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Aortic stenosis in the frail patient: maximizing the benefit of TAVI

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Abstract

Transcatheter aortic valve implantation (TAVI) is an increasingly common intervention for older patients with aortic stenosis deemed at high risk of complications from major cardiac surgery, but identifying those who will benefit can be challenging. Frailty, as a measure of physiological reserve, may be a useful prognostic marker in this population. In this brief review, we summarize the frailty tools that have been studied in TAVI cohorts and the reported outcomes for these patients. Frailty is associated with poorer outcomes after TAVI and assessment provides information beyond conventional surgical risk calculators, such as from the Society of Thoracic Surgeons (STS) and EuroSCORE. Of more use to the clinician is understanding that objective and reproducible physical frailty measures can identify patients at the very highest risk of early mortality or worsening disability after TAVI. Using these tools to help assess risk in older patients with aortic stenosis and guide patient selection for TAVI has great potential to maximize the benefit of treatment. ■ *Heart Metab*. 2018;76:13-17

Keywords: aortic stenosis; frailty; TAVI

Introduction

Transcatheter aortic valve implantation (TAVI) has opened the possibility of definitive treatment of aortic stenosis to a wider population of increasingly older and frailer patients. As the most common valvular disease in the Western World, rates of severe symptomatic aortic stenosis are rising as the population ages.[1] Increasingly, these patients have greater comorbidities and are considered at an excessive risk of death or complications from conventional surgical valve replacement. The PARTNER randomized controlled trial (Placement of AoRtic TraNscathetER valves) on TAVI vs medical management demonstrated a 45% reduction in the 12-month mortality with an intervention.[2] However, medical complexity continues to challenge decision-making in this area; among those who received TAVI in the PARTNER trial, nearly one-third had died within 12 months and a small, but significant, number experienced periprocedural strokes or major vascular complications. Uncertainty remains for many older individuals presenting with symptomatic severe aortic stenosis and multimorbidity. Increasingly, this risk calculation is framed by frailty, in an acknowledgement that current surgical tools, such as the Society of Thoracic Surgeons (STS) score, do not accurately represent the risk from TAVI in this aging population.[3,4]

Frailty describes the loss of strength, endurance, and physiological reserve across multiple body sys-

Abbreviations

CFS: Clinical Frailty Scale; **EFT:** Essential Frailty Toolset; **FRAILTY-AVR:** FRAILTY in older adults undergoing Aortic Valve Replacement study; **OCEAN-TAVI:** Optimized transCathEter vAlvular interventioN-Transcatheter Aortic Valve Implantation registry; **PARTNER:** Placement of AoRtic TraNscathetER valves trial; **STS:** Society of Thoracic Surgeons; **TAVI:** transcatheter aortic valve implantation

tems that increases the risk of dependency or death.[5] Proponents of frailty assessment in TAVI argue that such a holistic evaluation may maximize the benefits by targeting interventions to those most likely to gain functional benefit, while protecting others at excessively high risk from potential harm. However, applying such theories to individualized patient management is not simple. For example, there are over 60 frailty tools in the literature[6] and decompensated heart failure is a well-recognized driver of the frailty state, which may therefore be responsive to TAVI.[7,8] In this review, we summarize the current evidence for the use of frailty assessment to guide the management of older patients with an aortic stenosis.

Studies describing frailty in TAVI patients

The European Society of Cardiology (ESC) guidelines covering patient selection for TAVI have been unable to recommend an optimum tool for frailty, instead suggesting a "heart team" assessment, including cardiologists, cardiac surgeons, and imaging specialists, with the potential to include general practitioners, geriatricians, and intensive care doctors.[9] The lack of consensus around an optimum frailty measure is reflected across the eleven key cohort studies summarized in *Table I*.[10-21] While the mean age of patients

Author, year	Country	Definition of frailty	n	Mean age (years)	Proportion frail (%)	Mortality at 1 year (%)	Relative risk for frail patients (compared with nonfrail patients)
Ewe et al, 2010[13]	Netherlands/ Italy	Fried criteria based on gait speed, grip strength, weight loss, physical activity, and exhaustion	147	80	33	15	MACCE* at 9 months (RR, 4.20; 95% CI, 2.00-8.84) adjusted for logistic EuroSCORE, PVD, previous CABG, and baseline LVEF
Stortecky et al, 2012[14]	Switzerland	Frailty index based on geriatric assessment of cognition, nutrition, timed get-up-and-go, ADLs, and disability. Scored 0-7 with ≥3 considered frail	100	84	49	19	MACCE* at 30 days (RR, 4.78; 95% CI, 0.96-23.77) All-cause mortality at 30 days (RR, 8.33; 95% CI, 0.99-70.48) MACCE* at 1 year (RR, 4.17; 95% CI, 1.37-12.72) adjusted for STS score All-cause mortality at 1 year (RR, 2.93; 95% CI, 0.93-9.24) adjusted for STS score
Rodes-Cabau et al, 2012[15]	Canada	Subjective assessment by a multidisciplinary team	339	81	25	–	All-cause mortality at 42 months (RR, 1.41; 95% CI, 1.02-1.96) adjusted for AF, CVD, COPD, eGFR, and pulmonary hypertension
Kamga et al, 2013[16]	Belgium	SHERPA score (age, ADLs, cognitive decline, falls, and self-perceived health)	30	86	73 (moderate / high risk)	27	All-cause mortality at 1 year (RR, 2.74; 95% CI, 1.39-5.39) per point increase in SHERPA adjusted for sex, BMI, pulmonary hypertension, and diabetes
Zahn et al, 2013[17]	Germany	Presumed subjective assessment (limited detail)	1318	82	18	20	All-cause mortality at 1 year (RR, 1.50; 95% CI, 1.19-1.89)

***Table I** Selected studies and outcomes in TAVI cohorts measuring frailty. *MACCE defined as composite of death, nonfatal stroke, heart failure, or nonfatal myocardial infarction. **Poor quality of life defined as Kansas City Cardiomyopathy Questionnaire Overall Summary score <45 or a decrease of ≥10 points on serial testing before and after TAVI. +Only the Bonn subgroup that received frailty assessment was considered from this multicenter study. †Only the development cohort of this study was included. The validation data set does not contain frailty related outcome data.*

Abbreviations: *ADLs, activities of daily living; AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CSHA, Canadian Study on Health and Ageing; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease; STS, Society of Thoracic Surgeons.*

undergoing TAVI within these studies is consistent (80 to 86 years old), the prevalence of frailty shows significant heterogeneity (5% to 73%), reflecting the nine different tools employed. Subjective or "end-of-the-bed" assessment is the most frequently reported measure, but this is clearly open to variable interpretations by clinicians. In community cohorts, such assessments of frailty demonstrate low sensitivity and specificity for the gold-standard Fried frailty phenotype,[22] which is defined by displaying at least three of five measurable frailty markers: weakness, slowness, low physical activity, weight loss, or exhaustion.[23]

We have previously performed a systematic review and meta-analysis of studies in which frailty measures have been reported in relation to outcomes following TAVI.[24] Across 10 cohort studies and 4592 patients undergoing TAVI, frailty was associated with increased short-term mortality at 30 days (HR, 2.35; 95% CI, 1.78-3.09; *P*<0.001) and later mortality at 1 year (HR, 1.63; 95% CI, 1.34-1.97; *P*<0.001). For this latter outcome, objective frailty tools appeared to identify TAVI patients at the highest risk compared with those classified as nonfrail (HR, 2.63; 95% CI, 1.87-3.70; *P*<0.001). Since this meta-analysis, two major studies including a further 1861 TAVI patients have been reported. The recent FRAILTY-AVR study (FRAILTY in older adults undergoing Aortic Valve Replacement) provided a comprehensive direct comparison of seven different frailty tools in a large multicenter cohort including 646 TAVI and 374 con-

Puls et al, 2014[18]	Germany	Katz index of ADLs (score <6 frail)	300	82	48	28	All-cause mortality at 30 days (RR, 3.05; 95% CI, 1.40-5.70) Minor bleeding at 30 days (RR, 1.50; 95% CI, 1.05-2.16) Renal failure requiring dialysis at 30 days (RR, 2.01; 95% CI, 1.09-3.70) All-cause mortality at 18 months (RR, 2.67; 95% CI, 1.70-4.30) adjusted for age and sex
Seiffert et al, 2014[19]	Germany	CSHA Clinical Frailty Scale[25] (frailty scored at ≥6)	347[+]	81	5	24	All-cause mortality at 1 year (RR, 1.41; 95% CI, 1.23-1.63) adjusted for age and sex
Capodanno et al, 2014[20]	Italy	Geriatric Status Scale based on ADLs, cognition, continence, and mobility. Scored 0-3 with ≥2 labelled frail	1256[†]	82	24	–	All-cause mortality at 30 days (RR, 2.09; 95% CI, 1.30-3.37)
Debonnaire et al, 2015[21]	Netherlands/ Italy	Presumed subjective assessment	511	82	19	16	All-cause mortality at 1 year (RR, 1.29; 95% CI, 0.80-2.06)
Green et al, 2015[12]	USA	Frailty score composed of serum albumin, grip strength, gait speed, and ADLs. Scored between 0-12 with ≥6 considered frail	244	86	45	24	All-cause mortality at 30 days (RR, 1.34; 95% CI, 0.59-3.04) All-cause mortality at 1 year (RR, 2.50; 95% CI, 1.40-4.35) adjusted for baseline variables with univariate significance All-cause mortality or poor quality of life[**] at 1 year (RR, 2.40; 95% CI, 1.14-5.05) adjusted for baseline variables with univariate significance
Afilalo et al, 2017[10]	Canada, USA, France	Essential Frailty Toolset composed of timed chair rises, cognitive impairment, hemoglobin, and albumin levels (frailty scored at ≥3 points)	646	82	37	14	All-cause mortality at 1 year (RR, 3.36; 95% CI, 2.20-5.13) adjusted for STS score
Shimura et al, 2017[11]	Japan	CSHA Clinical Frailty Scale[25] (frailty scored at ≥5 points)	1215	84	29	9	All-cause mortality at 1 year (RR, 1.62; 95% CI, 1.12-2.34) adjusted for logistic EuroSCORE and multiple baseline variables

Table I *Continued.*

Heart Metab. (2018) 76:13-17

ventional surgical valve replacement patients.[10] An even larger cohort of 1215 Japanese TAVI registry patients were assessed using the Clinical Frailty Scale (CFS)[25] in the OCEAN-TAVI study (Optimized trans-CathEter vAlvular interventioN-Transcatheter Aortic Valve Implantation).[11] In both studies, a frail state was independently associated with mortality beyond conventional surgical risk assessments.

The FRAILTY-AVR study compared the frailty phenotype with a further five tools: (i) the CFS; (ii) the Short Physical Performance Battery; (iii) the Bern scale; (iv) the Columbia scale; and (v) the Essential Frailty Toolset (EFT).[10] This latter measure comprises a score between 0 and 5 for completion of 5 timed chair rises (up to 2 points if unable), cognitive impairment measured by a mini-mental state examination (1 point), anemia (1 point), and low serum albumin (1 point). The EFT proved the strongest predictor of 1-year mortality and improved discrimination of the STS score. After adjustment, patients identified as frail by EFT had a 3-fold greater 1-year mortality than nonfrail patients (OR, 3.36; 95% CI, 2.20-5.13).

The CFS provides a brief semiquantitative enhancement to the subjective frailty assessment and was an independent predictor of mortality in the OCEAN-TAVI study beyond the logistic EuroSCORE and standard baseline variables.[11] While it does not require specialist equipment, such as grip strength dynamometers, the CFS necessitates knowledge of symptoms, functional status, and disability. Shimura et al[11] demonstrated that this tool correlated with measurable physical frailty markers, such as gait speed and grip strength.

Outcomes beyond mortality

Despite the variation in frailty tools employed across these studies, there is a clear and consistent link between frailty and poor outcomes after TAVI. The ESC guidelines for TAVI state that patients should have a life expectancy of at least 1 year and be anticipated to gain improvement in quality of life after the procedure.[26] As shown in *Table I*, the majority of patients did survive to 1 year, although 12-month mortality rates varied from 9% to 28% across these studies. For an elderly patient approaching the end of life with symptomatic aortic stenosis, quality rather than quantity of life may take precedence. However, study outcomes to date have focused on mortality after TAVI rather than functional changes in survivors, with the exception of two studies. In the subgroup of patients within the PARTNER trial who underwent frailty assessments, a strong association between frailty and adverse outcomes was observed when a poor or worsening Kansas City Cardiomyopathy Questionnaire score was added to mortality at 1 year as a composite outcome (RR, 2.40; 95% CI, 1.14-5.05).[12] The frailty tool used was an index consisting of physical measures, functional ability, and serum albumin. In the FRAILTY-AVR study cohort, 35% were either dead or more disabled 1 year after TAVI, and preprocedure frailty, measured by EFT, was an independent predictor of this outcome.[10] The Valve Academic Research Consortium also defined important and reportable procedural outcomes after TAVI, including stroke, major bleeding, and the requirement for renal replacement therapy. Unfortunately, data on these outcomes in relation to frailty status is limited.[27]

Choice of frailty tool

The weight of evidence is therefore converging on the use of a specific tool rather than subjective assessments of frailty. The inclusion of physical measurements, such as timed chair rises or gait speed, have demonstrated incremental value in the prediction of functional recovery after TAVI, rather than simply a risk of death. The aim of frailty assessments should not be to deny patients the potential symptomatic benefit achieved through a successful TAVI procedure,[2] but to help make informed discussions using an individualized risk assessment. Frail patients undergoing TAVI could be targeted for additional periprocedural support, including involvement of specialist geriatric services. It is arguable that clinicians seeking the tool with the best evidence to predict the likelihood of a “good outcome” should add the EFT to their routine assessment of patients under consideration for TAVI. The CFS is attractive as a more rapid tool without requiring specific physical or cognitive testing; its inclusion in a consecutive Japanese TAVI patient registry suggests feasibility for adoption into routine clinical care. However, the CFS has not yet been shown to help predict important nonmortality outcomes after TAVI. Crucially, an objective frailty evaluation also identifies a population of patients without frailty, who may otherwise be denied intervention based on a subjective assessment that may bias against the oldest, but fittest individuals.

Conclusions

Frailty assessment in the workup of patients for TAVI provides important information on prognosis that is independent of conventional cardiac surgical risk assessment. The use of objective measurement tools has the potential to improve individualized decision-making in an older population at risk of harm or limited benefit from invasive interventions. ■

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