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ORIGINAL ARTICLE

Impact of Valvulo-Arterial Impedance on Long-Term Quality of Life and Exercise Performance After Transcatheter Aortic Valve Replacement

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BACKGROUND: In aortic stenosis, valvulo-arterial impedance (Zva) estimates the overall left ventricular afterload (valve and arterial component). We investigated the association of Zva (≥5 versus <5 mm Hg mL^{-1} m^{-2}) on quality of life (QOL) and exercise performance (EP) ≥1 year after transcatheter aortic valve replacement (TAVR).

METHODS: The study population consists of 250 TAVR patients in whom baseline Zva and follow-up QOL was prospectively assessed using EuroQOL-5-dimensions instruments; EP was assessed in 192 patients who survived ≥1 year after TAVR using questionnaires related to daily activities. In 124 patients, Zva at 1-year was also available and was used to study the change in Zva (baseline to 1 year) on QOL/EP.

RESULTS: Elevated baseline Zva was present in 125 patients (50%). At a median of 28 (IQR, 17–40) months, patients with elevated baseline Zva were more limited in mobility (88% versus 71%; P=0.004), self-care (40% versus 25%; P=0.019), and independent daily activities (taking a shower: 53% versus 38%, P=0.030; walking 100 meter: 76% versus 54%, P=0.001; and walking stairs: 74% versus 54%, P=0.011). By multivariable analysis, elevated Zva predicted unfavorable QOL (lower EuroQOL-5-dimensions-Utility Index, odds ratio, 1.98; CI, 1.15–3.41) and unfavorable EP (any limitation in ≥3 daily activities, odds ratio, 2.55; CI, 1.41–4.62). After TAVR, the proportion of patients with elevated Zva fell from 50% to 21% and remained 21% at 1 year and was found to be associated with more limitations in mobility, self-care, and daily activities compared with patients with Zva <5 mm Hg mL^{-1} m^{-2}.

CONCLUSIONS: Elevated Zva was seen in half of patients and predicted unfavorable long-term QOL and EP. At 1 year after TAVR, the prevalence of elevated Zva was 21% but remained associated with poor QOL/EP.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: aortic valve ■ arterial pressure ■ echocardiography ■ quality of life ■ transcatheter aortic valve replacement

Aortic stenosis (AoS) is a common valvular heart disease associated with a poor prognosis if left untreated.[1–3] The hemodynamic effects of AoS consist of increased left ventricular (LV) afterload, reduced myocardial compliance, and increased myocardial workload.[2,3] Transcatheter aortic valve replacement (TAVR) effectively reduces afterload and wall stress and improves survival and health-related quality of life (QOL).[4–7]

However, not all patients benefit from TAVR. This may in part be explained by the fact that the excess in afterload in patients with AoS is not only caused by the valve but also by a reduction in arterial compliance.[8] The latter may be explained by the fact that AoS is a manifestation

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WHAT IS KNOWN

- In aortic stenosis, valvulo-arterial impedance (Zva) estimates global left ventricular afterload imposed by the valve and reduced arterial compliance, and predicts mortality after transcatheter aortic valve replacement (TAVR).

WHAT THIS STUDY ADDS

- This study prospectively assessed the association between baseline Zva and health-related quality of life and exercise performance ≥1 year after TAVR and explored the changes in Zva before, after, and at 1 year after TAVR and its association with long-term quality of life.
- Elevated Zva was found in 50% of patients before and 21% after TAVR and remained 21% at 1-year follow-up.
- Baseline elevated Zva independently predicted unfavorable quality of life and exercise performance at a median of 28 months after TAVR.
- Patients with persistent elevated Zva at 1 year after TAVR also had worse quality of life and exercise performance at follow-up.

Nonstandard Abbreviations and Acronyms

AoS	aortic stenosis
BNP	B type natriuretic peptide
EP	exercise performance
LV	left ventricular
NYHA	New York Heart Association
OR	odds ratio
QOL	quality of life
SVI	stroke volume index
TAVR	transcatheter aortic valve replacement
Zva	valvulo-arterial impedance

of a systemic atherosclerotic process involving all parts of the arterial tree.[9,10] Age-related structural changes of the arterial wall result in reduced compliance that becomes particularly manifest in the elderly.[11] As a result, the LV in patients with AoS is exposed to a valvular load caused by the obstructive valve and an arterial load imposed by a decrease in systemic arterial compliance.[8] Previous studies demonstrated that the global LV hemodynamic load can be estimated using an index that quantifies the sum of the valvular and vascular load, the valvulo-arterial impedance (Zva).[8,12] This parameter has shown to predict LV systolic and diastolic dysfunction[8] and mortality in patients with moderate AoS and in patients with severe AoS who underwent TAVR.[13,14] Yet, the impact of Zva on health-related QOL and exercise performance (EP) after TAVR is unknown and was subject of this observational study encompassing 250 patients. In addition, we studied the changes in Zva early (ie, baseline discharge) and late (ie, >1 year) after TAVR and its association with QOL at follow-up in a subset of 124 patients with serial echocardiographic examinations.

METHODS

Study Population

From January 2014 until June 2017, a total of 437 patients with symptomatic severe AoS underwent TAVR in the Erasmus Medical Center, Rotterdam, the Netherlands. The association of Zva and long-term QOL was assessed in 250 patients, including 58 patients who died during follow-up (details in statistical analyses; cohort 1A, Figure). The association of Zva and EP was assessed in 192 patients surviving ≥1 year after TAVR (cohort 1B). The secondary objective (changes in Zva and effect on QOL) was studied in 124 patients with echocardiographic examination at baseline, post-TAVR and at 1 year (cohort 2). All patients were enrolled in the multidisciplinary TAVR Care and Cure program described elsewhere, which consists of a multidisciplinary assessment, treatment decision, and treatment in addition to a structured in-hospital and post discharge follow-up using prospective collection of a comprehensive set of predefined variables.[15] In short, all patients undergo a full medical history inventory including antecedent events, current comorbid conditions, and symptoms (New York Heart Association [NYHA], Canadian Cardiovascular Society class) followed by clinical evaluation and examination by the geriatrician using the TAVR Care and Cure protocol in which all measures and variables to be collected are defined. Among others, frailty was collected and defined by an Erasmus Frailty Score ≥3 which has been shown to predict delirium and mortality late after TAVR.[15] Cardiovascular imaging includes cardiac ultrasound, coronary angiography, and multislice computed tomography for the assessment of technical suitability and access site.[16,17] All patients are subsequently discussed in the multidisciplinary heart-team meeting consisting of interventional cardiologists, cardiac surgeons, an echocardiographist, and a geriatrician.[18] The study was approved by the institutional review committee, and all patients provided informed consent at the end of the pre-TAVR outpatient clinic visit during which the objective of anonymous data collection in the framework of the TAVR Care and Cure protocol were explained. The data, methods, and materials used to conduct the study will not be made available to other researchers for the purpose of reproducing the results or replication the procedure used to conduct the study. This study complies with the Declaration of Helsinki.

Echocardiography

Two-dimensional (Doppler) echocardiography was performed at baseline, post-TAVR (before discharge) and at 1-year follow-up using a Philips iE33 or a Epiq7 system (Philips, Best, the Netherlands) with the patient in a left lateral decubitus position. Standard echocardiographic evaluation of AoS severity was assessed according to European Association of Echocardiography/American Society of Echocardiography recommendations.[19] The aortic jet velocity was assessed in various acoustic windows, and aortic valve area was calculated using the continuity equation.[19] Systolic LV function

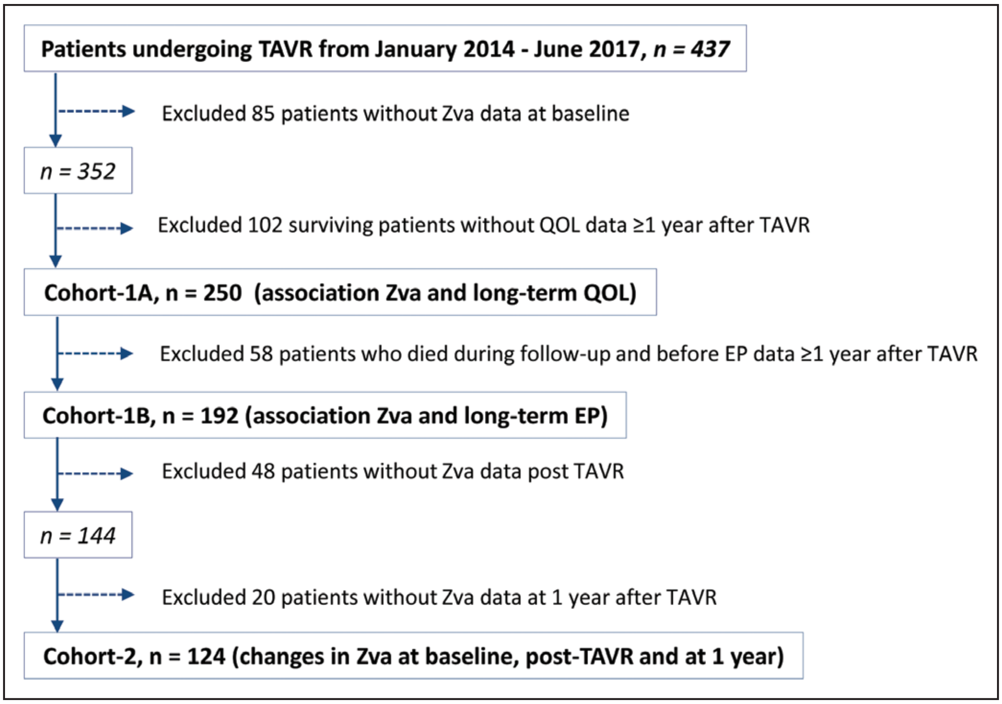

Figure. Patient selection flow chart.
EP indicates exercise performance; QOL indicates quality of life; TAVR, transcatheter aortic valve replacement; and Zva, valvulo-arterial impedance.

was assessed according to biplane modified Simpson rule, and diastolic function was assessed according to the 2016 American Society of Echocardiography/European Society of Cardiovascular Imaging guidelines.[20] LV dimensions were obtained in the parasternal long-axis view as previously described[6]; LV mass was calculated using the Devereux formula[21] and indexed to body surface area (LV mass index). LV stroke volume was calculated in the LV outflow tract from the pulsed wave Doppler recordings and indexed to body surface area (stroke volume index [SVI]).

Hemodynamic Parameters

The global LV hemodynamic load was estimated using Zva defined by the sum of the mean transaortic gradient and the systolic blood pressure divided by the LV SVI.[8] The systolic blood pressure (using an arm-cuff sphygmomanometer) and heart rate were recorded after at least 3 minutes supine position for the assessment of baseline Zva; the assessment of Zva post-TAVR and at 1 year was done using blood pressure measurements at the bedside before discharge and at 1-year outpatient clinic visits, respectively. A cutoff value for Zva of 5 mm Hg mL^{-1} m^{-2} was taken on the basis of prior studies that showed favorable outcomes in case of a low Zva (Zva <5 mm Hg·mL^{-1}·m^{-2}) as compared with a high Zva (Zva ≥5 mm·Hg mL^{-1}·m^{-2}).[8,13,14] Pulse pressure was defined by the difference between systolic and diastolic arterial blood pressure; systemic vascular resistance was calculated by the ratio of 80×mean arterial pressure divided by the cardiac output. Systemic arterial compliance was defined by the ratio of SVI to pulse pressure[22]; total arterial load was approximated using the effective arterial elastance index and estimated by the formula 0.9×systolic arterial blood pressure/SVI.[23]

Follow-Up, QOL, and EP

First, survival status was checked using the Dutch Civil Registry. After confirmation of survival, QOL/EP was measured in patients who survived ≥1 year after TAVR using the EuroQOL-5-dimensions-5 levels questionnaires, the NYHA functional classification in addition to questions related to physical fitness (taking a shower, walking 100 meter, walking 1 flight of stairs, and gardening).

The EuroQOL-5-dimensions-5 levels comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[24–26] Each dimension has 5 levels (no, slight, moderate, severe, and extreme problems) by which a unique health state per item is determined. These health states are converted into weighted health states (EQ-5D utility index) by applying scores on which full health has a value of 1 and death a value of 0. Therefore, patients who died before QOL assessment (n=58) were assigned an EQ-5D utility index of 0, a method used similar to the approach by Arnold et al[27] for the Kansas City Cardiomyopathy Questionnaire. Using the same methodology as Grandy and Fox[28] an ordinal variable for the EQ-5D Utility Index was created by categorizing the continuous variable into 4 levels for the purpose of regression analyses, with level 1 and 4 corresponding to (most) favorable versus unfavorable QOL, respectively.

In patients who survived ≥1 year after TAVR (n=192), EP was assessed by the Exercise Limitation Index which is composed of a summary score with 1 point assigned per limitation in daily activity out of the 5 items that were significantly associated with Zva ≥5 mm·Hg mL^{-1}·m^{-2} (mobility, self-care, showering, walking 100 meter, and walking stairs). Participants were classified as having an Exercise Limitation Index ranging from 0 to 5, with level 0 and 5 corresponding to (most) favorable versus unfavorable EP, respectively. QOL/EP data were not complete at baseline and are not included in the analysis.

For the assessment of serial changes in Zva (baseline, post-TAVR, 1 year after TAVR), we performed a sub-analysis in 124 patients with a complete set of data of both echocardiography/Zva and QOL assessment ≥1 year after TAVR allowing paired analyses. Compared with the 126 patients excluded from this analysis, the included 124 patients were less symptomatic and at lower operative risk (NYHA class ≥3: 58% versus 76%; EuroScore: 15% versus 20%), and showed better systolic and diastolic LV function in addition to a better renal function (ejection fraction 56% versus 52%; diastolic dysfunction 35% versus 52%; and creatinine 133 versus 100 mmol/L; Table I in the Data Supplement).

Statistical Analysis

Categorical variables are presented as frequencies and percentages and were compared with the χ^2 test or Fisher exact test. Normality of distributions was assessed with the Shapiro Wilk test. Normal and skewed continuous variables are presented as means (SD) and medians (interquartile range), respectively. Continues variables were compared using the Student *t* test, Mann Whitney *U* test, or Wilcoxon rank-sum test when appropriate.

We applied ordinal logistic regression analyses with Zva as the independent (continuous) variable and unfavorable QOL (measured by EQ-5D Utility Index, ordinal variable) as the dependent variable (cohort 1A). Analyses were then repeated with inclusion restricted to surviving patients ≥1 year post-TAVR (cohort 1B), with unfavorable QOL and unfavorable EP (measured by Exercise Limitation Index, ordinal variable) as the dependent variables. The results are presented as odds ratios with 95% CIs. All analyses were adjusted for variables known to be associated with Zva, QOL, and EP: age, gender, COPD, peripheral vascular disease, aortic valve area, baseline NYHA functional class, frailty, and time to death or measurement of QOL/EP.

Changes in continuous variables from baseline until follow-up were compared using 1-way repeated measures ANOVA (within-subjects ANOVA). All statistical analyses were performed using Statistical Package for Social Science for Windows version 21. Two sided *P* values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

Clinical baseline-, echocardiographic-, and hemodynamic characteristics of the total population and in patients with normal and elevated impedance (ie, Zva <5 and ≥5 mm Hg $mL^{-1}\cdot m^{-2}$) are presented in Tables 1 and 2. An elevated impedance (Zva ≥5 mm Hg $mL^{-1}\cdot m^{-2}$) was observed in 125 patients (50%) who—in comparison to those with normal impedance—had a higher prevalence of atrial fibrillation (42% versus 28%; *P*=0.024) and falling incidents (33% versus 21%; *P*=0.032), but less frequent use of calcium antagonists and ≥3 antihypertensive agents (16% versus 29%; *P*=0.017 and 10% versus 21%; *P*=0.023, respectively).

Also, patients with a Zva ≥5 mm Hg $mL^{-1}\cdot m^{-2}$ had a lower LV ejection fraction, SVI, cardiac index, and a lower systemic arterial compliance (51±13% versus 57±12%, *P*=0.001; 30±7 versus 44±9 mL/m^2, *P*<0.001 and 0.44±0.13 versus 0.68±0.22 $mL^{-1}\cdot m^{-2}$ mm Hg, *P*<0.001, respectively) and a higher heart rate (71±12 versus 67±11, *P*=0.006), MAP (102±14 versus 93±12 mm Hg, *P*<0.001), systemic vascular resistance (2167±596 versus 1449±312 dyne·s·cm^{-5}, *P*<0.001), and total arterial load (4.7±1.0 versus 2.9±0.5 mm Hg $mL^{-1}\cdot m^{-2}$, *P*<0.001). Their outflow tract diameter (21±2 versus 22±2 mm, *P*<0.001) was smaller as well as their aortic valve area (0.66±0.17 versus 0.84±0.20 cm^2, *P*<0.001) as compared with patients with Zva <5 mm Hg $mL^{-1}\cdot m^{-2}$.

Long-Term QOL and EP

Table 3 summarizes long-term QOL and EP data in patients with normal and elevated Zva. In an analyses including all patients, those with Zva ≥5 mm Hg $mL^{-1}\cdot m^{-2}$ showed a trend towards unfavorable QOL as compared with patients with Zva <5 mm Hg·$mL^{-1}\cdot m^{-2}$ (median EQ-5D Utility Index: 0.69 versus 0.77, *P*=0.12). In a repeated analyses restricted to surviving patients ≥1 year post-TAVR, this association became more apparent but did not reach statistical significance (EQ-5D Utility Index: 0.75 versus 0.80, *P*=0.056). With respect to EP, patients with Zva ≥5 mm Hg·$mL^{-1}\cdot m^{-2}$ more frequently reported limitations in mobility (88% versus 71%, *P*=0.004), self-care (40% versus 25%, *P*=0.019) and daily activities including taking a shower (53% versus 38%, *P*=0.030), walking 100 meter (76% versus 54%, *P*=0.001), and walking 1 flight of stairs (74% versus 54%, *P*=0.011) resulting in a lower Visual Analogue Score (70 versus 75 points, *P*=0.048) and a worse Exercise Limitation Index (3.3 versus 2.4, *P*<0.001) in addition to a higher frequency of NYHA functional class ≥III (37% versus 21%, *P*=0.017).

Multivariable ordinal logistic regression analyses for the associations with long-term unfavorable QOL and EP are presented in Table 4. In an analyses including all patients, baseline Zva was independently associated with unfavorable QOL (odds ratio [OR], 1.27 per mm Hg·$mL^{-1}\cdot m^{-2}$; CI, 1.04–1.57; *P*=0.023). This finding was confirmed in an analysis restricted to surviving patients (n=192; OR, 1.37 per mm Hg·$mL^{-1}\cdot m^{-2}$; CI, 1.08–1.73; *P*=0.010). Also, Zva was independently associated with unfavorable EP (OR, 1.31 per mm Hg·$mL^{-1}\cdot m^{-2}$; CI, 1.04–1.66; *P*=0.023). As a binary variable, Zva ≥5 mm Hg·$mL^{-1}\cdot m^{-2}$ was associated with a 2-fold higher risk of unfavorable QOL (OR, 1.98 [CI, 1.15–3.41]; *P*=0.014) and a 2.5-fold higher risk of unfavorable EP (OR, 2.55 [CI, 1.41–4.62]; *P*=0.002).

Changes in Hemodynamics Early and Late After TAVR

Table 5 summarizes the echocardiographic and hemodynamic changes before, post-TAVR and at 1-year in a

Table 1. Patient Characteristics According to Baseline Zva in Patients Undergoing TAVR

Baseline Characteristics	Total	Zva <5 mm Hg·mL^{-1}·m^{-2}	Zva ≥5 mm Hg·mL^{-1}·m^{-2}	*P* Value
	n=250	n=125	n=125	
Age, y	81±6	80±6	81±6	0.17
Male gender	116 (46)	58 (46)	58 (46)	1.0
Body mass index, kg/m^2	27.2±4.9	26.7±4.9	27.8±4.9	0.064
Body surface area, m^2	1.87±0.21	1.84±0.20	1.89±0.22	0.064
Diabetes mellitus	74 (30)	31 (25)	43 (34)	0.096
Hypertension	198 (79)	100 (80)	98 (78)	0.76
Hypercholesterolemia	158 (63)	73 (58)	85 (68)	0.12
Creatinine, mmol/L	117±92	122±118	112±55	0.39
Current or recent smoker	148 (59)	73 (58)	75 (60)	0.80
Chronic obstructive pulmonary disease	57 (23)	26 (21)	31 (25)	0.47
Previous malignancy	41 (16)	23 (18)	18 (14)	0.39
Active treatment for malignancy	12 (5)	6 (5)	6 (5)	1.0
Previous falling incident	67 (27)	26 (21)	41 (33)	0.032
Vertigo/dizziness	93 (37)	40 (32)	53 (42)	0.15
Peripheral vascular disease	121 (48)	56 (45)	65 (52)	0.26
Previous myocardial infarction	53 (21)	31 (25)	22 (18)	0.16
Previous coronary artery bypass graft	49 (20)	26 (21)	23 (18)	0.63
Previous percutaneous coronary intervention	80 (32)	37 (30)	43 (34)	0.42
Previous cerebrovascular event	26 (10)	14 (11)	12 (10)	0.68
Cognitive disorder	37 (15)	19 (15)	18 (14)	0.86
Medication				
Betablockers	155 (62)	81 (65)	74 (60)	0.40
ACE inhibitors/angiotensin receptor blockers	148 (59)	76 (61)	72 (58)	0.66
Calcium antagonists	56 (23)	36 (29)	20 (16)	0.017
Nitrates	33 (13)	19 (15)	14 (11)	0.36
≥3 antihypertensive medication classes	39 (16)	26 (21)	13 (10)	0.023
Atrial fibrillation	87 (35)	35 (28)	52 (42)	0.024
Permanent pacemaker	24 (10)	12 (10)	12 (10)	0.61
New York Heart Association class ≥III	167 (67)	84 (67)	83 (67)	0.97
Canadian cardiovascular society class ≥II	52 (21)	23 (19)	29 (23)	0.40
Erasmus Frailty score ≥III	68 (27)	33 (27)	35 (28)	0.78
Logistic European System for Cardiac Operative Risk Evaluation, %	17.2±11.6	16.5±10.2	17.9±12.9	0.32
Society of Thoracic Surgeons' Score, %	5.6±3.3	5.5±3.0	5.6±3.6	0.68

Categorical variables are presented as numbers (percentage), continuous variables are presented as mean±SD. TAVR indicates transcatheter aortic valve replacement; and Zva, valvuloarterial impedance.

paired analysis of 124 patients. As expected, the aortic valve area increased from 0.75±0.21 cm^2 at baseline to 1.79±0.51 cm^2 post-TAVR (P<0.001) and remained stable at 1-year follow-up that was associated with a reduction of the mean aortic gradient from 41±14 to 11±4 mm Hg after TAVR and 10±6 mm Hg at follow-up (P<0.001) and a reduction of the LV mass index (113±28, 108±27, 102±27 g/m^2; P<0.001). There were no significant changes in SVI.

After TAVR, there was a significant reduction in systolic and diastolic blood pressure (146±21 versus 135±19 mm Hg, P<0.001 and 73±12 versus 69±10 mm Hg, P=0.001, respectively), albeit that at follow-up blood pressures approached baseline values (140±25 and 75±11 mm Hg, respectively). The pulse pressure, however, was lower immediately after TAVR and remained so at 1-year. Overall, there was a significant increase in systemic arterial compliance (from 0.56±0.23 mL^{-1}·m^{-2}·mm Hg at baseline to 0.61±0.21 mL^{-1}·m^{-2}·mm Hg and 0.63±0.26 mL^{-1}·m^{-2}·mm Hg post-TAVR and 1-year, P<0.042) and a significant decrease in Zva (from 5.3±1.6 at baseline to 4.1±1.2 and 4.1±1.2 mm Hg·mL^{-1}·m^{-2}, post-TAVR and 1-year P<0.001). The proportion of patients with a Zva ≥5 mm Hg·mL^{-1}·m^{-2} at baseline decreased significantly post-TAVR (48% versus 21%, P<0.001) and remained 21% at 1 year.

Table 2. Echocardiographic and Hemodynamic Characteristics According to Baseline Zva in Patients Undergoing TAVR

	Total	Zva <5 mm Hg·mL^{-1}·m^{-2}	Zva ≥5 mm Hg·mL^{-1}·m^{-2}	*P* Value
	n=250	n=125	n=125	
Echocardiographic characteristics				
Left ventricular ejection fraction (%)	54±13	57±12	51±13	0.001
Left ventricular end-diastolic diameter, mm	53±9	53±10	52±7	0.47
Left ventricular end-systolic diameter, mm	39±12	39±13	40±11	0.47
Diastolic dysfunction				
Normal or relaxation abnormality	105 (57)	56 (54)	49 (61)	0.37
Pseudonormal or restrictive	80 (32)	48 (38)	32 (26)	0.36
No sufficient data	54 (22)	17 (14)	37 (30)	0.002
Aortic valve area, cm^2	0.75±0.21	0.84±0.20	0.66±0.17	<0.001
Mean aortic gradient, mm Hg	40±14	40±14	38±14	0.14
Left ventricular outflow tract velocity time index, cm	20±5	22±5	17±5	<0.001
Left ventricular outflow tract diameter, mm	21±2	22±2	21±2	<0.001
Stroke volume index, mL/m^2	37±10	44±9	30±7	<0.001
Cardiac index, L/min per m^2	2.5±0.7	2.9±0.7	2.1±0.5	<0.001
Left ventricular mass index*				
Gram per square meter	116±32	118±33	114±31	0.32
Normal or mildly abnormal	145 (61)	71 (61)	74 (61)	1.0
Moderately abnormal	30 (13)	12 (10)	18 (15)	0.29
Severely abnormal	64 (27)	34 (29)	30 (25)	0.44
Aortic regurgitation ≥moderate	31 (13)	21 (17)	10 (8)	0.055
Mitral regurgitation ≥moderate	56 (23)	26 (21)	30 (24)	0.57
Hemodynamic characteristics				
Heart rate (beats per minute)†	69±11	67±11	71±12	0.006
Systolic blood pressure, mm Hg	143±25	141±24	144±25	0.35
Diastolic blood pressure, mm Hg	76±13	75±12	78±13	0.021
Mean arterial blood pressure, mm Hg	97±14	93±12	102±14	<0.001
Pulsatile arterial load, mm Hg	71±21	69±21	72±22	0.20
Systemic arterial compliance, mL^{-1}·m^{-2}·mm Hg	0.56±0.22	0.68±0.22	0.44±0.13	<0.001
Systemic vascular resistance, dyne·s·cm^{-5}	1816±598	1449±312	2167±596	<0.001
Total arterial load, mm Hg·mL^{-1}·m^{-2}	3.78±1.17	2.92±0.47	4.65±1.01	<0.001
Zva, mm Hg·mL^{-1}·m^{-2}	5.32±1.50	4.19±0.57	6.46±1.25	<0.001
Valve type				
Self-expanding valve	73 (29)	38 (31)	35 (28)	0.73
Balloon-expanding valve	92 (37)	43 (35)	49 (40)	
Mechanical-expanding valve	83 (34)	43 (35)	40 (32)	

Categorical variables are presented as numbers (percentage), continuous variables are presented as mean±SD. TAVR indicates transcatheter aortic valve replacement; and Zva, valvulo-arterial impedance.

*Left ventricular mass index (LVMI) was considered normal or mildly abnormal if LVMI was <132 g/m^2 in men and <109 in women; moderately abnormal if LVMI was 131–149 g/m^2 in men and 108–122 in women; severely abnormal if LVMI was >148 g/m^2 in men and >121 g/m^2 in women.

†Minimum and maximum heart rate was 45 and 99 beats per minute, respectively.

Association Between Zva and QOL at Follow-Up

Table II in the Data Supplement shows the association between Zva post-TAVR and Zva at 1 year with long-term QOL/EP. Changes in QOL/EP between patients with normal and elevated Zva became apparent during follow-up. Patients with Zva ≥5 mm Hg·mL^{-1}·m^{-2} at 1-year follow-up were more frequently limited in mobility, self-care and daily activities (taking a shower, walking 100 meter, and walking 1 flight of stairs) as also reflected by a worse QOL (median EQ-5D index, 0.70 versus 0.81; *P*=0.008) and worse EP (mean exercise limitation index, 3.8 versus 2.5; *P*=0.001) in the context of higher NT-proBNP values (120 versus 60 mmol/L; *P*=0.025), as compared with patients with Zva <5 mm Hg·mL^{-1}·m^{-2} at 1-year follow-up.

Table 3. Association Between Baseline Zva and Long-Term Quality of Life and Exercise Limitation During Follow-Up

Parameters at Follow-Up	Total	Zva <5 mm Hg·mL^{-1}·m^{-2}	Zva ≥5 mm Hg·mL^{-1}·m^{-2}	*P* Value
All Patients	n=250	n=125	n=125	
EQ-5D utility index*	0.73 (0.22–0.88)	0.77 (0.28–0.88)	0.69 (0.10–0.83)	0.12
Survivors ≥1 y post-TAVR	n=192	n=96	n=96	
EQ-5D (n, % of patients indicating a problem)				
Mobility	150 (80)	67 (71)	83 (88)	0.004
Self-care	61 (32)	23 (25)	38 (40)	0.019
Usual activities	121 (64)	58 (62)	63 (67)	0.45
Pain/discomfort	107 (57)	52 (54)	55 (59)	0.55
Anxiety/depression	50 (27)	26 (28)	24 (26)	0.74
Visual analogue score	70 (60–80)	75 (60–85)	70 (55–80)	0.048
EQ-5D utility index	0.79 (0.60–0.89)	0.80 (0.66–0.92)	0.75 (0.57–0.88)	0.056
Daily activities (n, % of patients indicating a problem)				
Taking a shower	87 (45)	36 (38)	51 (53)	0.030
Walking 100 meter	125 (65)	52 (54)	73 (76)	0.001
Walking stairs (1 flight of)	121 (63)	52 (54)	69 (74)	0.011
Gardening	134 (70)	64 (67)	70 (73)	0.35
Exercise limitation index†	2.8±1.7	2.4±1.7	3.3±1.6	<0.001
New York Heart Association class ≥III	55 (29)	20 (21)	35 (37)	0.017
NT-proBNP, mmol/L at 1 y‡	75 (31–180)	69 (24–175)	75 (35–185)	0.23

Categorical variables are presented as numbers (percentage), continuous variables are presented as mean±SD or median (interquartile range). EQ-5D indicates EuroQOL-5-dimensions; NT-proBNP, N-Terminal Pro-B-Type Natriuretic Peptide; TAVR, transcatheter aortic valve replacement; and Zva, valvulo-arterial impedance.

*Fifty-eight patients who died before quality of life assessment at a median of 7 mo were assigned an EQ-5D utility score of 0. Of these, 29 patients (50%) had a baseline Zva ≥5 mm Hg·mL^{-1}·m^{-2}.

†Exercise limitation index indicates a summary score with 1 point assigned per limitation in daily activity out of the 5 items that were significantly associated with baseline Zva ≥5 mm Hg·mL^{-1}·m^{-2} by univariable analysis (mobility, self-care, showering, walking 100 meter, walking stairs). The index ranges from level 0 to 5 corresponding to (most) favorable vs. unfavorable long-term exercise performance, respectively.

‡NT-proBNP was assessed at a median of 368 days (IQR: 361-375) post-TAVR (data available in 167 patients).

DISCUSSION

We found that an elevated Zva was present in half of the patients with severe AoS undergoing TAVR and was found to be associated with an unfavorable long-term health-related QOL and EP. Despite significant improvements in Zva following TAVR, 21% of the patients continued to have an elevated Zva late after TAVR and this was associated with an unfavorable QOL and EP.

These findings need to be interpreted in the light of the fact that the present study concerns a single-center observational series with a rather limited sample size. Also, the outcome measure of interest (ie, QOL/EP) is of subjective nature notwithstanding the prospective use of a standard questionnaire and, therefore, can be influenced by other variables some of which are easy to define and collect (eg, age, comorbid conditions) but some of which are less so such as psychological and personality factors and others. For these reasons, we also included the Erasmus Frailty Score in our analysis which is composed of an extensive geriatric assessment that includes data from the Mini-Mental State Examination, the Malnutrition Universal Screening Tool, hand-grip strength, the Katz Index for scoring activities of daily living, and the Lawton and Brody index for scoring instrumental activities of daily living.[15] We indeed found that an Erasmus Frailty Score ≥III independently predicts QOL. Interestingly, multivariable analysis revealed that not only well known comorbid conditions such as chronic obstructive pulmonary disease, but also both frailty and baseline elevated Zva were strong and independent predictors of unfavorable outcomes during follow-up.

The question remains to what extent Zva affects QOL/EP in patients with AoS treated with TAVR and its pathophysiologic basis and, whether, Zva should be used in clinical practice, for example, patient selection and adjunctive pharmacological therapy. By multivariable analysis, we found that an elevated Zva was associated with a 2-to-2.5-fold increased risk of unfavorable QOL/EP at follow-up after TAVR. Obviously, it remains to be seen what this point estimate of this risk would be in a larger and different population and in the presence of a more comprehensive data set of variables potentially affecting QOL. In addition, more research is needed to define the optimal Zva cutoff value to predict adverse outcomes in elderly patients undergoing TAVR, since currently available studies found various cutoff levels ranging from ≥3.5 up to ≥5.5 mm Hg·mL^{-1}·m^{2}.[1,12]

Table 4. Multivariable Ordinal Logistic Regression Analyses for Associations Between Baseline Zva and Long-Term Unfavorable QOL and EP After TAVR Stratified According to Survival Status

	Unfavorable QOL in All Patients (n=250)		Unfavorable QOL in Survivors ≥1 y (n=192)		Unfavorable EP in Survivors ≥1 y (n=192)	
	(According to EQ-5D Utility Index*)		(According to EQ-5D Utility Index*)		(According to Exercise Limitation Index†)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age per year	0.99 (0.95–1.03)	0.53	0.99 (0.94–1.04)	0.59	1.02 (0.97–1.07)	0.50
Male gender	1.98 (1.17–3.37)	0.011	1.86 (1.00–3.45)	0.049	1.63 (0.89–2.98)	0.12
Chronic obstructive pulmonary disease	2.63 (1.42–4.85)	0.002	1.66 (0.82–3.39)	0.16	3.40 (1.65–7.0)	0.001
Peripheral vascular disease	1.48 (0.89–2.46)	0.14	0.71 (0.38–1.33)	0.29	0.72 (0.40–1.32)	0.29
Aortic valve area, per cm^2	2.19 (0.44–10.9)	0.34	0.89 (0.78–15.1)	0.21	0.59 (0.10–3.60)	0.57
Baseline NYHA class, per category	1.77 (1.21–2.58)	0.003	1.76 (1.12–2.78)	0.014	2.08 (1.32–3.26)	0.001
Erasmus frailty score ≥III	2.23 (1.31–4.00)	0.004	4.05 (1.98–8.30)	<0.001	2.49 (1.26–4.92)	0.009
Time to death or measurement of EQ-5D-index/exercise limitation index, per month	0.94 (0.92–0.95)	<0.001	1.04 (1.01–1.06)	0.008	1.02 (1.0–1.05)	0.12
Zva, per $mmHg \cdot mL^{-1} \cdot m^{-2}$ ‡	1.27 (1.04–1.57)	0.023	1.37 (1.08–1.73)	0.010	1.31 (1.04–1.66)	0.023
Zva ≥5 $mmHg \cdot mL^{-1} \cdot m^{-2}$‡	1.98 (1.15–3.41)	0.014	1.93 (1.06–3.52)	0.031	2.55 (1.41–4.62)	0.002

EP indicates exercise performance; EQ-5D, EuroQOL-5-dimensions; NYHA, New York Heart Association; OR, odds ratio; QOL, quality of life; TAVR, transcatheter aortic valve replacement; and Zva, valvulo-arterial impedance.

*EQ-5D utility index was categorized in level 1 to 4 corresponding to (most) favorable vs unfavorable long-term quality of life, respectively.

†Exercise limitation was categorized in level 0 to 5 corresponding to (most) favorable vs unfavorable long-term exercise performance, respectively.

‡All multivariable odds ratios are based on the inclusion of Zva as continuous variable. The odds ratio for Zva ≥5 $mmHg \cdot mL^{-1} \cdot m^{-2}$ was obtained by using this variable instead of Zva as continuous variable.

From a pathophysiologic point of view, the findings of the present study intuitively make sense and in particular in the elderly patients referred for TAVR. Given the etiology of AoS in such patients (degenerative atherosclerotic process) the correction of the valvular load may not suffice to (completely) restore QOL. Interestingly, we found that patients with an elevated valvuloarterial load also had a lower systemic arterial compliance and a higher systemic vascular resistance and total arterial load. In addition, there was only a modest decrease in Zva after TAVR that was also reported by Katsanos et al[13] and 21% of the patients in the present series showed an elevated Zva at >1 year after TAVR. The latter may hinder the beneficial effects of aortic valve replacement on LV load as suggested by higher BNP (B type natriuretic peptide) levels at 1 year in patients with elevated Zva. Of note, Roşca et al. reported higher BNP concentrations in patients with aortic stiffness.[29]

Whether excess arterial afterload can effectively be targeted in patients who received TAVR by medical intervention remains uncertain. Similar to Giannini et al,[14] we found that arterial compliance improved (ie, increase of ≈12%) during follow-up indicating the potential beneficial effects of adjunctive medical treatment aimed at enhancing arterial compliance, thereby, improving QOL. Lindman et al[31] reported that sildenafil was associated with a significant increase in stroke volume due a reduction of the systemic vascular resistance independent of valve load in patients with severe symptomatic AoS and normal ejection fraction.[30] Also, enalapril has been shown to improve symptoms and 6-minute walk test in a randomized trial of patients with symptomatic AoS.[32]

Despite these promising results, routine measures aimed at improving arterial afterload are lacking in current clinical practice. Nevertheless, clinicians taking care of AoS patients may still find Zva useful in improving risk stratification and clinical decision-making. Current guidelines recommend valve replacement based on valve-specific criteria (aortic valve area, mean gradient) to define severe AoS without addressing the vascular indices of excess afterload.[33,34] Zva is an easy to obtain measure and provides an integrated evaluation of valvular and vascular loads with prognostic relevant information in patients with asymptomatic moderate/severe AoS[1] and those undergoing TAVR.[13,14] Our findings demonstrate that Zva also identifies patients at risk for unfavorable long-term QOL, which is sometimes equally important as life-expectancy especially in elderly patients who are currently referred for TAVR.

Limitations

As mentioned above, the present study concerns a single-center multidisciplinary prospective study during which all variables and outcomes have been defined before starting the study (TAVR Care & Cure program). Yet, the sample size was rather small and might have been subjected to selection bias due to the fact that ultrasound data before, after and at 1 year had to be available of sufficient quality. This also held for QOL/EP assessment. Although unfavorable

Table 5. Echocardiographic and Hemodynamic Changes Before, After, and at 1-Year Follow-Up After TAVR (Subanalysis 124 Patients)

	Pre-TAVR	Post-TAVR	1 y After TAVR	*P* Value	*P* Value	*P* Value
	n=124	n=124	n=124	(Pre vs Post)	(Pre vs 1-y)	(Post vs 1-y)
Echocardiographic characteristics						
Left ventricular ejection fraction, %	56±11	56±11	53±13	1.0	0.19	0.17
Left ventricular end-diastolic diameter, mm	52±7	50±7	51±7	0.017	0.19	1.0
Left ventricular end-systolic diameter, mm	38±11	36±9	36±9	0.43	1.0	1.0
Diastolic dysfunction						
Normal or relaxation abnormality	60 (65)	58 (73)	64 (74)	0.39	0.12	1.0
Pseudonormal or restrictive	32 (35)	22 (28)	23 (26)	0.39	0.12	1.0
No sufficient data	32 (35)	44 (35)	37 (30)	NA	NA	NA
Aortic valve area, cm^2	0.75±0.21	1.79±0.51	1.77±0.48	<0.001	<0.001	0.99
Mean aortic gradient, mm Hg	41±14	11±4	10±6	<0.001	<0.001	0.43
Left ventricular outflow tract velocity time index, cm	20±5	20±5	20±5	1.0	0.86	0.94
Left ventricular outflow tract diameter, mm	21.0±2	21.2±2	21.5±2	0.61	0.004	0.055
Stroke volume index, mL/m^2	38±11	39±11	38±10	1.0	1.0	1.0
Stroke volume index <35 mL/m^2	50 (40)	52 (42)	47 (38)	0.88	0.76	0.51
Left ventricular mass index*						
Gram per square meter	113±28	108±27	102±27	0.30	<0.001	0.054
Normal or mildly abnormal	79 (67)	81 (71)	85 (74)	0.56	0.28	0.70
Moderately abnormal	14 (12)	12 (11)	13 (11)	0.82	1.0	0.66
Severely abnormal	25 (21)	21 (18)	17 (15)	0.77	0.12	0.21
Aortic regurgitation ≥moderate	15 (12)	6 (5)	10 (8)	0.049	0.50	0.29
Mitral regurgitation ≥moderate	19 (15)	19 (16)	26 (21)	1.0	0.17	0.14
Hemodynamic characteristics						
Systolic blood pressure, mm Hg	146±21	135±19	140±25	<0.001	0.061	0.22
Diastolic blood pressure, mm Hg	73±12	69±10	75±11	0.001	0.45	<0.001
Mean arterial blood pressure, mm Hg	97±14	90±11	97±13	<0.001	1.0	<0.001
Pulsatile arterial load, mm Hg	73±20	66±16	64±23	0.002	0.004	1.0
Systemic arterial compliance, mL^{-1}·m^{-2}·mm Hg	0.56±0.23	0.61±0.21	0.63±0.26	0.11	0.042	1.0
Total arterial load, mm Hg·mL^{-1}·m^{-2}	3.8±1.2	3.4±1.0	3.5±1.0	0.012	0.12	1.0
Zva, mm Hg·mL^{-1}·m^{-2}	5.3±1.6	4.1±1.2	4.1±1.2	<0.001	<0.001	1.0

Categorical variables are presented as numbers (percentage), continuous variables are presented as mean±SD. TAVR indicates transcatheter aortic valve replacement; and Zva, valvulo-arterial impedance.

*Left ventricular mass index (LVMI) was considered normal or mildly abnormal if LVMI was <132 g/m^2 in men and <109 in women; moderately abnormal if LVMI was 131–149 g/m^2 in men and 108–122 in women; severely abnormal if LVMI was >148 g/m^2 in men and >121 g/m^2 in women.

QOL as measured by the EuroQOL questionnaire concerns a well-validated tool in cardiovascular medicine, the use of the exercise limitation index (consisting of items from EQ-5D instruments and questions related to physical fitness) lacks validation and, thus, concerns a limitation in this study. Nevertheless, it should be noted that dedicated assessment tools for such purposes specifically designed for, and validated in elderly patients undergoing TAVR are currently not available. Of note, blood pressure data were not collected during the echocardiographic assessment and may have influenced the assessment of Zva albeit that the frequency of elevated Zva at baseline and early and late after TAVR was similar in this and other studies.[13] Also, certain conditions such as atrial fibrillation are known to affect the quantification of Zva as SVI estimation is dependent on the average of multiple CW Doppler tracings. At last, moderate/severe aortic regurgitation generally increases systolic blood pressure and mean gradient both affecting Zva quantification.[1]

Conclusions

Baseline elevated Zva in patients with AoS undergoing TAVR exists in half of the patients and has unfavorable impact on health-related QOL and EP at long-term follow-up. Despite successful TAVR, one-fifth of the patients has elevated Zva during early and long-term follow-up and remains associated with impaired QOL and EP.

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