated with less substantial improvements in the SF-36 PCS than in the overall cohort, and patients with either a moderate to severe paravalvular leak or a length of stay ≥9 days had a less impressive and non-significant reduction in the MLHFQ. Similarly, in the analysis by Stortecky et al[15], "clinical non-response" (present in 32% of all patients) was more prevalent among those who experienced a periprocedural complication than those who did not, although the difference did not reach statistical significance. In the absence of definitive data among TAVR patients, important lessons may be translated from the surgical literature.

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With surgical AVR, as with TAVR, both patient and procedural factors have been associated with clinical non-response. For example, a lack of pre-operative contractile reserve (<20% increase in stroke volume at maximal dobutamine infusion) may be a marker of an irreversible pathophysiologic insult and has been associated with both increased operative mortality and limited functional improvement among SAVR patients[14]. Likewise, the relative size of the implanted aortic valve prosthesis (and, subsequently, the residual post-operative AS gradient) has been strongly associated with functional recovery[16]. However, the extent to which lessons learned in the surgical experience will translate to the TAVR experience is unknown.

Summary

Taken as a whole, available data suggest that when functional recovery is achieved post-TAVR, the results are generally sustained; however, up to one-third of high-risk operable patients receive little or no measurable clinical benefit with TAVR. As with

SAVR, patient selection does influence the observed balance between the risks and benefits of TAVR, and in appropriately selected patients, procedural outcomes are likely affect long-term functional recovery.

In clinical practice, procedural success is ultimately judged on one of two levels: 1) Did the intervention prolong life? and, 2) Did the intervention relieve suffering? As our field matures toward one focused on the comparative effectiveness of alternative treatments (TAVR versus SAVR), we should not lose sight of this fundamental truth. At the end of the day, the success of transcatheter therapies will depend on impeccable patient selection as much as flawless device delivery.

Conflict of interest statement

The author has no conflicts of interest to declare.

References

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363:1597-607.

2. Reynolds MR, Magnuson EA, Lei Y, Leon MB, Smith CR, Svensson LG, Webb JG, Babaliaros VC, Bowers BS, Fearon WF, Herrmann HC, Kapadia S, Kodali SK, Makkar RR, Pichard AD, Cohen DJ; Placement of Aortic Transcatheter Valves (PARTNER) Investigators. Health-Related Quality of Life After Transcatheter Aortic Valve Replacement in Inoperable Patients With Severe Aortic Stenosis / Clinical Perspective. *Circulation.* 2011;124: 1964-72.

3. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB; PARTNER Trial Investigators. Transcatheter Aortic-Valve Replacement for Inoperable Severe Aortic Stenosis. *N Engl J Med.* 2012;366:1696-704.

4. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. *N Engl J Med.* 2011;364:2187-98.

5. Fairbairn TA, Meads DM, Mather AN, Motwani M, Pavitt S, Plein S, Blackman DJ, Greenwood JP. Serial Change in Health-Related Quality of Life Over 1 Year After Transcatheter Aortic Valve Implantation: Predictors of Health Outcomes. *J Am Coll Cardiol.* 2012;59:1672-80.

6. Taramasso M, Latib A, Cioni C, Denti P, Buzzatti N, Godino C, Chieffo A, Alfieri O, Colombo A, Maisano F. Quality of life improvement is maintained up to two years after transcatheter aortic valve implantation in high-risk surgical candidates. *EuroIntervention*. 2012;8:429-36.

7. Krane M, Deutsch MA, Piazza N, Muhtarova T, Elhmidi Y, Mazzitelli D, Voss B, Ruge H, Badiu CC, Kornek M, Bleiziffer S, Lange R. One-Year Results of Health-Related Quality of Life Among Patients Undergoing Transcatheter Aortic Valve Implantation. *Am J Cardiol.* 2012;109:1774-81.

8. Grady KL, Lee R, Subačius H, Malaisrie SC, McGee EC Jr, Kruse J, Goldberger JJ, McCarthy PM. Improvements in Health-Related Quality of Life Before and After Isolated Cardiac Operations. *J Thorac Cardiovasc Surg.* 2011;91:777-83.

9. Sedrakyan A, Vaccarino V, Paltiel AD, Elefteriades JA, Mattera JA, Roumanis SA, Lin Z, Krumholz HM. Age does not limit quality of life improvement in cardiac valve surgery. *J Am Coll Cardiol.* 2003;42:1208-14.

10. Ware JE Jr, Bayliss MS, Rogers WH, Kosinski M, Tarlov AR. Differences in 4-year health outcomes for elderly and poor, chronically ill patients treated in HMO and fee-for-service systems. Results from the Medical Outcomes Study. *JAMA.* 1996;276: 1039-47.

11. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS; Cardiovascular Outcomes Research Consortium. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J.* 2005;150:707-15.

12. Rector TS, Tschumperlin LK, Kubo SH, Bank AJ, Francis GS, McDonald KM, Keeler CA, Silver MA. Use of the Living With Heart Failure questionnaire to ascertain patients' perspectives on improvement in quality of life versus risk of drug-induced death. *J Card Fail.* 1995;1:201-6.

13. Bach DS, Cimino N, Deeb GM. Unoperated patients with severe aortic stenosis. *J Am Coll Cardiol.* 2007;50:2018-9.

14. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR, Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation.* 2002;106:809-13.

15. Stortecky S, Schmid V, Windecker S, Kadner A, Pilgrim T, Buellesfeld L, Khattab AA, Wenaweser P. Improvement of Physical and Mental Health After Transfemoral Transcatheter Aortic Valve Implantation. *EuroIntervention* 2012 ;8:437-43.

16. Bleiziffer S, Ali A, Hettich IM, et al. Impact of the indexed effective orifice area on mid-term cardiac-related mortality after aortic valve replacement. *Heart.* 2010;96:865-71.