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ORIGINAL RESEARCH

Valvuloarterial Impedance Predicts Heart Failure Readmissions in Patients Undergoing Transcatheter Aortic Valve Replacement

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ABSTRACT

Background: Elevated valvuloarterial impedance (Zva) has been associated with mortality in severe aortic stenosis (AS) patients. However, its role in predicting heart failure (HF) readmissions after transcatheter aortic valve replacement (TAVR) remains unknown.

Methods: We evaluated 198 consecutive patients who underwent TAVR at our institution from 2012 to 2016. Clinical, laboratory, procedural, echocardiographic (ECHO) data and HF readmissions at 1-year were collected. Zva was calculated from ECHO as (systolic blood pressure + transvalvular gradient)/stroke volume index.

Results: The mean age of all patients was 82 ± 7 years, 51% were males and 95% were Caucasians. Median duration of follow-up was 9 (Interquartile range: 12) months. The majority of patients had hypertension (93%) and 24.7% had heart failure symptoms with reduced EF (<50%). Use of beta-blockers was 64%, diuretics was 64%, angiotensin converting enzyme inhibitors was 25%, aldosterone receptor blockers was 16%, and potassium-sparing diuretics was 8%. Patients with a high pre-TAVR Zva (≥6.3 mmHg. $mL^{-1}.m^2$) were more likely to present with HF readmissions at 1-year in both unadjusted (34.2% vs. 18.1%, $p = 0.03$) and adjusted analysis (Hazards Ratio [HR] = 2.08 [95%CI: 1.00–4.29], $p = 0.04$). Patients with a Zva that either remained unchanged or increased post-TAVR had significantly higher mortality at 1-year post-procedure in the unadjusted (18.2% vs. 6.3%, $p = 0.02$) and adjusted analysis (HR = 2.97 [95%CI: 1.07–8.25], $p = 0.04$).

Conclusion: Zva is a novel prognostic marker for HF readmissions at 1-year post-TAVR and can be routinely measured on ECHO. Further prospective studies validating the utility of Zva for risk stratification are warranted.

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KEYWORDS Heart failure; mortality; readmissions; transcatheter aortic valve replacement; valvuloarterial impedance

Introduction

Transcatheter aortic valve replacement (TAVR) is a well-established treatment for severe aortic stenosis in symptomatic patients who are prohibitive, high- or intermediate-risk for surgical aortic valve replacement.[1,2] Due to the increased utilization of TAVR for management of aortic stenosis (AS), there is growing emphasis on risk stratifying these patients to ensure they have improved outcomes following the procedure. In addition to standardized risk assessment tools[3] based on presence of risk factors, certain echocardiographic (ECHO)-based indices, such as valvuloarterial impedance (Zva), which is used to assess the global left ventricular hemodynamic load, have been growing in importance.[4,5] This concept takes into consideration the left ventricular afterload caused by the stenotic valve, as well as vascular resistance. In elderly patients, the etiology of AS is often due to degeneration and calcification of the valve, which also occurs in the rest of the systemic circulation, thereby, contributing to decreased effective arterial elastance [Ea]—a measure of vascular resistance calculated as systolic blood pressure (SBP)/stroke volume (SV).[6–8] Zva is a novel ECHO-based index for assessment of both these parameters and has been shown to be superior to standard measurements of AS and, more importantly, has been demonstrated to have prognostic significance.[4,5]

With changing reimbursement policies, one outcome that has gained increasing focus is hospital readmission rate for heart failure (HF) following TAVR procedure. HF readmission is one of the most common cardiac-related readmissions within the first year post-TAVR.[9] Several studies have looked at causes for unexpected readmission in the first year post-TAVR.[10,11] Repeat hospital admissions are associated with worse outcomes, poor quality of life, and increased healthcare expenditure.[11] The patient demographic undergoing TAVR is often frail, with significant comorbidities, which also increases the risk of readmissions. Thus, risk stratification of patients at increased risk of repeat hospitalization post-TAVR is imperative. In this study, we sought to evaluate the impact of Zva on outcomes following TAVR with a specific focus on predicting heart failure readmissions.

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Using a prospective registry from our tertiary care center, we performed a retrospective analysis aimed to address the following key questions: (1) to determine the ECHO parameters associated with increased Zva with attention to low-flow, low-gradient aortic stenosis; (2) to determine if increased Zva is associated with higher risk of HF readmissions; (3) to determine if Zva post-TAVR is predictive of worse outcomes and all-cause mortality.

Materials and methods

Study population

All patients (N = 383) were enrolled from the prospective TAVR registry of consecutive patients undergoing the procedure at our tertiary care center (Gates Vascular Institute, Buffalo, New York) from January 2012 to July 2016. Patients in whom follow-up was unavailable at 1-month post-TAVR were excluded. Those patients in whom an ECHO demonstrated evidence of moderate to severe aortic insufficiency (n = 69) and/or evidence of moderate-to-severe mitral regurgitation (n = 98) were excluded from the study. Additionally, those patients in whom pre-TAVR ECHO was not available (n = 18) were excluded. The remainder of the patients (n = 198) were used for analysis and formed the final study group (Figure 1). All data variables were obtained using the standardized definitions, conforming to the standards of the Society of Thoracic Surgeons and American College of Cardiology's National Transcatheter Valve Therapy registry.[12] All patients underwent routine follow-up post-TAVR at 30 days and 1 year, as per the above guidelines.

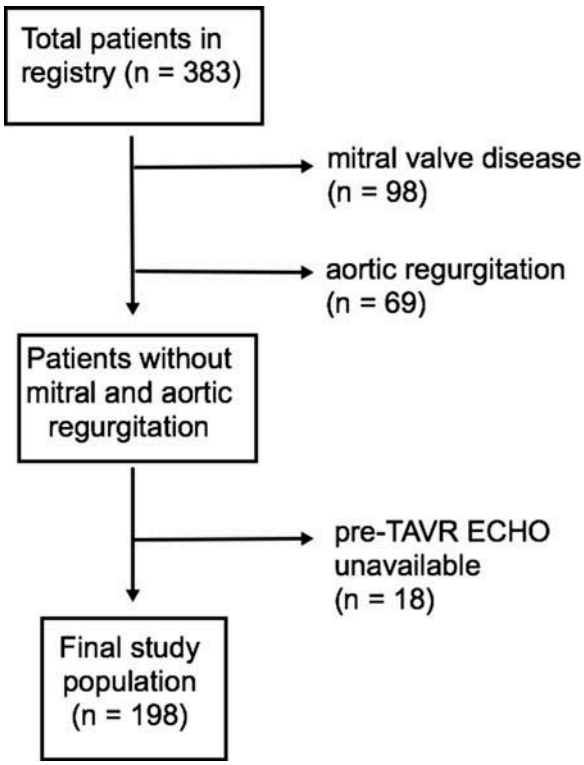

Figure 1. Flowchart showing selection of the study population. ECHO, echocardiogram.

Clinical characteristics

Patient demographics, baseline characteristics, relevant clinical variables including comorbid conditions were collected on all patients. Data regarding patients' home medications were collected including use of diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, aldosterone receptor blockers, and potassium sparing diuretics. Additionally, anti-platelet agents, vitamin K antagonist (warfarin), and direct oral anticoagulant (Dabigatran, Rivaroxaban, Apixaban, and Edoxaban) use were obtained. The procedural, laboratory, and noninvasive testing, including routine electrocardiograms, were collected. Laboratory data including brain natriuretic peptide, creatinine, hemoglobin, platelet count, and liver function tests were obtained pre-TAVR and during 1-month follow-up.

Echocardiographic parameters

All study participants enrolled in the study underwent a comprehensive ECHO evaluation both pre-TAVR, at 1-month and at 1-year post-TAVR. All measurements were obtained according to the current American Society of Echocardiography guidelines.[13] The assessment of the severity of aortic stenosis, including mean and peak velocities, were obtained using continuous-wave Doppler assessment. The transvalvular gradients were subsequently calculated using the modified Bernoulli equation. The stroke volume was calculated as the product of left ventricular (LV) outflow tract area and velocity-time integral on pulsed-wave Doppler echocardiography of the LV outflow tract and was indexed for body surface area (stroke volume index [SVi]). The left ventricular ejection fraction (LVEF) was calculated using the biplane method of discs (modified Simpson rule).[13] The Zva was obtained using the formula: Zva = (systolic arterial pressure + mean transvalvular pressure gradient)/SVi.[14] Zva represents the pressure recovery downstream from the stenosed aortic valve and is affected by factors associated with the valve as well as increased arterial resistance opposing LV ejection.

Outcomes assessment

The primary outcome of our study was HF readmissions at 1-year during follow-up post-TAVR. HF readmission was defined using the standard definitions of the Multi-ethnic Study of Atherosclerosis study[15] as the presence of 2/3 criteria: (1) inpatient hospitalization for a patient receiving medical treatment for HF diagnosed by a physician; (2) pulmonary edema/congestion seen on chest roentgenogram; and (3) evidence of LV systolic dysfunction by ECHO. The occurrence of all-cause mortality post-TAVR was evaluated in all patients up to 1-year post-procedure. Mortality data was obtained from the electronic medical records of the patients and from the USS Social Security Death Index and New York State Death Index records. The University at Buffalo Institutional Review Board approved all procedures with a waiver of individual informed consent.

Statistical analysis

The categorical variables were described as frequency (%) and compared using either Chi-square tests of independence or Fishers Exact test, as appropriate. Continuous variables were summarized as mean ± SD for normally distributed data and medians with interquartile range (IQR) if the data was skewed. Continuous variables were compared across groups using a two-sample/paired *t*-test or Mann-Whitney U test, as appropriate. Patients with the highest quartile Zva (≥6.3 mmHg.mL^{-1}.m^2) were compared with those with the lower three quartiles. Correlation between Zva and ECHO variables was performed using Pearson's correlation. Univariate analysis was performed to determine predictors of HF hospitalization post-TAVR. The variables that were significantly associated with HF hospitalization in univariate analyses were then entered in the multivariate model to adjust for confounders associated with Zva and HF hospitalization post-TAVR. Next, the assumptions of proportional hazards were confirmed for performing Cox Regression analysis evaluating the cumulative occurrence of HF hospitalization as a function over time to obtain the hazards ratio (HR). The event curves were created to compare survival among (1) patients with high Zva (≥ 6.3 mmHg.mL^{-1}.m^2) pre-TAVR compared to (2) those without lower Zva (< 6.3 mmHg.mL^{-1}.m^2) pre-TAVR. Statistical analysis was performed using STATA v13.0 (StataCorp, College Station, Texas). A *p*-value of <0.05 was considered significant.

Results

Study population

The baseline demographic and clinical characteristics of all patients (*N* = 198) are outlined in Table 1. Median duration of follow-up was 9 (IQR: 1,13) months. For the primary analysis, pre-TAVR Zva measurements were utilized. Patients in the highest quartile Zva (≥ 6.3 mmHg.mL^{-1}.m^2) had similar baseline characteristics compared to those in the lower three quartiles (< 6.3 mmHg.mL^{-1}.m^2). However, patients in the highest quartile Zva were more likely to have a history of atrial fibrillation/flutter compared to those within the lower three quartiles (p = 0.01). The most common presenting symptom was shortness of breath (n = 167, 84.3%) and this did not differ among patients within the highest quartile compared to the lower three quartiles. The New York Heart Association (NYHA) functional class during presentation did not differ significantly among patients in the highest quartile Zva compared to the lower three quartiles. Additionally, medication use including diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, aldosterone receptor blockers, and potassium sparing diuretics did not differ between the two groups, as shown in Table 1.

Echocardiographic characteristics

Detailed ECHO parameters obtained pre-TAVR are outlined in Table 2. The LV geometry including LV internal diameter, posterior wall thickness, and septal wall thickness did not differ among patients with the highest quartile Zva and the lower three quartiles. Although LVEF was not significantly different, the indexed stroke volume (SVi) was significantly lower among patients within the highest quartile Zva. The patients in the highest quartile Zva had higher valvular load (i.e. more severe valvular stenosis) evident by a lower indexed aortic valve area (AVAi), and a lower dimensionless valve index. The transvalvular peak and mean gradients did not differ significantly among those in the highest quartile

Table 1. Baseline clinical characteristics of all patients.

Variables	Zva < 6.3 (n = 160)	Zva ≥ 6.3 (n = 38)	All patients (n = 198)	p-value
Demographics				
Sex (male)	20 (45.5)	175 (51.6)	195 (50.9)	0.44
Age at procedure	82 ± 8	84 ± 9	82 ± 7	0.14
Body Mass Index	33.7 ± 7.9	35.8 ± 9.4	34.4 ± 8.2	0.16
Race (White)	152 (95)	36 (94.7)	188 (94.9)	0.95
Clinical characteristics				
Smoker	5 (3.1)	0 (0)	5 (2.5)	0.59
Diabetes	60 (37.5)	18 (47.4)	78 (39.4)	0.26
Hypertension	151 (94.4)	34 (89.5)	185 (93.4)	0.28
Systolic heart failure	37 (23.6)	11 (29.7)	48 (24.7)	0.44
Peripheral vascular disease	68 (42.5)	14 (36.8)	82 (41.4)	0.52
Society of Thoracic Surgeons Risk Score	8.8 (6.7, 11.0)	9.0 (6.4, 12.3)	8.8 (6.2, 11.0)	0.32
Prior myocardial infarction	25 (15.6)	7 (18.4)	32 (16.2)	0.67
Atrial fibrillation/flutter	59 (36.9)	23 (60.5)	82 (41.4)	0.01
NYHA Functional class (III or higher)	140 (87.5)	36 (94.7)	176 (88.9)	0.39
Presenting symptom				
Shortness of breath	135 (84.4)	32 (84.2)	167 (84.3)	0.89
Chest pain	11 (6.9)	2 (5.3)	13 (6.6)	
Syncope	14 (8.8)	4 (10.5)	18 (9.1)	
Home medications				
Diuretics	100 (62.5)	27 (71.1)	127 (64.1)	0.32
Beta blockers	105 (65.6)	21 (55.3)	126 (63.6)	0.23
Calcium channel blockers	35 (21.9)	10 (26.3)	45 (22.7)	0.56
Angiotensin converting enzyme inhibitor	38 (23.8)	11 (28.9)	49 (24.7)	0.51
Aldosterone receptor blockers	28 (17.5)	4 (10.5)	32 (16.2)	0.46
Potassium sparing diuretics	12 (7.5)	4 (10.5)	16 (8.1)	0.52

Note. Values are mean ± standard deviation, median (Interquartile range), *n* (%).
Zva, valvuloarterial impedance; NYHA, New York Heart Association.

Table 2. Echocardiographic characteristics of patients based on valvuloarterial impedance (Zva).

Variables	Zva < 6.3 (n = 160)	Zva ≥ 6.3 (n = 38)	All patients (n = 198)	p-value
LV geometry				
LV internal diameter (mm) systole	31 (25, 38)	31 (26, 38)	32 (25, 38)	0.92
LV internal diameter (mm) diastole	43 (37, 49)	44 (35, 50)	43 (37, 50)	0.74
Septal wall thickness (mm)	13 (12, 15)	14 (11, 15)	13 (12, 15)	0.80
Posterior wall thickness (mm)	13 (11, 14)	12 (12, 16)	13 (11, 14)	0.24
LV systolic function				
LV EF (%)	58 (50, 63)	55 (48, 62)	58 (50, 63)	0.10
Stroke volume indexed for Body Surface Area (mL/m^2)	38.6 (32, 47)	21.7 (19.2, 25.9)	35.2 (28, 44.2)	< 0.001
Left atrium				
Left atrial indexed volume (cm^3/m^2)	42 (35, 51)	35 (34, 49)	42 (35, 50)	0.15
Aortic stenosis severity				
Transvalvular peak gradient	66 (53, 80)	65 (53, 85)	65 (52, 79)	0.79
Transvalvular mean gradient	40 (32, 48)	42 (37, 54)	40 (32, 48)	0.08
Aortic valve indexed area (cm^2/m^2)	0.37 ± 0.1	0.29 ± 0.1	0.37 ± 0.1	< 0.001
Dimensionless valve index	0.26 (0.21, 0.32)	0.19 (0.14, 0.25)	0.25 (0.2, 0.32)	< 0.001
Vascular load				
Right ventricular systolic pressure (mm Hg)	41 (34, 52)	50 (38, 70)	43 (35, 54)	0.01
Systolic arterial pressure (mm Hg)	129 ± 20	133 ± 21	130 ± 20	0.34
Elastance pre-TAVR (mmHg.mL^{-1})	1.8 (1.5, 2.3)	3.2 (2.8, 3.6)	2.0 (1.6, 2.5)	< 0.001
Valvuloarterial impedance	4.5 (3.6, 5.4)	8 (6.8, 8.5)	4.9 (3.1, 6.2)	< 0.001

Note. Values are mean ± standard deviation, median (Interquartile range), *n* (%).
LV, left ventricle; EF, ejection fraction.

compared to the lower three quartiles of Zva. As expected, patients in the highest quartile Zva had higher systolic arterial pressures and higher vascular resistance measured by effective arterial elastance, as shown in Table 2.

Correlation with low-flow low-gradient state

We evaluated the correlation of Zva measured pre-TAVR with key parameters of low-flow, low-gradient state including: AVAi, and posterior wall thickness. As shown in Figure 2A, pre-TAVR Zva correlated negatively with AVAi (Pearson's coefficient: −0.46, $p < 0.001$). Zva correlated positively with posterior wall thickness but did not reach statistical significance (Pearson's coefficient: 0.12, $p = 0.09$), Figure 2B.

Heart failure hospitalizations

The primary outcome was HF hospitalizations at 1-year post-TAVR, which occurred among 41 (21%) patients. As shown in Figure 3, in unadjusted analysis, the patients with the highest quartile Zva had a significantly higher risk of HF hospitalizations post-TAVR (34.2% vs. 18.1%, $p = 0.03$). Next, univariate analysis was performed to identify predictors of HF hospitalizations as shown in Table 3. After adjusting for significant variables identified during the univariate analysis ($p < 0.1$) and known risk factors, a high Zva (≥ 6.3 mmHg.mL^{-1}.m^2) (HR = 2.08 [95%CI: 1.00–4.29], $p = 0.04$) and NYHA functional Class II or higher (HR = 2.41 [95%CI: 1.27–4.60], $p = 0.007$) remained independent predictors of HF hospitalizations post-TAVR.

Change in Zva post-TAVR

ECHO obtained at 1-month post-TAVR demonstrated a significant reduction in the Zva post-procedure (3.8 [IQR: 3.0, 5.9] vs. 4.9 [IQR: 3.9, 5.9], $p < 0.001$). However, among 50 (20.2%) patients, the Zva remained unchanged or increased post-TAVR. Table 4 outlines patient characteristics among those in whom Zva decreased compared to those in whom Zva remained unchanged or increased post-TAVR. The clinical characteristics were similar between the two groups except diabetes which was less frequent in patients in whom Zva remained unchanged or increased post-TAVR. During follow-up, the mean systolic blood pressure (sBP) remained significantly higher (137 ± 17 vs. 128 ± 16 mmHg, $p = 0.002$) in patients in whom Zva remained unchanged or increased post-TAVR. However,

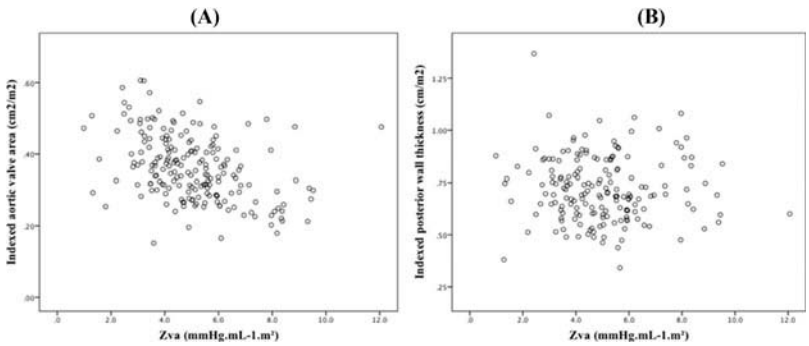

Figure 2. Correlation of Zva with (A) indexed aortic valve area and (B) indexed posterior wall thickness.
Pre-TAVR Zva correlated negatively with indexed aortic valve area (Pearson's coefficient: −0.46, $p < 0.001$) and correlated positively with indexed posterior wall thickness (Pearson's coefficient: 0.12, $p = 0.09$) respectively. Zva, valvuloarterial impedance; TAVR, transcatheter aortic valve replacement.

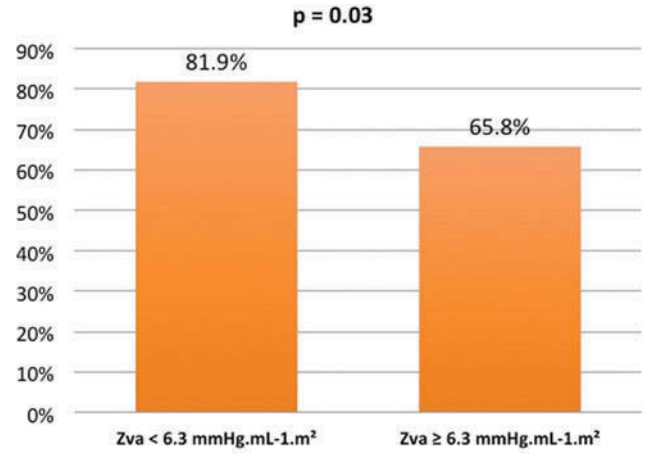

Figure 3. Heart failure readmissions among patients with the highest quartile valvuloarterial impedance (Zva) pre-transcatheter aortic valve replacement (TAVR) compared with the lower three quartiles.

Patients with highest quartile Zva pre-TAVR had significantly higher risk of heart failure readmissions ($p = 0.03$) compared to the lower three quartiles of Zva. Zva, valvuloarterial impedance; TAVR, transcatheter aortic valve replacement.

Table 3. Univariate predictors of heart failure hospitalizations among all patients at 1-year post-transcatheter aortic valve replacement (TAVR).

Variables	Odds Ratio	(95% Confidence Intervals)	p-value
Risk factors			
Age	1.02	0.98–1.07	0.31
Sex (female)	0.85	0.44–1.64	0.62
Hypertension	0.62	0.19–2.03	0.43
Diabetes	0.97	0.49–1.91	0.92
Prior myocardial infarction	0.34	0.10–1.17	0.09
Prior stroke	0.38	0.09–1.66	0.20
Current smoker	1.90	0.36–10.15	0.45
Atrial flutter/fibrillation	0.67	0.33–1.34	0.25
Peripheral vascular disease	1.05	0.77–1.43	0.77
Systolic heart failure	1.11	0.50–2.43	0.80
Society of Thoracic Surgeons Risk Score	1.06	0.99–1.13	0.09
Procedural characteristics			
Anesthesia type (general)	0.86	0.44–1.66	0.64
Post-procedure BNP	1.00	1.00–1.01	0.13
Post-procedure NYHA Class II or higher	3.34	1.67–6.69	0.001
Echocardiographic characteristics			
Post-TAVR LVEF	0.98	0.95–1.01	0.19
Stroke volume (indexed)	1.01	0.99–1.02	0.62
LV internal diameter (diastole)	0.85	0.59–1.23	0.39
Mitral regurgitation	1.32	0.93–1.86	0.12
Tricuspid regurgitation	1.01	0.74–1.40	0.93
Peak transvalvular velocity	1.39	0.95–2.03	0.09
Vascular load			
RV systolic pressure	1.02	0.99–1.04	0.08
Valvuloarterial impedance ($\geq$ 6.3 mmHg.mL^{-1}.m^2)	2.36	1.08–5.17	0.03

Note. BNP, brain natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; RV, right ventricle.

transvalvular gradient among patients in whom post-TAVR Zva decreased [Median 5 (IQR: 3.0, 7.3)] was similar to those in whom Zva remained unchanged or increased post-TAVR (Median 5.0 [IQR: 3.0, 7.0] mmHg, $p = 0.73$). The vascular resistance post-TAVR measured by the effective arterial elastance (Ea) was significantly higher among patients in whom Zva remained unchanged or increased post-TAVR (Median 2.7 [IQR: 2.3, 3.4] vs. 1.8 [IQR: 1.5, 2.4], $p < 0.001$).

Table 4. Patient characteristics based on change in valvuloarterial impedance (Zva) post transcatheter aortic valve replacement (TAVR).

Variables	Zva decreased post-TAVR (n = 122)	Zva increased or unchanged post-TAVR(n = 50)	p-value
Demographics			
Sex (male)	62 (50.8)	23 (46)	0.57
Age at procedure	83 ± 7	82 ± 7	0.69
Body Mass Index	34.3 ± 8.2	33.1 ± 8.8	0.40
Race (White)	114 (93.4)	49 (98)	0.45
Clinical characteristics			
Smoker	2 (1.6)	1 (2)	1.00
Diabetes	52 (42.6)	12 (24)	0.02
Hypertension	115 (94.3)	47 (94)	1.00
Systolic heart failure	28 (23.3)	11 (22.9)	0.95
Peripheral vascular disease	50 (41)	23 (46)	0.55
Society of Thoracic Surgeons Risk Score	9.2 (7.0, 11.6)	8.5 (5.9, 10.8)	0.21
Prior myocardial infarction	21 (17.2)	5 (10)	0.23
Atrial fibrillation/flutter	55 (45.1)	18 (36)	0.27
Elastance pre-TAVR (mmHg.mL^{-1})	1.6 (1.2, 2.2)	2.2 (1.8, 2.7)	0.08

Note. Values are mean ± standard deviation, median (Interquartile range), *n* (%).

Change in Zva post-TAVR and mortality

During follow-up, 18 (9%) patients died and among them, 10 patients' vital statistics were determined from the Social Security and NY State Death Index records. In an unadjusted analysis, those patients in whom Zva either remained unchanged or increased post-TAVR had significantly higher mortality at 1-year post-procedure (18.2% vs. 6.3%, $p = 0.02$). As shown in Figure 4, survival at 1-year remained significantly worse among patients in whom Zva either remained unchanged or increased post-TAVR. After adjusting for age, the Society of Thoracic Surgeons risk score, and presence of atrial fibrillation in a Cox proportional hazards model, lack of reduction or increase in Zva post-TAVR remained a strong

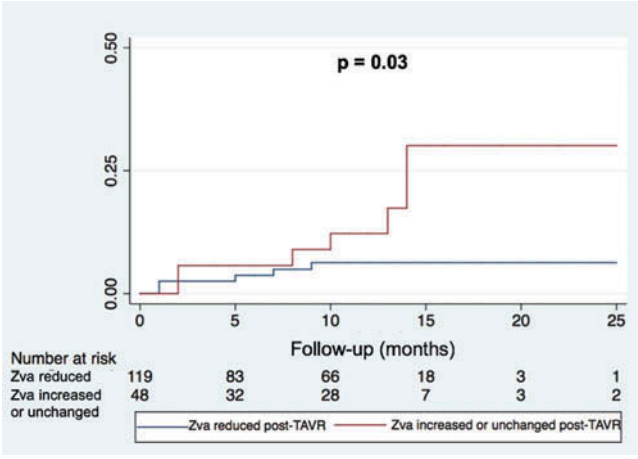

Figure 4. Hazard curves comparing survival among patients in whom valvuloarterial impedance (Zva) either remained unchanged or increased with those in whom Zva was reduced post-TAVR.

Survival at 1-year remained significantly worse among patients in whom Zva either remained unchanged or increased post-TAVR ($p = 0.03$). Zva, valvuloarterial impedance; TAVR, transcatheter aortic valve replacement.

predictor of 1-year survival (HR = 2.97 [95%CI: 1.07–8.25], $p = 0.04$).

Discussion

We demonstrated the utility of Zva, a novel ECHO-based parameter, in risk stratification of patients undergoing TAVR for prediction of HF readmissions. Our study has the following key findings: (1) a high Zva corresponds to higher valvular load with higher systolic arterial pressures, and increased vascular resistance; (2) Zva correlated negatively with AVAi, and positively with posterior wall thickness, which corresponds with a low-flow, low-gradient state; (3) higher Zva was identified to be an independent predictor of HF readmissions post-TAVR; and (4) lack of change or increase in Zva post-TAVR, which was primarily driven by sBP and vascular resistance, remained a strong predictor of 1-year mortality post-TAVR.

Significance of Zva in AS/TAVR

The primary physiology of aortic stenosis involves degenerative and atherosclerotic changes in the aortic valve which is also seen downstream in the vascular bed and systemic circulation. The LV has to push blood against two forces, for the following reasons: (1) increased valvular load due to AS; and (2) increased arterial load due to vascular resistance. Pibarot and colleagues introduced a novel ECHO parameter (Zva), which measures the combined hemodynamic load of the above two forces on the LV. The Zva is calculated as the (systolic arterial pressure + mean transvalvular pressure gradient)/SVi,[14] and represents the pressure recovery downstream of the stenosed aortic valve, factors associated with the valve, and increased vascular resistance opposing LV ejection. The added load of systolic arterial pressure may cause onset of symptoms at a larger aortic valve area size, secondary to additive effects of AS and concomitant increased vascular resistance.[16] Thus, Zva plays a key role in AS and its management requires measures to address reducing systemic arterial resistance in addition to valve replacement.

Zva and impact on LV function

Presence of high Zva is suggestive of increased afterload, which may not resolve completely post-TAVR, thus, delaying LV remodeling post-TAVR.[17] The additive effects of valvular and arterial load contribute to accelerated deterioration of LV function over time.[18] Studies have shown systemic vascular compliance to be independently correlated with reduced LV function, increased LV filling pressures, and brain natriuretic peptide levels.[19] Briand and colleagues, in a seminal paper, demonstrated Zva to be an independent hemodynamic factor to be associated with LV systolic and diastolic dysfunction.[14] The extent of myocardial dysfunction is often underestimated in the presence of high Zva especially in patients with low-flow, low-gradient AS.[20] Likewise, in our cohort, although patients with high Zva did not have significantly lower EF, the SVi was significantly lower in this group. Thus, an increased Zva is associated with poor LV systolic and diastolic function with a corresponding increase in HF readmissions.

Zva in low-flow, low-gradient AS

Another key finding of our study was the association of higher Zva with low-flow, low-gradient AS parameters on ECHO. In our cohort, a high Zva correlated with lower AVAi and higher posterior wall thickness, seen in low-flow, low-gradient state. The presence of low-flow, low-gradient state often creates a diagnostic dilemma eventually leading to delay in decision making regarding aortic valve replacement. Hachicha and colleagues found that a high Zva was present in the majority (72%) of patients with low-flow, low-gradient state with 80% having severe AS.[5] Evaluation of Zva by ECHO may be helpful in this sub-group to determine the overall hemodynamic load on the LV which is usually underestimated by the low-flow state. Zva can, therefore, be used as a diagnostic tool in this sub-group to help improve identification of patients with severe AS, thus, promoting appropriate and timely referral for valve replacement.

Association of Zva and HF readmissions

One of the novelties of this paper as compared to prior studies is the use of Zva in risk stratifying patients at high risk for HF admission 1-year post-TAVR. HF readmissions are a significant focus of our current healthcare payment model and hospital administrations nationwide are trying to minimize HF readmissions while trying to identify patients that are at risk of HF admissions in order to utilize more resources in the outpatient setting. In this article, patients with the highest quartile pre-TAVR Zva had significantly higher HF readmission rates in the first year compared to their counterparts in the lower three quartiles. Furthermore, even after adjusting for predictors of HF hospitalizations using the univariate analysis, Zva was still an independent predictor of HF hospitalization post-TAVR. This is a significant finding as clinicians can use pre-TAVR Zva to identify patients that are at risk for HF readmission post-TAVR and accordingly, divert more resources towards these patients in the follow-up period, perhaps, by having them follow-up with their cardiologists more often or establishing a transitional care program in order to monitor them more closely. Additionally, in our cohort, post-TAVR LVEF was not found to be a statistically significant predictor of HF hospitalizations. Instead, the NYHA functional class post-TAVR was found to be a strong predictor of HF readmissions. This is likely due to the fact that our study population was much older, where the functional class of patients was more important in predicting HF readmissions.

Change in Zva post-TAVR

A key finding of our study was that among 20% of patients, the Zva did not decrease post-TAVR in spite of similar clinical characteristics compared to those in whom the Zva decreased post-TAVR. Although the transvalvular gradient did not differ between the two groups, the systolic arterial

pressure and vascular resistance was significantly higher among patients in whom Zva did not change or increase post-TAVR. These findings have prognostic implications and demonstrate the utility of Zva for evaluating patients who may or may not benefit with the procedure. Our study suggests that systolic arterial pressure and vascular resistance may play a key role in patients who fail to have clinical improvement post-TAVR and will most likely not benefit with the procedure.

Association of Zva and mortality

Studies have shown that patients with high Zva have higher overall mortality, even in asymptomatic patients with at least moderate AS.[5,21] In a prospective study, a high Zva (≥ 4.9 mm Hg/ml per m^2) was associated with worse survival as well.[4] Katsanos and co-workers evaluated the impact of high Zva on 2-year outcomes post-TAVR.[22] They showed that although there was a reduction in the post-procedural Zva, there was no reduction in vascular resistance. Furthermore, their study demonstrated that baseline Zva score was an independent predictor of mortality over 2 years following TAVR. Additionally, post-TAVR Zva is expected to be reduced secondary to reduced valvular load, with improvement in LV function. Thus, lack of change or increase in Zva post-TAVR would be suggestive of worse long-term outcomes, as seen in our cohort. Additionally, atrial fibrillation, which is common in this age group, may contribute to poor outcomes by reducing atrial contribution to cardiac output. In our cohort, Zva continued to remain a strong predictor of mortality post-TAVR even after adjusting for atrial fibrillation, age, and Society of Thoracic Surgeons risk score.

Limitations

Our study has several limitations: Since it was a single-center study, there is potential for selection bias and the cohort may not be well representative of the general population. Patients who were lost to follow-up could represent sicker patients who may have different outcomes compared to our cohort. Accurate estimation of Zva is dependent on obtaining Doppler measurements, which is operator-dependent, and thus, variable. Nonetheless, all the ECHO assessments were uniformly performed according to the current American Society of Echocardiography guidelines. We used indexed values for Zva to maintain uniformity with the current literature, although depending on the circumstances there is clinical utility in looking at both indexed and non-indexed values as well. Although we adjusted for the majority of factors associated with HF readmissions, there may be additional variables that are not routinely measured which may be at play and could potentially confound the results.

Conclusion

In conclusion, Zva is an easily obtainable ECHO index, which can be used for risk stratification of patients post-TAVR who are at an increased risk for HF readmissions. This has the potential to translate into reduced hospitalizations, increased cost-savings, and overall improvement in the quality of life of patients undergoing TAVR. Zva is particularly useful in patients with low-flow, low-gradient AS, where the low gradients may lead to the erroneous estimation of AS severity, thus, delaying treatment. Lack of decrease in Zva post-TAVR has prognostic significance and should be routinely measured during follow-up in patients post-TAVR.

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Disclosure statement

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