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SEVERE AORTIC STENOSIS AND TRANSCATHETER AORTIC VALVE REPLACEMENT IN ELDERLY PATIENTS: UTILITY VS FUTILITY

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ABSTRACT

Introduction. Recently, transcatheter aortic valve replacement (TAVR) has emerged as established standard treatment for symptomatic severe aortic stenosis, providing an effective, less-invasive alternative to open cardiac surgery for inoperable or high-risk older patients.

Evidence acquisition. In order to assess the anticipated benefit of aortic replacement, considerable interest now lies in better identifying factors likely to predict outcome. In the elderly population frailty and medical comorbidities have been shown to significantly predict mortality, functional recovery and quality of life after transcatheter aortic valve replacement. Scientific literature focused on the three items will be discussed.

Evidence synthesis. High likelihood of futility is described in patients with severe chronic lung, kidney, liver disease and/or frailty. The addition of frailty components to conventional risk prediction has been shown to result in improved discrimination for death and disability following the procedure and identifies those individuals least likely to derive benefit. Several dedicated risk score have been proposed to provide new insights into predicted "futile" outcome. However, assessment of frailty according to a limited number of variables is not sufficient, while a multi-dimensional geriatric assessment significantly improves risk prediction.

Conclusions. A multidisciplinary heart team that includes geriatricians can allow the customization of therapeutic interventions in elderly patients to optimise care and avoid futility.

Key Words: Transcatheter aortic valve replacement – Frailty - Older adults

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has emerged as a less invasive alternative to the established standard of surgical care and has offered substantial reductions in mortality and improvement in quality of life compared with medical therapy [1,2]. Attention was initially focused on inoperable patients and those at high surgical risk [1,3]. Thereafter, the indications have expanded for both intermediate and low-risk patients with excellent success rates and long-term outcomes [4,5]. Although indication for TAVR has extended to also include younger groups, the majority of TAVR patients are older with significant multimorbidity. Choice of therapy in the elderly is difficult due to individual characteristics, including frailty, disability and impaired cognition [6]. As a consequence, the elderly may have suboptimal results with surgical or TAVR with higher rates of morbidity and a worse quality of life [6,7]. Since long-term outcomes may be poorer with advancing age and with markers of advanced frailty, there remains a marked heterogeneity in outcome with up to 30% experiencing little symptomatic benefit or death within 1 year of TAVR [6]. Appropriate individual decision making in elderly care is complex and must be balanced between two opposite situations: on one hand, the less invasive nature of TAVR with its lesser morbidity is attractive; on the other hand, we often face with patients deemed as “too sick”, in which TAVR is expected to be futile.

TAVR IN ELDERLY PATIENTS: RISK PREDICTION

TAVR is now considered equivalent to conventional surgical aortic valve replacement in patients at high surgical risk and is the only options for patients with a profile of risk serious enough to be considered “inoperable”. It has become evident that chronologic age and comorbidities are insufficient to accurately predict risk and benefits of TAVR procedure and that some patients do not improve functionally or live longer after TAVR. Since frailty predisposes patients to mortality, morbidity, and poor functional recovery, assessment of frailty has assumed a central role in the preprocedural evaluation and shared decision-making process of potential TAVR candidates. Although the precise definition of frailty remains a subject of debate, frailty has been usually described as a clinical multifactorial geriatric syndrome involving multisystem impairment that results in reduced physiological reserve and increased vulnerability to stressors. The 2017 American College of Cardiology Guidelines on valvular heart disease [8] highlight A) 5 min gate speed, B) disability for activities of daily living, C) cognitive impairment, D) depression, and E) malnutrition as core indicators of frailty that should be routinely assessed pre-TAVR.

Frailty and general risk score. The Society of Thoracic Surgeons (STS) score and European System for Cardiac Operative Risk Evaluation (EuroSCORE) are developed to predict patients' outcomes for conventional cardiac surgery procedures. However, surgical risk models have some limitations and poorly predict TAVR outcomes [9,10], because they do not consider frailty parameters. In the case of elderly patients, we must opt for a comprehensive preoperative assessment that is not limited to surgical risk [11]. Geriatric assessment involves an evaluation of functional status, cognitive capacity, and social situation. In addition, the elderly might have different goals and expectations of care than younger patient. Older frail patients often value functional independence more than longevity [12]. In contrast, current cardiac risk stratification estimates 30-day mortality and major adverse cardiac events as primary endpoints. Among TAVR candidates, only 7% of older patients cited survival as their main target, while a majority of patients described a desire to perform a particular activity (48%) or maintain independence (30%) [13] as their primary goal. Accordingly, prediction of personcentered outcomes, such as functional status, may be especially relevant to high-risk TAVR candidates. This is why procedural outcomes should not only include clinical events but also account for quality of life and levels of functionality. Accurately measuring TAVR outcomes should consider integration of functional as well as frailty parameters to increase predictive power in commonly employed risk scores. Unfortunately, commonly used surgical risk score do not assess functional status and/or quality of life. Therefore, multidisciplinary cardiology teams that include geriatricians has been proposed to optimize TAVR elderly patients' care.

Frailty and outcome. Frailty has proven to be associated with an increased mortality and a higher rate of poor outcome up to 1 year after TAVR [14,15]. An increasing number of frailty markers have been identified in smaller cohorts and have been associated with significantly higher risk of adverse outcomes after TAVR [7,15-18]. In short, malnutrition and reduced mobility with their counterparts ipo-albuminemia and reduced gait speed are powerful markers of frailty status and poor outcome. Stortecky et al. showed that a comprehensive geriatric assessment of 100 consecutive TAVR patients (assessing cognition, nutrition, mobility, activities of daily living, and frailty) significantly improved risk prediction compared with common general risk scores [19]. Moreover, Schoenenberger et al. observed an index of frailty to strongly predict post-TAVR functional decline when adjusted for both the STS and EuroSCOREs [20]. However, multiple published frailty scores show marked variability and have divergent prevalence estimates [21]. Wide range of frailty frequencies is observed depending on the assessment score used (ranging between 35% and 74% in the FRAILTY-AVR study[7]). This is a major reason why frailty is often not measured in clinical practice. Moreover, typical screening tools are often complex and time consuming. To this regard, Afilalo et al. evaluated several frailty scores to predict outcome after TAVR [7]. Essential Frailty Toolset (EFT risk score including albumin, anaemia, ability to perform chair raises and Mini-Mental State Exam) outperformed prior described frailty scores in predicting mortality as well as worsening disability [7]. Accordingly, the 2019 Canadian Cardiovascular Society Position Statement for TAVR acknowledged the EFT as a simple and predictive tool assessment tool [22]. Likewise, a recent study of Kiani et al. [23] identified a simplified tool constituted by serum albumin, 5-min gate speed and anaemia status. Each marker incrementally improved predictive value for poor outcome including bleeding and readmission for heart failure. Adjusted hazard ratios for the presence of all 3 markers was 1.4 and 2.5 for 30-days and 1-year mortality [23]. No significant interaction was found between age and the selected frailty variables, highlighting the relationship between frailty and outcome irrespective of age. In summary, the Kiani et al. model [23] represents a simple, yet powerful, algorithm and could be proposed as a useful screening tool in clinical practice. However, although frailty indexes represent a further important step forward in our ability to refine risk stratification and provide useful information for shared decision making, it is unclear if treatment of these frailty markers will impact outcomes. In practice, many frailty variables may be modifiable, since anaemia could be corrected, hypoalbuminemia could be addressed and rehabilitation might improve mobility. It seems reasonable to argue that improvements of frailty status may result in improvement of symptoms. However, better understanding of how improvement of these markers will lead to change in outcomes remains a priority to be thoroughly investigated.

TAVR IN ELDERLY PATIENTS: FUTILITY

A sizeable group of patients do not fully benefit from TAVR despite a successful procedure. This distinction between technically "perfect" intervention and "futile" outcome [24] is important, since periprocedural results might differ much more than long-term ones. Thus, prediction of TAVR risk can be framed in two aspects: (a) the timing of outcome (early vs. late) and (b) the type of outcome (mortality vs. quality of life). Futility in medicine is not uniformly defined and is under debate. From a TAVR perspective futility is usually defined by the combination of death and/or no objective symptomatic improvement in the New York Heart Association class. Accordingly, a poor post-TAVR outcome has been recently proposed to include both mortality and quality-of-life measures within a single composite endpoint [25]. Furthermore, definition of a futile TAVR is varying in literature on the basis of patients' individual life goals. In clinical practice, considerable interest lies in the ability to better identify reasons for not proceeding with TAVR [26-28]. However, attention has been often focused on comorbidities and symptoms, while objective evaluations of frailty has not been systematically considered.

Futility and Frailty. Recently, a consensus paper defined subgroups of patients for which TAVR may not be beneficial: 1) patients with life expectancy <1 year; 2) patients with “survival with benefit” probability of <25% at 2 years. The authors described “survival with benefit” as improvement of at least one of the followings: a) 1 class in the New-York Heart Association function class; b) 1 Canadian Cardiovascular Society class angina symptoms; c) improvement in the quality of life or life expectancy [29]. An emerging consensus incorporating a more holistic approach suggests the importance of frailty as a factor to better identify those patients in whom TAVR is likely to be futile [14-16, 30,31]. However, little is known on the impact of frailty on quality of life after TAVR [16]. A sub-study of the PARTNER Trial showed that frailty was associated with impaired quality of life 6 months after TAVR, but this association was not found after 12 months [16]. In contrast, two other studies found that frailty at baseline is an independent predictor of deterioration of quality of life 1 year after TAVR [32, 33]. In current literature the most commonly cited tools for frailty, namely 5-m gait speed and the Fried scale, have shown a predictive effect on mortality, but a modest C-statistic improvement of 0.004 when added to clinical risk models [34, 35]. These findings suggest that the assessment of a single marker or a limited number of frailty variables may be not sufficient to achieve a reliable prediction of long-term risk. It is reasonable to evaluate risk stratification for TAVR by integrating markers of frailty with comorbidity and comprehensive geriatric assessment [11].

Futility and comorbidities. Beyond frailty, current data indicate that TAVR has a high likelihood to be futile in severe chronic lung or kidney disease, low-flow low-gradient aortic stenosis or severe mitral regurgitation. In details, although avoiding intubation in lung disease with transfemoral TAVR may be desirable and 50% of patients with severe COPD demonstrated improvement of pulmonary function [36], the need for oxygen supplements must raise the discussion of futility. Chronic kidney disease is present in 30–50% of older TAVR patients because of the inevitable decline in renal function with increasing age. However, given the broad spectrum of chronic kidney disease, isolating the subpopulation of patients least likely to benefit from TAVR has been challenging. It is reasonable to consider that end-stage kidney disease and dialysis dependent patients as strong predictors of poor late survival and futility [37]. In liver disease TAVR is indicated in early-stage because of its lower procedural bleeding risk but is associated with poor late survival and high probability of futility in very advanced liver disease [38]. Finally, in severe aortic stenosis lower gradients and low transvalvular flow are usually due to left ventricular dysfunction often combined with a small left ventricular cavity and severe mitral regurgitation [39]. In such patients TAVR is generally indicated, since it might improve left ventricle function and mitral insufficiency. However, in the case of severe left ventricular dysfunction without contractile reserve the results of TAVR are poor and the probability of futility must be discussed. Recently, scientific evidence has consistently demonstrated that aortic valve stenosis (AS) in older patients referred for TAVR is frequently associated with cardiac amyloidosis (CA). The concurrence of AS-CA affects around one in eight elderly patients [40], ten times higher than it is thought to be in healthy ageing people [41]. AS and transthyretin CA has worse functional capacity and a trend towards worse prognosis particularly if left untreated. Some concern has been raised about futility of TAVR in AS-CA [42], mostly based on limited data in small observational studies. However, the prognostic significance of this dual diagnosis is still uncertain. Dual AS-CA pathology is different to lone AS with the patients being slightly older and having distinct clinical risk profiles including history of carpal tunnel syndrome, elevated biomarkers, increased septal thickness, and right bundle-branch-block and lower voltages on ECG. Although underlying pathophysiological aspects of AS-CA are still unclear, there are suggestions of a causal relationship between AS and CA. In particular, the increased LV afterload posed by AS may cause an abnormal transthyretin deposition through a mechano-enzymatic cleavage process [43]. Valve intervention per se could reduce mechanical stress and may actually reverse amyloid deposition [43]. Thus, it is not surprising that several studies have recently reported no mortality difference between TAVR patients with and without cardiac amyloidosis [44-46]. Based on this data, TAVR should therefore not be withheld in patients with AS-CA and the benefit–risk ratio of TAVR should be evaluated by the local heart team.

Futility and Risk Score. A combined endpoint including mortality and quality-of-life measures was applied to the PARTNER trial to identify patients at high risk for a poor outcome post-TAVR [31]. Baseline predictors of poor outcomes included reduced exercise capacity (measured using 6 minutes walking test), lower baseline mean aortic valve gradients, oxygen-dependent lung disease, chronic kidney disease and poor baseline cognition. Despite the inclusion of two indices of functional and cognitive capacity, this model demonstrated a limited performance, identifying only 10% of patients with a ≥50% likelihood of a poor post-TAVR outcome [31]. However, several important additional factors in the multi-geriatric assessment of patients were not considered. More recently, a new TAVR futility risk model derived from prespecified variables of existing literature has been proposed by Zusman et al. [47]. Final risk score included mean AV gradient, use of diuretics, baseline NYHA functional class, haemoglobin and creatinine levels, nonfemoral access, previous oncological disease, and previous implantation of permanent pacemaker. The model's performance was fairly good, producing a risk of futility of 7%, 17% and 49% respectively for low, moderate and high-risk subgroups. This risk model on the validation cohort (AUC 0.70) outperformed STS (AUC 0.60), Euroscore2 (AUC 0.55), TVT score (AUC 0.56), and TAVR 2-score (0.53) (p = .03 for difference in AUC) [47]. The authors concluded that the prediction score may help to identify patients at risk of futility, having a risk of death that may outweigh the potential benefit anticipated with TAVR. Finally, Lantelme et al. developed a Futile TAVR Simple score (FTS) validated for 1-year all-cause deaths after TAVR (considered as futility) [48]. The final logistic regression model included older age, simple clinical variables and markers of depression and denutrition. The FTS score (AUC 0.674) outperformed EuroSCORE II (AUC 0.627), Charlson comorbidity index (AUC 0.562), and frailty index (AUC 0.486) for identifying futility [48]. Moreover, using 3 risk categories the FTS showed a good performance to predict futility in high-risk group [48] (1-year death rate at 43%, which is very similar to that of severe aortic stenosis medically treated). In general, TAVR-specific risk scores show significant limitations. Firstly, quantitative rather than binary coding of comorbities and markers of frailty might not properly assess the long-term risk of TAVR. Secondly, the addition of a limited number of variables leads only to a moderate improvement in the predictive value of multivariate models. Therefore, TAVR risk score would likely be a compromise between a multidimensional approach versus more isolated and simplistic tests. While expecting further data and fine-tuning the definitions of futility for TAVR, we should consider the use of balloon-aortic-valvuloplasty for highly symptomatic patients as a "bridge to decision" therapy.

CONCLUSION

In conclusion, current evidence suggests that older patients who undergo TAVI have similar outcomes to younger patients. However, there is marked heterogeneity in outcome and a considerable proportion of patients fail to obtain a functional or mortality benefit from TAVR. General surgical scores do not take into account TAVR-specific variables and are not reliable to estimate operative risk for TAVR. In older patients, frailty and co-morbidities are of great importance as predictors of death and

disability following TAVR. In particular, TAVR has a high likelihood to be futile or result in a poor outcome in patients with severe chronic lung, kidney, liver disease and/or frailty. Thus, the role of frailty and comorbidity should be part of a holistic evaluation of the patient and must be integrated into a clinical decision-making process. However, several reports suggest that the assessment of frailty according to a limited number of variables is not sufficient, while a multi-dimensional geriatric assessment significantly improved risk prediction. A multidisciplinary cardiology team that includes geriatricians can provide appropriate selection of elderly patients to optimise care and avoid futility.

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Authors' contribution:

All authors read and approved the final version of the manuscript