Clinical risk assessment pre-TAVI

Introduction

Degenerative aortic valve stenosis is the most common valvular heart disorder in industrialized countries, with a prevalence rate of 4–5% in adults aged >65 years. [1] The advent of transcatheter aortic valve implantation (TAVI) has represented a paradigm shift for treating patients with severe aortic stenosis (AS).

Clinical risk assessment in potential TAVI candidates has been based largely on the STS and EuroSCORE which were initially developed to predict short-term risk following cardiac surgery, based largely on the extent of baseline medical co-morbidities. [2, 3] Although these risk scores have been applied in the TAVI population, their utility for this purpose is limited given their frequent discordance and modest correlations with 30-day and mid-term post-TAVI outcomes. [4, 5]

Post hoc analysis of data from the PARTNER trial has been used as a means of identifying patients at high risk for a poor outcome post-TAVI. [6] The most important baseline predictors of poor outcomes included reduced exercise capacity (measured using 6MWT), lower baseline mean aortic valve gradients, oxygen-dependent chronic lung disease (CLD), chronic kidney disease (CKD) and poor baseline cognition. Interestingly, the STS score was not a significant predictive factor.

In both European and American guidelines, it is recommended that the decision regarding intervention in valvular heart disease should be performed by the “Heart Team” consisting of a number of specialists [7]. Nonetheless, identification of potential TAVI candidates unlikely to benefit from this procedure in the clinic setting remains an important skill for all clinical cardiologists in order to facilitate discussion with patients regarding potential treatment strategies. This review aims to outline the patient factors and co-morbidities currently known to be associated with a futile post-TAVI outcome, and thus help clarify which patients may be unlikely to benefit from TAVI.

Impaired ejection fraction

There is conflicting data regarding the outcome post-TAVI and impaired ejection fraction. In one study by Urena *et al*., pooled analysis of over 3 700 patients who underwent TAVI with either a balloon- or self-expanding prosthesis identified that a baseline LVEF of ≤40% was independently associated with death due to advanced heart failure or sudden cardiac death during a mean follow-up period of ~2 years [8]. However, a study by Passeri *et al*. also addressed this question and found that the impact of LVEF was of less significance. This study used data from 342 inoperable patients included in the PARTNER trial randomised to

TAVI or optimal medical therapy (OMT). Impaired LVEF was diagnosed in fewer than 50% of this cohort meaning that the absolute number of patients included in this study was small. Impaired EF had no effect on survival at 1 year post-TAVI but was associated with a worse outcome in the OMT group. [9] Given that there is currently conflicting data concerning the impact of LVEF in outcome post TAVI, it would not be unreasonable to suggest that low LVEF should not be used as an isolated factor for determining futility post-TAVI. Interestingly, a separate *post hoc* analysis of the full PARTNER cohort demonstrated that a low-flow state (defined as stroke volume index ≤ 35 mL/m^2) was independently associated with increased 2-year mortality, irrespective of LVEF, although the clinical significance of this in terms of selection for TAVI is not clear. [10]

Right heart function

Few studies have evaluated the effect of significant tricuspid regurgitation (TR) on outcome in patients undergoing TAVI. Lindman *et al*. addressed this question by analyzing the results from the 542 patients with symptomatic AS included in the PARTNER II trial. In this inoperable cohort of patient, those with more significant TR prior to TAVI had increased 1-year mortality: 32.6% for moderate TR and 61.1% for severe TR compared to 16.9% and 17.2% for those with no/trace or mild TR respectively (p<0.001). After multivariable adjustment, severe TR (HR 3.20, 95% CI 1.50–6.82, p=0.003) and moderate TR (HR 1.60, 95% CI 1.02–2.52, p=0.042) remained associated with increased mortality as did RA and RV enlargement, but not RV dysfunction. [11]

However, it is important to highlight this association between moderate or severe TR and increased hazard of death was only observed in those with minimal MR at baseline and that this correlation did not exist in patients with concurrent mitral regurgitation. While it would not be prudent to make binary decisions on patient selection for TAVI based on one single study, it appears that severe TR in the context of minimal MR is associated with a 3-fold increase in the hazard of 1-year mortality after multivariable adjustment which may have implications on treatment decisions concerning TAVI.

Pulmonary hypertension

Data from the PARTNER trial and registry suggests that while pulmonary hypertension (PH) does not influence peri-procedural mortality, one year mortality was increased. In a post-hoc analysis of the PARTNER trial by Lindman et al., one year all-cause mortality was 18.6% in patients with no pulmonary hypertension. This increased to 22.7% in patients with mild PH and 25% in patients with moderate/severe PH . In this study, invasive measurement of mean pulmonary artery pressure (mPAP) was used and moderate/severe PH was defined as an mPAP ≥35 mm Hg.[12] Another single centre study identified 50mmHg (measured non-invasively) as an optimum cut-off to predict post-TAVI outcomes. [13] However, this relationship between mortality and moderate/severe PH is likely to be complex and vary depending on the aetiology of PH. In a study by O'Sullivan *et al.*, the impact of PH on the outcomes of 433 patients undergoing TAVI was assessed based on several invasive haemodynamic parameters. This study demonstrated that isolated post-capillary PH did not appear to have a significant impact on mortality. However, patients with pre-capillary PH and combined pre-capillary and post-capillary PH had a significant increase in one year mortality. [14]

Mitral regurgitation

The relationship of outcomes with mitral regurgitation and aortic valve replacement is complex and highly dependent on the aetiology of mitral regurgitation. In general, both 30 day and one year mortality is higher post-TAVI if there is concomitant moderate or severe MR. In contrast to primary mitral regurgitation, it is conceivable that functional or secondary mitral regurgitation may improve post-TAVI. Data from a meta-analysis by Nombela-Franco *et al*. suggests that if the patient in question has functional moderate or severe MR, this will get better in 22.5% of patients, no change in 77% of patients and worse in 7.6% of patients. Secondary MR (as opposed to primary MR) therefore supports a move towards TAVI with the caveat that overall mortality is higher with an odd ratio of 1.49 (95% CI 1.16-1.92) at 30 days and 1.32 (95% CI 1.12-1.56) at one year. [15]

Severe chronic lung disease

There is now a body of research to suggest that baseline spirometric variables are associated with pulmonary complications post-TAVI in patients with chronic lung disease (CLD). [16] Therefore, predicting this correlation between CLD and a poor outcome post-TAVI requires a quantitative assessment of the severity of CLD. However, no threshold has been shown yet to be predictive of futility.

Mok *et al.* evaluated the factors specifically associated with a poor outcome post-TAVI in patients with CLD. A shorter distance walked during the 6-minute walking test (6MWT) was the main factor associated with poor outcomes. Approximately 75% of patients whose pre-TAVI 6MWT was <150 m died at follow-up compared with nearly 25% of patients whose baseline 6MWT yielded ≥150 m. [17] *Post hoc* analysis of outcomes of patients with CLD undergoing TAVI from the PARTNER trial demonstrated that poor mobility (defined as a distance < 50 m during the 6MWT) and oxygen-dependency are independently associated with greater mortality rates. [18]

While some discrepancies exist regarding the specific 6MWT distance cut-off determining prohibitive risk, it seems that there is a very high likelihood of a poor post-TAVI outcome in those patients unable to walk at least 100 m during the 6MWT. Oxygen-dependent CLD patients are also at very high risk of poor outcomes, and a very thoughtful and extensive evaluation should be undertaken before accepting these patients for TAVI.

Chronic kidney disease

One year mortality rates post-TAVI in those with severe CKD are in excess of 30%. [19] Allende *et al*. pooled the clinical results of over 2 000 patients who underwent TAVI, with the aim of evaluating factors predictive of poorer outcomes within the CKD population. The presence of more advanced CKD, defined as an eGFR less than 30 mL/min, was independently associated with early and late mortality post-TAVI. In addition, the presence of atrial fibrillation and dialysis-dependence were observed to be potent predictors of mortality. Of note, the mortality rates among patients with advanced CKD and atrial fibrillation was 40% at 1 year, and increased to 70% when combined with dialysis-dependence. [20] Current available data may be helpful in the clinical decision-making process of potential TAVI candidates. In particular, the combination of dialysis-dependence and atrial fibrillation appears to significantly elevate risk of mortality post TAVI. However, while this data can help inform decisions, data from a limited number of trials cannot be applied generically to this subgroup of patients to make important binary decisions regarding treatment and more evidence is therefore required on the treatment of patients with CKD and aortic stenosis.

Frailty

The contribution of mobility, cognition and nutrition is increasingly being evaluated as a means of identifying potential TAVI candidates unlikely to benefit from this procedure. [21] Therapeutic futility is a generic term corresponding to a lack of medical efficacy. Although there is currently no uniform definition, futility from a TAVI perspective is usually defined by the combination of death and/or absence of functional improvement during short-term follow-up post-procedure (6 months to 1 year). [22, 23] There is increasing recognition that some patients simply fail to derive a functional, morbidity or mortality benefit post-TAVI. Given the associated risks associated with TAVI, accurately identifying subgroups of patients in whom TAVI is likely to be futile remains a priority.

Assessment of frailty pre-TAVI has been examined by Yamamoto *et al*. who analysed data from the prospective OCEANTAVI registry. This is a Japanese register which encompasses 1 215 high-risk patients who underwent TAVI at 9 centres in Japan between 2013 and 2016. The Rockwood's Clinical Frailty Scale (CFS) was used to assess frailty and this information was ascertained by trained medical professionals who had direct contact with the patients and their families prior to TAVI. The CFS is a semi-quantitative tool that provides a global score ranging from 1 ("very fit") to 9 ("terminally ill") to reflect the following domains: disability for basic and instrumental activities of daily living (ADLs), mobility, activity, energy, and disease-related symptoms. Patients with CFS scores of greater or equal to 7 were designated as having severe frailty with complete dependence for personal care. This group faced the highest risk of 1-year mortality (45%); whereas CFS scores of 1-6 faced a lower risk (7-18%). [24] This study is subject to criticism due to the small number of patient included with a CFS score greater or equal to 7 (N=48). However, similar results have been demonstrated when this process was applied to another dataset i.e. the Frailty-AVR study. [25]

There are a large number of frailty tools and there have been multiple studies to attempt to identify a definitive tool that can be used universally to assess frailty pre-TAVI. All these tools have pros and cons. For example, it can be argued that the CFS score is limited in that it is unable to discriminate potentially reversible cases of frailty such as sarcopenia, which may improve with exercise and nutrition interventions. However, results from the FRAILTY-AVR study (Frailty Assessment Before Cardiac Surgery and Transcatheter Interventions) have demonstrated that the Essential Frailty Toolset (EFT), a relatively simple composite score of four indicators, is highly predictive of mortality after TAVI and surgical aortic valve replacement.

The FRAILTY-AVR study was a prospective cohort study encompassing 1,020 patients and was carried out across 14 centres in 3 countries (Canada, USA, and France) from 2012 to 2016. This study compared the following frailty scales: Fried, Fried+, Rockwood, Short Physical Performance Battery, Bern, Columbia, and the Essential Frailty Toolset (EFT). The primary outcome was all-cause mortality and disability 1 year after the procedure. Interestingly, the Essential Frailty Toolset, a brief 4-item scale encompassing lower-extremity weakness, cognitive impairment, anaemia and hypoalbuminaemia, outperformed other frailty scales and has therefore been recommended for use in this setting [25].

Regardless of the tool used, it is likely to encompass a number of “red flags” which have been associated with futility post-TAVI. These include inability to complete a short-distance gait speed test or chair rise test, being dependent for most basic activities of daily living, being malnourished with low serum albumin and unintentional weight loss, being significantly anaemic (in the absence of a clearly reversible cause), having advanced dementia, having oxygen dependent lung disease and having severe chronic kidney or liver disease. [26]

Conclusion

In summary, identifying the non-cardiac and cardiovascular factors leading to poor outcomes post-TAVI remains a challenging and unresolved issue. With regards to non-cardiac conditions, a large body of evidence supports that CLD, CKD and frailty predict futility post-TAVI. However, it remains difficult to deny TAVI based on a single variable related to respiratory of renal function. Furthermore, it is unlikely that any single cardiovascular factor is sufficient to identify a group of patients for whom TAVI is likely to be truly futile. However, the collective assimilation of these co-morbidities and assessment of frailty is likely to be of high utility in helping to identify patients in whom TAVI is likely to be futile.

References

1) Lung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde J-L, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231–124

2) O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP, Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2 – isolated valve surgery. Ann Thorac Surg 2009;88(1 Suppl.):S23–S42.

3) Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15:816–822; discussion 822–3.

4) Arangalage D, Cimadevilla C, Alkhoder S, Chiampan A, Himbert D, Brochet E, Iung B, Nataf P, Depoix JP, Vahanian A, Messika-Zeitoun D. Agreement between the new EuroSCORE II, the Logistic EuroSCORE and the Society of Thoracic Surgeons score: implications for transcatheter aortic valve implantation. Arch Cardiovasc Dis 2014;107:353–360. Google ScholarCrossRefPubMed

5) Silaschi M, Conradi L, Seiffert M, Schnabel R, Schon G, Blankenberg S, Reichenspurner H, Diemert P, Treede H. Predicting risk in transcatheter aortic valve implantation: comparative analysis of EuroSCORE II and established risk stratification tools. Thorac Cardiovasc Surg 2015;63:472–478.

6) Arnold SV, Reynolds MR, Lei Y, Magnuson EA, Kirtane AJ, Kodali SK, Zajarias A, Thourani VH, Green P, Rodes-Cabau J, Beohar N, Mack MJ, Leon MB, Cohen DJ, Investigators P. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. Circulation 2014;129:2682–2690.

7) Helmut Baumgartner Volkmar Falk Jeroen J Bax Michele De Bonis Christian Hamm Per Johan Holm Bernard Iung Patrizio Lancellotti Emmanuel Lansac Daniel Rodriguez Muñoz. ESC/EACTS Guidelines for the management of valvular heart disease Show more European Heart Journal, Volume 38, Issue 36, 21 September 2017, Pages 2739–2791.

8) Urena M, Webb JG, Eltchaninoff H, Munoz-Garcia AJ, Bouleti C, Tamburino C, Nombela-Franco L, Nietlispach F, Moris C, Ruel M, Dager AE, Serra V, Cheema AN, Amat-Santos IJ, de Brito FS, Lemos PA, Abizaid A, Sarmento-Leite R, Ribeiro HB, Dumont E, Barbanti M, Durand E, Alonso Briales JH, Himbert D, Vahanian A, Imme S, Garcia E, Maisano F, del Valle R, Benitez LM, Garcia del Blanco B, Gutierrez H, Perin MA, Siqueira D, Bernardi G, Philippon F, Rodes-Cabau J. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. J Am Coll Cardiol 2015;65:437–448.
9) Passeri JJ, Elmariah S, Xu K on behalf of the PARTNER Investigators, et al. Transcatheter aortic valve replacement and standard therapy in inoperable patients with aortic stenosis and low EF. Heart 2015;101:463-471.
10) Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, Tuzcu EM, Babaliaros V, Thourani V, Szeto WY, Bavaria JE, Kodali S, Hahn RT, Williams M, Miller DC, Douglas PS, Leon MB. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. Circulation 2013;127:2316–2326.
11. Lindman BR et al. Effect of Tricuspid Regurgitation and the Right Heart on Survival After Transcatheter Aortic Valve Replacement Insights From the Placement of Aortic Transcatheter Valves II Inoperable Cohort; Circulation: Cardiovascular Interventions April 2015, Volume 8, Issue 4
12) Lindman BR et al. Risk stratification in patients with pulmonary hypertension undergoing transcatheter aortic valve replacement. Heart. 2015 Oct;101(20):1656-64. doi: 10.1136/heartjnl-2015-308001. Epub 2015 Aug 11.
13) Barbash IM, Escarcega RO, Minha S, Ben-Dor I, Torguson R, Goldstein SA, Wang Z, Okubagzi P, Satler LF, Pichard AD, Waksman R. Prevalence and impact of pulmonary hypertension on patients with aortic stenosis who underwent transcatheter aortic valve replacement. Am J Cardiol 2015;115:1435–1442.
14) O'Sullivan CJ, Wenaweser P, Ceylan O, Rat-Wirtzler J, Stortecky S, Heg D, Spitzer E, Zanchin T, Praz F, Tuller D, Huber C, Pilgrim T, Nietlispach F, Khattab AA, Carrel T, Meier B, Windecker S, Buellesfeld L. Effect of pulmonary hypertension hemodynamic presentation on clinical outcomes in patients with severe symptomatic aortic valve stenosis undergoing transcatheter aortic valve implantation: insights from the new proposed pulmonary hypertension classification. Circ Cardiovasc Interv 2015;8:e002358.
15) Nombela-Franco L et al. Clinical impact and evolution of mitral regurgitation following transcatheter aortic valve replacement: a meta-analysis. Heart. 2015 Sep;101(17):1395-405. doi: 10.1136/heartjnl-2014-307120. Epub 2015 Jun 9.
16) Chopard R, Meneveau N, Chocron S, Gilard M, Laskar M, Eltchaninoff H, Iung B, Leprince P, Teiger E, Chevreul K, Prat A, Lievre M, Leguerrier A, Donzeau-Gouge P, Fajadet J, Schiele F. Impact of chronic obstructive pulmonary disease on Valve Academic Research Consortium-defined

outcomes after transcatheter aortic valve implantation (from the FRANCE 2 Registry). Am J Cardiol 2014;113:1543–1549.
17) Mok M, Nombela-Franco L, Dumont E, Urena M, DeLarochelliere R, Doyle D, Villeneuve J, Cote M, Ribeiro HB, Allende R, Laflamme J, DeLarochelliere H, Laflamme L, Amat-Santos I, Pibarot P, Maltais F, Rodes-Cabau J. Chronic obstructive pulmonary disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes, prognostic markers, and functional status changes. JACC Cardiovasc Interv 2013;6:1072–1084.
18) Dvir D, Waksman R, Barbash IM, Kodali SK, Svensson LG, Tuzcu EM, Xu K, Minha S, Alu MC, Szeto WY, Thourani VH, Makkar R, Kapadia S, Satler LF, Webb JG, Leon MB, Pichard AD. Outcomes of patients with chronic lung disease and severe aortic stenosis treated with transcatheter versus surgical aortic valve replacement or standard therapy: insights from the PARTNER trial (placement of AoRTic TraNscathetER Valve). J Am Coll Cardiol 2014;63:269–279.
19) Dumonteil N, van der Boon RM, Tchetche D, Chieffo A, Van Mieghem NM, Marcheix B, Buchanan GL, Vahdat O, Serruys PW, Fajadet J, Colombo A, de Jaegere PP, Carrie D. Impact of preoperative chronic kidney disease on short- and long-term outcomes after transcatheter aortic valve implantation: a Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC-Plus) initiative substudy. Am Heart J 2013;165:752–760.
20) Allende R, Webb JG, Munoz-Garcia AJ, de Jaegere P, Tamburino C, Dager AE, Cheema A, Serra V, Amat-Santos I, Velianou JL, Barbanti M, Dvir D, Alonso-Briales JH, Nuis RJ, Faqiri E, Imme S, Benitez LM, Cucalon AM, Al Lawati H, Garcia del Blanco B, Lopez J, Natarajan MK, DeLarochelliere R, Urena M, Ribeiro HB, Dumont E, Nombela-Franco L, Rodes-Cabau J. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. Eur Heart J 2014;35:2685–2696.
21) Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.
22) Schneiderman LJ, Jecker NS, Jonsen AR. Medical futility: its meaning and ethical implications. Ann Intern Med 1990;112:949–954.
23) Puri R. et al. TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation European Heart Journal, Volume 37, Issue 28, 21 July 2016, Pages 2217–2225.
24) Yamamoto M, Shimura T, Kano S, Kagase A, Kodama A, Koyama Y, Tada N, Yamanaka F, Naganuma T, Araki M, Shirai S, Watanabe Y, Hayashida K. Impact of the Clinical Frailty Scale on Clinical Outcomes after Transcatheter Aortic Valve Implantation. Circulation.xxx; xxx, xxx

25) Afilalo J, Lauck S, Kim DH, Lefèvre T, Piazza N, Lachapelle K, Martucci G, Lamy A, Labinaz M, Peterson MD, Arora RC, Noiseux N, Rassi A, Palacios I, Genereux P, Lindman BR, Asgar A, Kim CA, Trnkus A, Morais JA, Langlois Y, Rudski LG, Popma JJ, Webb JG, Perrault LP. Frailty in Older Adults Undergoing Transcatheter or Surgical Aortic Valve Replacement: The Frailty-AVR Study. J Am Coll Cardiol. 2016;67:8.
26) Arnold SV, Afilalo J, Spertus JA, Tang Y, Baron SJ, Jones PG, Reardon MJ, Yakubov SJ, Adams DH, Cohen DJ, U.S. CoreValve Investigators. Prediction of Poor Outcome After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016;68:1868–1877.