ORIGINAL RESEARCH

Prognostic Value of Ventricular-Arterial Coupling After Transcatheter Aortic Valve Replacement on Midterm Clinical Outcomes

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BACKGROUND: Ventricular-arterial coupling predicts outcomes in patients with heart failure. The arterial elastance to end-systolic elastance ratio (Ea/Ees) is a noninvasively assessed index that reflects ventricular-arterial coupling. We aimed to determine the prognostic value of ventricular-arterial coupling assessed through Ea/Ees after transcatheter aortic valve replacement to predict clinical events.

METHODS AND RESULTS: We retrieved data on 1378 patients (70% women) who underwent transcatheter aortic valve replacement between October 2013 and May 2017 from the OCEAN-TAVI (Optimized transCathEter VAluval iNtervention) Japanese multicenter registry. We determined the association between Ea/Ees and the composite end point of hospitalization for heart failure and cardiovascular death by classifying the patients into quartiles based on Ea/Ees values (group 1: <0.326; group 2: 0.326–0.453; group 3: 0.453–0.666; and group 4: >0.666) during the midterm follow-up after transcatheter aortic valve replacement. During a median follow-up period of 736 days (interquartile range, 414–956), there were 247 (17.9%) all-cause deaths, 89 (6.5%) cardiovascular deaths, 130 (9.4%) hospitalizations for heart failure, and 199 (14.4%) composite events of hospitalization for heart failure and cardiovascular death. The incidence of the composite end point was significantly higher in group 2 (hazard ratio [HR], 1.76; 95% CI, 1.08–2.87 [P=0.024]), group 3 (HR, 2.43; 95% CI, 1.53–3.86 [P<0.001]), and group 4 (HR, 2.89; 95% CI, 1.83–4.57 [P<0.001]) than that in group 1. On adjusted multivariable Cox analysis, Ea/Ees was significantly associated with composite events (HR, 1.47 per 1-unit increase; 95% CI, 1.08–2.01 [P=0.015]).

CONCLUSIONS: These findings suggest that a higher Ea/Ees at discharge after transcatheter aortic valve replacement is associated with adverse clinical outcomes during midterm follow-up.

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Key Words: heart failure • transcatheter aortic valve replacement • ventricular-aortic coupling

While cardiac contractile reserve is predictive of prognosis in patients with heart failure (HF),1 conventional analysis of left ventricular (LV) wall motion—including ejection fraction—is affected by cardiac load. Therefore, these measurements of cardiac performance can sometimes lead...
Blood flow from the left ventricle to the systemic arterial circulation depends on interactions between preload, afterload, and contractility; assessment of optimal cardiac function must consider not only LV performance but also LV coupling to the large arterial system (ventricular-arterial coupling [VAC]). VAC is an important element of cardiac energy efficiency for the process of delivering blood from the heart to the arterial system. Considering a load-independent physiological method to assess VAC, a noninvasive tool using echocardiography has been recently developed. End-systolic ventricular elastance (Ees) is a minimally load-independent index of LV myocardial contractility. Arterial elastance (Ea) is an index of afterload related to systemic vascular resistance and inversely related to total arterial compliance. Their ratio (Ea/Ees) is used as one of several indices for VAC assessment.

VAC is associated with the prognosis of patients with various comorbidities such as HF with reduced ejection fraction; however, it has not yet been fully estimated in patients with aortic valve stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR). This study aimed to determine the prognostic value of VAC assessed using the noninvasive Ea/Ees index after TAVR for the prediction of clinical events in patients registered in the OCEAN-TAVI (Optimized Transcatheter Valvular Intervention) registry, a large TAVR registry in Japan.

**METHODS**

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

**Study Population**

The OCEAN-TAVI registry is an ongoing multicenter, observational registry of symptomatic patients with severe AS who underwent TAVR with Edwards Sapien XT or Edwards Sapien 3 (Edwards Lifesciences) or Medtronic CoreValve or Medtronic EvolutR (Medtronic) prosthesis at 14 collaborating high-volume centers in Japan. This registry was designed to record procedural results, postprocedural clinical outcomes, and transitional examination data after TAVR.

Between October 2013 and May 2017, 2588 symptomatic patients who underwent TAVR were prospectively enrolled in the OCEAN-TAVI registry. Of these, we analyzed 1378 patients who had complete data on systolic blood pressure (SBP), LV end-systolic volume (LVESV) (measured using the modified Simpson or Teich method), and stroke volume (SV) at discharge, and who had experienced device success. We excluded some patients with registration of device success who had
prosthesis-patient mismatch when the pressure gradient through the prosthesis was not resolved. Prosthesis-patient mismatch was defined according to current Valve Academic Research Consortium (VARC-2) criteria.9

The study protocol was designed in accordance with the 1975 Declaration of Helsinki and was approved by the ethics committee of each participating hospital. All patients provided written informed consent. The authors had full access to the data and are responsible for its integrity. This registry is registered with the University Hospital Medical Information Network (UMIN000020423).

Assessment of Noninvasive Cardiac Energy Efficiency
In this study, LV performance was evaluated using surrogates reflecting pressure volume (PV) change, which were obtained from the indirect measures of pressure and volume slope. The slope of the end-systolic pressure-volume relationship (Ees) is a load-independent index of myocardial contractility3,10,11; when contractility increases, the slope shifts the relationship toward the upper left, leading to an increased Ees.4 Conversely, the arterial system can be described by the relationship between the SV and LV end-systolic pressure (LVESP).4,12 The effective Ea comprises the negative slope connecting the PV loops between the end-systolic point and the point on the volume axis at end-diastole5 (Figure 1). The ratio of Ea (describing the arterial system) to Ees (describing LV function) — Ea/Ees — was calculated for the noninvasive assessment of VAC.

SBP and diastolic blood pressure were measured, and echocardiograms were obtained before the procedure and at discharge, which were evaluated at the individual hospitals participating in the registry. LVESP was estimated noninvasively as 0.90×SBP, and SBP was assessed using manual cuff or arterial measurements. Figure 1 represents the index of cardiac efficiency on PV loops. The value of Ea, which is the negative slope of the PV loops between the end-systolic point and the point on the volume axis at end-diastole,6 was defined as the ratio of LVESP to SV. The value of Ees, which is defined as the slope of the end-systolic PV relationship, is theoretically derived from the equation Ees=LVESP/(LVESV−V0), where V0 is the LV volume when no pressure is reproduced and is assumed to be negligible when LVESV>>>V0.13–15 Thus, the equation can be rewritten as Ees=LVESP/LVESV, and the Ea/Ees reflecting the state of VAC was calculated as LVESV/SV. Stroke work (SW) is calculated as the product of SV and mean systolic pressure during ejection, and the PV area can be defined as the sum of SW and potential energy16. Potential energy is the remaining energy stored in the myofilaments at the end of systole that is not dissipated as external SW.17 As an index of cardiac energy efficiency, the ratio of SW to PV area (SW/PV area) was also calculated using the following formula: 1/(1+0.5×Ea/Ees).18

Study End Point and Follow-up
The primary end point of this study was the composite end point of hospitalization for HF and cardiovascular death. The secondary end points were all-cause mortality, cardiovascular death, and hospitalization for HF during the midterm follow-up after TAVR. In patients who experienced multiple cardiovascular events, only the first event was included in the analysis. We classified the patients into quartiles (groups 1–4) according to ascending Ea/Ees values (group 1: <0.326; group 2: 0.326–0.453; group 3: 0.453–0.666; and group 4: >0.666) and evaluated the differences in clinical outcomes between the groups. We evaluated the indices associated with worse clinical outcomes. Follow-up surveys were conducted at the time of each outpatient visit or by telephone interviews after 30 days, 6 months, and then yearly.
End point events were defined according to VARC-2 criteria. Any death of unknown cause was defined as cardiovascular-related death.

**Subanalysis**
The normal value of Ea/Ees in patients with severe AS undergoing TAVR was unknown; therefore, as a subanalysis, we classified the patients into 2 groups according to a cutoff value calculated using a receiver operating characteristic curve for the primary end point outcome. We determined the cutoff value at the maximum of sensitivity plus specificity. We compared the primary and secondary end points between the groups (low and high groups).

**Statistical Analysis**
All data were collected from the OCEAN-TAVI registry database. Continuous variables were expressed as mean±SD or median with interquartile range, as appropriate. The Shapiro–Wilk test was used to assess the normality of data. Categorical variables were expressed as numbers and percentages. Chi-square or Fisher exact tests were used to compare the groups. Kaplan–Meier analysis was performed using log-rank test to compare the end points between the groups. When clinical outcomes were assessed, group 1 was used as the reference.

An adjusted multivariable Cox proportional hazard model was constructed using variables with P<0.10 in univariate analysis to identify the significant associations of clinical and echocardiographic parameters with the primary end point. Model 1 contained Ea/Ees as a continuous variable and clinical indices with P<0.10 in univariate analysis, including age, sex, New York Heart Association class III or IV, Society of Thoracic Surgeons score, clinical frailty score, albumin level, brain natriuretic peptide level, estimated glomerular filtration rate, hemoglobin level, β-blockers, diuretics, statins, chronic obstructive pulmonary disease, dyslipidemia, peripheral arterial disease, prior coronary artery bypass grafting, procedure situation, atrial fibrillation, and left bundle branch block. Model 2 comprised Ea/Ees as a continuous variable and postprocedural echocardiographic parameters with P<0.10 in univariate analysis, including E/e’, transcatheter heart valve mean pressure gradient, transcatheter heart valve peak velocity, systolic pulmonary artery pressure, left atrium diameter, and LV outflow tract-velocity time integral. Echocardiographic parameters that intersected one another were excluded. Model 3 included Ea/Ees as a continuous variable and combined all indices used in models 1 and 2. To identify the incremental prognostic value of Ea/Ees over clinical indices and postprocedural LV ejection fraction (LVEF), a hierarchical Cox regression analysis was used. A P value <0.05 was considered statistically significant. Relationships between Ea/Ees and the clinical and echocardiographic parameters were assessed using Spearman rank correlations. All statistical analyses were performed using Stata version 16 (StataCorp LLC) and EZR version 3.6.0.

**RESULTS**

**Preprocedural and Baseline Patient Characteristics**
Of the 2588 patients who underwent TAVR between October 2013 and May 2017, 893 with missing data on postprocedural SBP, SV, and LVESV; 257 patients with device failure or no information about device success; and 60 patients with missing data on postprocedural indexed effective orifice area were excluded. Finally, 1378 patients (53.2% of the total registry population; median age, 85 years; 70% women) were included in this study (Figure S1). Preprocedural baseline characteristics of the participants are summarized in Table 1 and Table S1. On group comparison, the group with the higher Ea/Ees had a higher ratio of men, higher body surface area, lower blood pressure (BP), lower LVEF and SV, tendency for a larger LVESV and LVEDV, and lower relative wall thickness (all P<0.05). Regarding AS severity, indexed aortic valve area decreased with increasing quartiles (P=0.002). Nevertheless, mean pressure gradient (PG) and peak velocity showed no consistent tendencies.

**Procedural Characteristics and Postprocedural Echocardiography**
Table S2 summarizes procedural characteristics. The access site for the TAVR procedure was not significantly different between the groups; the most commonly implanted valves were Edwards Sapien XT (62.6%) and balloon-expandable (87.2%). Table 2 and Table S3 summarize postprocedural echocardiographic parameters. In 97 patients, postprocedural LVESV was measured using the Teich method. Moderate or more severe paravalvular leak occurrence was not significantly different between the groups (P=0.318), and residual mean PG was low in all groups.

**VAC and LV Energetics**
Table 3 summarizes postprocedural LV energetics. The overall median Ees was 3.76 mm Hg/mL (0.23–18.59 mm Hg/mL).
Table 1. Baseline Characteristics of the Overall Population and Classified Population Along Ea/Ees Quartiles

|                          | Overall        | Group 1        | Group 2        | Group 3        | Group 4        | P Value |
|--------------------------|----------------|----------------|----------------|----------------|----------------|---------|
| Age, y                   | 85.00 [81.00–88.00] | 85.00 [82.00–88.00] | 84.00 [81.00–88.00] | 85.00 [82.00–88.00] | 85.00 [81.00–87.00] | 0.079   |
| Women, n (%)             | 953 (69.2)     | 272 (78.8)     | 249 (72.4)     | 234 (68.0)     | 198 (57.4)     | <0.001  |
| STS score, %             | 6.58 [4.52–9.20] | 6.16 [4.36–8.32] | 6.18 [4.33–8.62] | 6.51 [4.60–8.88] | 7.61 [4.90–11.80] | <0.001  |
| **Medication**           |                |                |                |                |                |         |
| Renin-angiotensin system inhibitor, n (%) | 723 (52.5) | 170 (49.3) | 168 (48.8) | 210 (61.0) | 175 (50.7) | 0.003   |
| β-Blocker, n (%)         | 477 (34.6)     | 107 (31.0)     | 105 (30.5)     | 135 (39.2)     | 130 (37.7)     | 0.027   |
| **Medical history**      |                |                |                |                |                |         |
| Hypertension, n (%)      | 1037 (75.3)    | 257 (74.5)     | 264 (76.7)     | 262 (76.2)     | 254 (73.6)     | 0.762   |
| Diabetes mellitus, n (%) | 297 (21.6)     | 75 (21.7)      | 64 (18.6)      | 66 (19.2)      | 92 (26.7)      | 0.041   |
| Previous PCI, n (%)      | 168 (12.2)     | 32 (9.3)       | 37 (10.8)      | 54 (15.7)      | 45 (13.0)      | 0.055   |
| Previous CABG, n (%)     | 75 (5.4)       | 7 (2.0)        | 13 (3.8)       | 16 (4.7)       | 39 (11.3)      | <0.001  |
| **Baseline electrocardiography** |            |                |                |                |                |         |
| Atrial fibrillation, n (%) | 287 (20.8) | 52 (15.1) | 64 (18.6) | 78 (22.7) | 93 (27.0) | 0.001   |
| Right bundle branch block, n (%) | 105 (8.9) | 18 (5.5) | 27 (8.0) | 38 (12.8) | 32 (9.4) | 0.037   |
| **Laboratory test**      |                |                |                |                |                |         |
| BNP, pg/mL               | 255.00 [118.00–539.67] | 173.40 [90.00–369.80] | 170.30 [96.00–368.05] | 259.40 [121.90–488.00] | 490.55 [270.25–934.25] | <0.001 |
| Preprocedural BP         |                |                |                |                |                |         |
| Systolic BP, mm Hg       | 126.00 [114.00–138.00] | 130.00 [117.00–144.00] | 127.00 [116.00–138.00] | 128.00 [116.00–139.00] | 121.00 [109.00–133.25] | <0.001 |
| Diastolic BP, mm Hg      | 67.00 [59.00–75.00] | 68.00 [61.00–76.00] | 68.00 [58.50–75.00] | 67.00 [59.00–76.00] | 65.00 [57.75–74.00] | 0.038   |
| Preprocedural echocardiographic data |            |                |                |                |                |         |
| LVEF (modifid Simpson or Teich), % | 62.00 [52.00–67.97] | 67.00 [62.30–72.50] | 64.83 [59.00–69.00] | 61.92 [54.00–66.35] | 46.40 [37.60–56.70] | <0.001 |
| LVESV (modifid Simpson or Teich), mL | 29.70 [21.80–47.08] | 22.00 [17.65–27.00] | 27.00 [21.40–34.82] | 32.40 [23.85–44.75] | 60.20 [40.45–81.28] | <0.001 |
| LVEDV (modifid Simpson or Teich), mL | 82.70 [64.35–106.38] | 69.70 [57.00–83.10] | 77.50 [63.00–94.40] | 85.10 [66.75–105.55] | 113.60 [86.60–137.96] | <0.001 |
| SV, mL                   | 65.00 [52.00–76.70] | 68.30 [58.00–80.00] | 66.95 [55.00–76.78] | 64.00 [50.88–75.00] | 59.40 [47.00–72.00] | <0.001 |
| AR ≥moderate, n (%)      | 125 (9.1)      | 25 (7.3)       | 20 (5.8)       | 32 (9.3)       | 48 (13.9)       | 0.001   |
| Indexed AVA, cm²/m²      | 0.44 [0.37–0.52] | 0.47 [0.40–0.54] | 0.45 [0.36–0.52] | 0.43 [0.36–0.51] | 0.43 [0.34–0.50] | 0.002   |
| Mean PG, mm Hg           | 47.50 [38.60–61.00] | 48.00 [38.85–61.00] | 49.25 [40.00–63.00] | 49.80 [40.22–62.55] | 44.00 [34.00–57.00] | <0.001  |
| Peak velocity, m/s       | 4.51 [4.05–5.10] | 4.54 [4.10–5.01] | 4.59 [4.12–5.20] | 4.60 [4.10–5.18] | 4.30 [3.82–4.90] | <0.001  |

Values are expressed as median [interquartile range] or number (percentage). Group 1: arterial elastance to end-systolic elastance ratio (Ea/Ees) <0.326; group 2: 0.326≤Ea/Ees≤0.453; group 3: 0.453≤Ea/Ees≤0.666; and group 4: 0.666 <Ea/Ees. AR indicates aortic valve regurgitation; AVA, aortic valve area; BNP, brain natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PCI, percutaneous coronary intervention; PG, pressure gradient; STS, Society of Thoracic Surgeons; and SV, stroke volume.
mm Hg/mL), and there was a significant difference between the 4 groups ($P<0.001$). The overall median $E_a$ was 1.61 mm Hg/mL (0.49–19.72 mm Hg/mL) with a significant difference between the 4 groups ($P<0.001$). The distribution of $E_a/E_e$ for each group is illustrated in Figure S2. The group with the lower $E_a/E_e$ resulted in significantly higher cardiac work efficiency, namely SW/PV area. Figure S3 illustrates the group-averaged PV loops post-TAVR. As the group number increased, the framework moved right. Table S4 illustrates the correlation of $E_a/E_e$ with various clinical indices and echocardiographic parameters. There was a weak but statistically significant correlation of $E_a/E_e$ with preprocedural and postprocedural AS parameters (indexed aortic valve area, indexed effective orifice area, mean PG, and peak velocity).

### Midterm Clinical Outcomes

Table 4 summarizes the clinical end points. Overall, 247 (17.9%) patients died after TAVR during a median follow-up period of 736 days (414–956 days); 89 (6.5%) deaths were from cardiovascular causes. Furthermore, 130 (9.4%) patients required hospitalization for worsening HF, and the composite end point was identified in 199 patients (14.4%). When compared with patients in group 1 as a reference, the incidence of the composite end point was significantly higher in group 2 (hazard ratio [HR], 1.76; 95% CI, 1.08–2.87 [$P=0.024$]), group 3 (HR, 2.43; 95% CI, 1.53–3.86 [$P<0.001$]), and group 4 (HR, 2.89; 95% CI, 1.83–4.57 [$P<0.001$]). Kaplan–Meier analysis demonstrated that there was no significant difference in cardiovascular death between the 4 groups (log-rank $P=0.078$). Nevertheless, overall mortality, hospitalization rates for HF, and composite end point occurrence were significantly different between the 4 groups (log-rank $P=0.024$, $P<0.001$, and $P<0.001$, respectively) (Figure 2).

### Association With Adverse Clinical Outcomes

Significant associations between the primary end point and adverse clinical outcomes identified using adjusted multivariable analysis are summarized in Table 5. Model 1 contained $E_a/E_e$ and clinical indices, model 2 comprised $E_a/E_e$ and postprocedural echocardiographic parameters, and model 3 included $E_a/E_e$ and all indices included in models 1 and 2. The HR of $E_a/E_e$ was 1.58 (95% CI, 1.25–1.98; $P<0.001$) in model 1, 1.33 (95% CI, 1.07–1.65; $P=0.009$) in model 2, and 1.47 (95% CI, 1.08–2.01; $P=0.015$) in model 3. Table S5 displays the results of the adjusted multivariable analysis in detail.
follow-up after TAVR. Moreover, prognostic associations were assessed in a hierarchical manner as performed clinically, then subsequently followed by postprocedural LVEF and Ea/Ees. When Ea/Ees was added to the model containing the previous factors (clinical indices plus postprocedural LVEF), it significantly improved the primary end point prediction ($P=0.015$, Figure 3).

**Subanalysis**

The cutoff value of Ea/Ees for the composite end point was calculated using a receiver operating characteristic curve (cutoff value: 0.459, area under the curve: 0.612, sensitivity: 0.653, specificity: 0.542) (Figure S4). We compared the primary and secondary end points of the low and high groups. Kaplan–Meier analysis demonstrated that the overall mortality, cardiovascular death, hospitalization rates for HF, and composite end point occurrence were significantly different between the 2 groups ($log-rank P=0.023$, $P=0.024$, $P<0.001$, and $P<0.001$, respectively) (Figure S5). The high group had a significantly worse prognosis (Table S6). These results were similar when patients were classified into quartiles.

**DISCUSSION**

In this study, we demonstrated that Ea/Ees at discharge after TAVR was significantly associated with prognosis during a midterm follow-up. The Kaplan–Meier curve analysis indicated that a high Ea/Ees after TAVR was significantly associated with an increased risk of all-cause death, hospitalization for HF, and composite end point occurrence of cardiovascular death and hospitalization for HF not only when patients were assigned into quartile groups but also when they were classified into 2 groups according to the cutoff value determined using a receiver operating characteristic curve. The adjusted multivariable Cox proportional hazard analysis revealed that Ea/Ees had a significant association with the primary end point. Moreover, hierarchical regression analysis demonstrated that Ea/Ees had an incremental effect on the primary end point over clinical indices and LVEF.

In patients with HF, VAC status worsens because cardiac function declines and arterial load increases to maintain systolic pressure.\(^5,20–22\) As it becomes higher, ventricular-arterial matching is significantly compromised, resulting in inefficient and ineffective cardiac contraction.\(^5\) Regarding patients with severe AS; Garcia et al.\(^23\) reported the cardiac elastance before and after surgical aortic valve replacement in 6 patients. Yamashita et al.\(^24\) reported that 56 patients with severe

**Table 3. Post-TAVR Cardiac Energetics of the Overall Population and Classified Population Along Ea/Ees Quartiles**

| Quartile | Ea/Ees Quartile | Ea/Ees (mm Hg/mL) | Ees/Ea (mm Hg/mL) | Ea/Ees (mm Hg/mL) | Ees/Ea (mm Hg/mL) | Ea/Ees (mm Hg/mL) | Ees/Ea (mm Hg/mL) | Ea/Ees (mm Hg/mL) | Ees/Ea (mm Hg/mL) |
|----------|----------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Group 1  | 0.453 ≤ E/Ees ≤ 0.666 | 1.85 [0.99–19.72] | 1.89 [0.85–8.68] | 1.86 [0.85–7.46] | 1.88 [0.85–7.46] | 1.86 [0.85–7.46] | 1.88 [0.85–7.46] | 1.86 [0.85–7.46] | 1.88 [0.85–7.46] |
| Group 2  | 0.666 < E/Ees ≤ 0.936 | 1.61 [0.49–19.72] | 1.61 [0.49–19.72] | 1.61 [0.49–19.72] | 1.61 [0.49–19.72] | 1.61 [0.49–19.72] | 1.61 [0.49–19.72] | 1.61 [0.49–19.72] | 1.61 [0.49–19.72] |
| Group 3  | 0.936 < E/Ees ≤ 1.197 | 1.57 [0.74–6.30]  | 1.57 [0.74–6.30] | 1.57 [0.74–6.30] | 1.57 [0.74–6.30] | 1.57 [0.74–6.30] | 1.57 [0.74–6.30] | 1.57 [0.74–6.30] | 1.57 [0.74–6.30] |
| Group 4  | 1.197 < E/Ees ≤ 1.453 | 1.38 [0.74–6.30]  | 1.38 [0.74–6.30] | 1.38 [0.74–6.30] | 1.38 [0.74–6.30] | 1.38 [0.74–6.30] | 1.38 [0.74–6.30] | 1.38 [0.74–6.30] | 1.38 [0.74–6.30] |
| Overall  | 1.20 ≤ E/Ees ≤ 1.453 | 1.46 [0.74–6.30]  | 1.46 [0.74–6.30] | 1.46 [0.74–6.30] | 1.46 [0.74–6.30] | 1.46 [0.74–6.30] | 1.46 [0.74–6.30] | 1.46 [0.74–6.30] | 1.46 [0.74–6.30] |

Values are expressed as median [interquartile range]. Group 1: arterial elastance (Ea) to end-systolic elastance (Ees) ratio (Ea/Ees) <0.326; group 2: 0.326 ≤ Ea/Ees ≤ 0.453; group 3: 0.453 ≤ Ea/Ees ≤ 0.666; and group 4: 0.666 < Ea/Ees. BP indicates blood pressure; PV, pressure volume; SW, stroke work; and TAVR, transcatheter aortic valve replacement.
Yokoyama et al Impact of VAC after TAVR on Clinical Outcomes

AS and preserved ejection fraction who underwent TAVR had early improvement in the afterload and LV efficiency, resulting in further decrease in the transvalvular PG without SV deterioration in the early postoperative period when compared with 61 patients who underwent surgical aortic valve replacement. Nevertheless, these reports did not mention the association of VAC with prognosis after the procedure, and we believe that the insight of PV loops' association with AVR is relatively novel and underreported. In severe AS, strong afterload is imposed on the left ventricle by the calcified aortic valve. Pibarot reported that Ea is not considered the true total load—which is the sum of the arterial and valvular hemodynamic load—on the left ventricle. To accurately estimate it, the calculation of preprocedural valvuloarterial impedance (ZVa, the ratio of the LV peak systolic pressure to the stroke volume index) was proposed. Therefore, the use of VAC for hemodynamic evaluation in patients with severe AS is undesirable. Hence, in this study, we did not calculate preprocedural VAC, and we excluded patients who experienced device failure including prosthesis-patient mismatch, when the PG through the prosthesis did not achieve relief from aortic valve obstruction. However, postprocedural valvuloarterial impedance was not associated with 2-year all-cause or cardiovascular mortalities among patients who underwent TAVR, therefore, after the TAVR procedure, we believe that VAC has a better prognostic value for clinical outcomes than preprocedural valvuloarterial impedance.

From the results shown in Table 3, the value of Ees (index of systolic function) differed more evidently between quartile groups than the value of Ea (index of afterload). This indicated that systolic function was more impaired than afterload was increased. Therefore, the cause of higher Ea/Ees seemed to be a lower Ees rather than a higher Ea. As mentioned above, Ees was the ratio of LVESP to LVESV, suggesting that a lower Ees indicates a higher LVESP and/or higher LVESV. Lindman et al published the association of post-TAVR BP with clinical outcomes. They concluded that a lower BP was paradoxically associated with higher all-cause and cardiovascular mortalities, and the study findings supported the hypothesis that a lower Ees, which leads to a higher Ea/Ees, was associated with adverse clinical outcomes. However, in the present study, postprocedural SBP was not significantly different between the quartile groups; therefore, we considered that one cause of higher Ea/Ees might be a higher LVESP, which was significantly different between quartile groups, rather than a lower BP, leading to adverse clinical outcomes.

The noninvasive assessment of VAC comprises indices measured by echocardiography. Regarding LV remodeling after TAVR, Magalhaes et al observed

| Table 3. Midterm Clinical Outcomes of the Overall Population and Classified Population Along Ea/Ees Quartile |
|---|---|---|---|---|
| Overall Group 1 | Overall Group 1 | Overall Group 1 | Overall Group 1 |
| Group 1 vs Group 1 | Group 2 vs Group 1 | Group 3 vs Group 1 | Group 4 vs Group 1 |
| HR (95% CI) | P Value | HR (95% CI) | P Value | HR (95% CI) | P Value | HR (95% CI) | P Value |
| Primary end point | Three-year composite end point | 199 (14.4) | 25 (7.2) | 44 (12.8) | 1.76 (1.08–2.87) | 0.024 | 62 (18.0) | 2.43 (1.53–3.86) | <0.001 | 68 (19.7) | 2.89 (1.83–4.57) | <0.001 |
| Secondary end point | Three-year all-cause death | 247 (17.9) | 47 (13.6) | 21 (6.1) | 1.27 (0.87–1.86) | 0.210 | 78 (22.6) | 1.71 (1.19–2.46) | 0.022 | 22 (6.4) | 1.79 (1.09–2.97) | 0.060 |
| | Three-year cardiovascular death | 89 (6.5) | 17 (4.9) | 21 (6.1) | 1.29 (0.79–2.09) | 0.130 | 29 (8.4) | 1.89 (1.19–3.03) | 0.013 | 42 (12.2) | 2.75 (1.53–4.96) | <0.001 |
| | Three-year hospitalization for heart failure | 130 (9.4) | 30 (8.4) | 26 (7.6) | 1.57 (0.92–2.78) | 0.091 | 46 (13.6) | 2.29 (1.19–4.41) | 0.013 | 47 (13.6) | 3.31 (1.83–5.91) | <0.001 |

Values are expressed as number (percentage). Group 1: arterial elastance to end-systolic elastance ratio (Ea/Ees) <0.326; group 2: 0.326 ≤Ea/Ees≤0.453; group 3: 0.453 ≤Ea/Ees≤0.666; and group 4: 0.666<Ea/Ees. HR indicates hazard ratio.
reverse LV remodeling in 24% of the analyzed patients 1 year after TAVR; conversely, 17% of these had adverse remodeling when analyzed with echocardiography. Nevertheless, it remains unclear when LV remodeling after TAVR is completed. Therefore, in this study, future LV remodeling was not considered, and VAC likely changes with time.

Our findings in the adjusted multivariable analysis demonstrated that postprocedural high Ea/Ees was associated with adverse clinical outcomes during a midterm follow-up after TAVR. By measuring LVESV, SV, and BP to calculate myocardial work, this index might be useful as an easily assessable marker for understanding the balance between LV function and the arterial system in patients with symptomatic severe AS undergoing TAVR.

In cardiology, structural heart disease interventions are increasing in frequency; however, the idea of assessing VAC using Ea/Ees remains uncommon. VAC may be helpful to understand the effects of structural heart disease interventions on hemodynamics in depth. Further studies are needed to accurately assess the usefulness of VAC in patients who have undergone TAVR.

**Limitations**

This study has several limitations. First, this was a retrospective analysis based on a prospective multicenter TAVR cohort registry. Moreover, patients who had missing BP or echocardiographic data and experienced device failure were excluded, which may represent a major limitation. Second, echocardiography was performed by experienced cardiologists or technicians in individual centers, and there was no centralized core laboratory analysis. Furthermore, postprocedural LVESV measured using Teich methods were included. Third, the rate of TAVR using the Sapien XT valve was relatively high in this study (>50% of all cases) because a sizable proportion of the analyzed population had an initial experience with TAVR. Therefore, clinical outcomes and complications associated with the procedure may differ from those of cases where only the current procedure system was used. Fourth, VAC after TAVR was calculated in the acute phase; therefore, its changes over time remain unclear. Fifth, while the idea of VAC is useful for the assessment of a patient’s hemodynamic status, we recognize the limitation of its use because VAC encompasses multiple physiologic aspects, many of which are not captured in PV loops. Chirinos have reported that the limitations of assessing VAC using PV loops were as follows: 1) Ea poorly characterizes pulsatile LV load and does not depend exclusively on arterial properties; and 2) the loading sequence, an important aspect of VAC, is neglected in PV analyses. Hence, when we seek to understand

Table 5. Association of Post-TAVR Ea/Ees With the Composite End Point in Univariable and Multivariable-Adjusted Cox Hazard Analysis

| Model | HR (per 1-Unit Increase) | 95% CI | P Value |
|-------|--------------------------|--------|---------|
| Model 1 | 1.51                     | 1.30–1.74 | <0.001 |
| Model 2 | 1.58                     | 1.30–1.74 | <0.001 |
| Model 3 | 1.33                     | 1.07–1.65 | 0.009 |

HR indicates hazard ratio; and TAVR, transcatheter aortic valve replacement.
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...a patient’s condition in detail, we should also obtain additional physiological information about the cardiovascular system. Finally, in our calculations, V0 was assumed to be nearly zero. V0 represents the point where ESPVR crosses the end-systolic pressure of 0 mm Hg. It is probable that V0 is not negligible when compared with LVESV; in such cases, VAC will change accordingly.

**CONCLUSIONS**

Our findings suggest that a high Ea/Ees at discharge after TAVR is significantly associated with adverse clinical outcomes during the midterm follow-up. Furthermore, Ea/Ees has an incremental effect on the association with prognosis beyond that of indices such as LVEF. Ea/Ees, a noninvasive assessment of VAC, may have some limitations when understanding patient status, and further studies are needed to accurately evaluate the usefulness of VAC in patients who have undergone TAVR.

**APPENDIX**

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Figure 3. Incremental prognostic value of ventricular-arterial coupling (VAC) over clinical indices and postprocedural left ventricular ejection fraction (LVEF).
Clinical indices: the same clinical indices in model 1 of multivariable-adjusted analysis (Table 5).

80.87 84.67 90.62
p=0.051 p=0.015

Global chi square
Clinical Clinical+LVEF Clinical+LVEF+VAC

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Disclosures

Dr Saito, Dr Yamamoto, Dr Tada, Dr Naganuma, Dr Shirai, Dr Mizutani, and Dr Watanabe are clinical proctors for Edwards Lifesciences and Medtronic.

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Supplementary Material

Tables S1–S6

Figures S1–S5

REFERENCES

1. Pinamonti B, Perkan A, Di Lenarda A, Gregori D, Sinagra G. Dobutamine echocardiography in idiopathic dilated cardiomyopathy: clinical and prognostic implications. *Europace*. 2009;11:387–395. DOI: 10.1093/europace/epn031.

2. Bakker S, Scholte W, Breukink J, et al. Hemodynamic and clinical outcomes after transcatheter aortic valve implantation: results from the Dutch Nationwide Registry. *J Am Heart Assoc*. 2018;7(11):e010330. DOI: 10.1161/JAHA.118.010330.

3. Kondo T, Nakamura H, Ito T, et al. Prognostic significance of ventricular load optimization by unloading therapy on cardiac mortality and hospitalization after transcatheter aortic valve replacement. *Eur Heart J*. 2016;37(37):2753–2762. DOI: 10.1093/eurheartj/ehw248.

4. Kwon YH, Kim HJ, Park YG, et al. Hemodynamic and clinical outcomes after transcatheter aortic valve implantation: results from the Korean Nationwide Registry. *J Am Heart Assoc*. 2018;7(11):e010330. DOI: 10.1161/JAHA.118.010330.

5. Kato T, Ueno T, Kurosawa K, et al. Hemodynamic and clinical outcomes after transcatheter aortic valve implantation: results from the Japanese Nationwide Registry. *Int J Cardiol*. 2018;276:21–29. DOI: 10.1016/j.ijcard.2018.03.184.

6. Ueno T, Kurosawa K, Iida M, et al. Hemodynamic and clinical outcomes after transcatheter aortic valve implantation: results from the Japanese Nationwide Registry. *Circulation*. 2018;137(15):1523–1533. DOI: 10.1161/CIRCULATIONAHA.117.032312.

7. Kato T, Ueno T, Kurosawa K, et al. Hemodynamic and clinical outcomes after transcatheter aortic valve implantation: results from the Japanese Nationwide Registry. *Int J Cardiol*. 2018;276:21–29. DOI: 10.1016/j.ijcard.2018.03.184.

8. Ueno T, Kurosawa K, Iida M, et al. Hemodynamic and clinical outcomes after transcatheter aortic valve implantation: results from the Japanese Nationwide Registry. *Circulation*. 2018;137(15):1523–1533. DOI: 10.1161/CIRCULATIONAHA.117.032312.

9. Kato T, Ueno T, Kurosawa K, et al. Hemodynamic and clinical outcomes after transcatheter aortic valve implantation: results from the Japanese Nationwide Registry. *Int J Cardiol*. 2018;276:21–29. DOI: 10.1016/j.ijcard.2018.03.184.

10. Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res*. 1973;32:314–322. DOI: 10.1161/01.RES.32.3.314.

11. Sagawa K. The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use. *Circulation*. 1981;63:1223–1227. DOI: 10.1161/01.CIR.63.6.1223.

12. Chandler PD, Lakatta EG, Najjar SS. Arterio-ventricular coupling: mechanics insights into cardiovascular performance at rest and during exercise. *J Appl Physiol*. 2008;105:1342–1351. DOI: 10.1152/japplphysiol.09060.2008.

13. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, Kass DA. Effective arterial elastance as index of arterial vascular load in humans. *Circulation*. 1992;86:513–521. DOI: 10.1161/01.CIR.86.5.513.

14. Zoccali C, Bia D, Armentano RL, Gonzalez-Moreno J, Varela G, Callier F, Reyes-Caorsi W. Resynchronization improves heart-arterial coupling reducing arterial load determinants. *European Circulation Journal*. 2013;35:554–565. DOI: 10.1002/euc2.0058.

15. Suga H. Total mechanical energy of a ventricle model and cardiac oxygen consumption. *Am J Physiol Heart Circ Physiol*. 1999;276:H496–H505. DOI: 10.1152/ajpheart.1999.276.3.H496.

16. Bastos MB, Burkhoff D, Maly J, Daemen J, den Uil CM, Ardesch RJ, Blom J, et al. Invasive left ventricle pressure-volume analysis: overview and practical clinical implications. *Eur Heart J*. 2020;41:1286–1297. DOI: 10.1093/eurheartj/ehz552.

17. Nozawa T, Yasumura Y, Futaki S, Tanaka N, Uenishi M, Suga H. Efficiency of energy transfer from pressure-volume area to external work in patients with congestive heart failure. *Circulation*. 1988;77:1116–1124. DOI: 10.1161/01.CIR.77.7.1116.

18. Kanda Y. Investigation of the freely-available easy-to-use software “EZR” (Easy R) for medical statistics. *Bone Marrow Transplant*. 2013;48:452–458. DOI: 10.1038/bmt.2012.244.

19. Araki T, Ichikawa S, Kameyama Y, Nakamura N, et al. Ventriculoarterial coupling in normal and failing heart in humans. *Circ Res*. 1989;65:483–493. DOI: 10.1161/01.RES.65.2.483.

20. Kameyama T, Araki T, Ichikawa S, Sasaki Y. Ventricular load optimization by unloading therapy in patients with heart failure. *J Am Coll Cardiol*. 1991;17:199–207. DOI: 10.1016/0735-1097(91)00728-R.

21. Feldman MD, Pak PH, Wu CC, Haber HL, Heech SM, Bergin JD, Powers ER, Cowart TD, Johnson W, Feldman AM, et al. Acute cardiovascular effects of OPC-18790 in patients with congestive heart failure. *Time-and dose-dependence analysis based on pressure-volume relations.* *Circulation*. 1996;93:474–483. DOI: 10.1161/01.01.CIR.93.3.474.

22. Garcia D, Barenbrug P, Pibarot P, Dekker AL, van der Veen FH, Maessen JG, Dumesnil JG, Durand LG. A ventriculo-vascular coupling model in presence of aortic stenosis. *Am J Physiol Heart Circ Physiol*. 2005;288:1874–1884. DOI: 10.1152/ajpheart.00754.2004.

23. Yamashita Y, Tanoue Y, Sonoda H, Ushijima T, Kimura S, Oishi Y, Tatewaki H, Hiasa K, Arita T, Shiose A. Comparison of cardiac energetics after transcatheter and surgical aortic valve replacements. *Interact Cardiovasc Thorac Surg*. 2019;28:587–593. DOI: 10.1093/icvts/ivy292.

24. Pibarot P. Ventriculo-arterial decoupling in aortic stenosis: when the ventricle and the arteries do not dance on the same tempo. *Rev Argent Cardiol*. 2016;84:295–297.

25. Nagura F, Kataoka A, Hara M, Kozuma K, Watanabe Y, Nakashima M, Hiko H, Kawashima H, Nara Y, Shirai S, et al. Association between valvular-arterial impedance after transcatheter aortic valve implantation and 2-year mortality in elderly patients with severe symptomatic aortic stenosis: the OCEAN-TAVI registry. *Heart Vessels*. 2019;34:1031–1039. DOI: 10.1007/s00380-018-01529-2.

26. Lindman BR, Otto CM, Douglas PS, Hahn RT, Elmariah S, Weissman NJ, Stewart WJ, Aylee GM, Zhong F, Zajarias A, et al. Blood pressure and arterial load after transcatheter aortic valve replacement for aortic stenosis. *Circ Cardiovasc Imaging*. 2017;10:e005308. DOI: 10.1161/CIRCIMAGING.116.005308.

27. Magalhães MA, Kollman E, Torguson R, Minha S, Gai J, Kimarniyan S, Escarcega RO, Baker NC, Wang Z, Goldstein S, et al. Outcome of left-sided cardiac remodeling in severe aortic stenosis patients undergoing transcatheter aortic valve implantation. *Am J Cardiol*. 2015;116:595–603. DOI: 10.1016/j.amjcard.2015.05.018.

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SUPPLEMENTAL MATERIAL
| Table S1. Baseline characteristics of overall population and classified population along Ea/Ees quartiles in detail |
|---------------------------------------------------------------|
| Overall | Group 1 | Group 2 | Group 3 | Group 4 | P-value |
|---------|---------|---------|---------|---------|---------|
| Age at TAVR, yrs | 85.00 [81.00, 88.00] | 85.00 [82.00, 88.00] | 84.00 [81.00, 88.00] | 85.00 [82.00, 88.00] | 85.00 [81.00, 87.00] | 0.079 |
| Female sex, n (%) | 953 (68.2) | 373 (69.9) | 246 (69.6) | 212 (67.3) | 93 (61.8) | 0.001 |
| Body surface area, m² | 1.40 [1.30, 1.51] | 1.40 [1.30, 1.51] | 1.40 [1.30, 1.52] | 1.41 [1.30, 1.55] | 1.44 [1.31, 1.57] | 0.005 |
| NYHA class II/IV, n (%) | 708 (53.1) | 352 (64.1) | 196 (54.1) | 216 (64.4) | 92 (60.6) | 0.006 |
| Clinical Frail Score | 4.00 [3.00, 5.00] | 4.00 [3.00, 5.00] | 4.00 [3.00, 5.00] | 4.00 [3.00, 5.00] | 4.00 [3.00, 5.00] | 0.001 |
| STS score, % | 6.58 [4.32, 9.20] | 6.16 [4.36, 8.32] | 6.18 [4.33, 8.62] | 6.32 [4.40, 8.88] | 7.63 [4.90, 11.80] | 0.004 |
| Medication | | | | | |
| Beta-blocker, n (%) | 548 (39.0) | 140 (40.6) | 151 (43.2) | 151 (43.2) | 122 (84.0) | 0.146 |
| Atrial fibrillation, n (%) | 287 (20.8) | 52 (15.1) | 64 (18.6) | 72 (21.7) | 93 (62.7) | 0.001 |
| Right bundle branch block, n (%) | 105 (7.6) | 16 (5.1) | 27 (7.8) | 38 (11.2) | 22 (14.7) | 0.037 |
| Left bundle-branch block, n (%) | 46 (3.8) | 5 (1.5) | 9 (2.6) | 11 (3.1) | 21 (6.9) | 0.008 |
| Past medical history | | | | | |
| Previous PCI, n (%) | 168 (12.2) | 32 (9.3) | 37 (10.9) | 54 (15.7) | 45 (11.9) | 0.055 |
| Previous CABG, n (%) | 75 (5.4) | 7 (2.0) | 13 (3.8) | 14 (4.1) | 39 (13.1) | 0.001 |
| Previous PMI, n (%) | 99 (7.2) | 20 (5.8) | 21 (6.1) | 28 (8.1) | 36 (8.7) | 0.355 |
| All stroke, n (%) | 178 (12.9) | 39 (11.3) | 47 (13.7) | 43 (12.3) | 49 (14.2) | 0.676 |
| Periperal arterial disease, n (%) | 182 (13.2) | 35 (10.1) | 44 (12.9) | 52 (15.1) | 51 (14.0) | 0.194 |
| COPD, n (%) | 223 (16.0) | 50 (14.5) | 59 (17.2) | 48 (14.0) | 66 (11.9) | 0.218 |
| Baseline echocardiography | | | | | |
| Indexed AVA, cm²/m² | 21.50 [17.73, 25.76] | 21.80 [17.73, 25.76] | 22.00 [17.73, 25.76] | 22.00 [17.73, 25.76] | 21.50 [17.73, 25.76] | 0.001 |
| LVEDV (modified Simpson or Teich), mL | 69.70 [57.00, 83.10] | 72.00 [57.00, 83.10] | 77.50 [63.00, 94.40] | 67.00 [59.00, 76.00] | 65.00 [57.75, 74.00] | 0.008 |
| LVESV (modified Simpson or Teich), mL | 43.60 [39.00, 48.40] | 43.50 [39.00, 48.40] | 44.20 [40.00, 46.00] | 44.20 [40.00, 46.00] | 43.60 [39.00, 48.40] | 0.001 |
| E/A ratio | 1.07 [0.80, 1.40] | 1.07 [0.80, 1.40] | 1.07 [0.80, 1.40] | 1.07 [0.80, 1.40] | 1.07 [0.80, 1.40] | 0.001 |
| Ee' | 9.00 [7.00, 11.00] | 9.00 [7.00, 11.00] | 9.00 [7.00, 11.00] | 9.00 [7.00, 11.00] | 9.00 [7.00, 11.00] | 0.001 |
| LV/Tricuspid valve area, m² | 0.28 (0.21, 0.34) | 0.28 (0.21, 0.34) | 0.28 (0.21, 0.34) | 0.28 (0.21, 0.34) | 0.28 (0.21, 0.34) | 0.001 |
| Peak AV velocity, m/s | 4.51 [4.05, 5.10] | 4.51 [4.05, 5.10] | 4.70 [4.20, 5.25] | 4.70 [4.20, 5.25] | 4.70 [4.20, 5.25] | 0.001 |
| COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LV = left ventricular; LVEF = LV ejection fraction; LVESV = LV end-systolic volume; LVEDV = LV end-diastolic volume; AVA = aortic valve area; BSA = body surface area; BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting; | | | | | |
LV end-diastolic volume; LVOT-VTI = LV outflow tract velocity time integral; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PG = pressure gradient; PMI = pacemaker implantation; RWT = relative wall thickness; STS = Society of Thoracic Surgeons.
| Table S2. Procedure characteristics |
|-------------------------------------|
|                                     | Overall | Group 1 | Group 2 | Group 3 | Group 4 | P value |
| Access site, n (%)                  |         |         |         |         |         |         |
| Trans-femoral                        | 1177 (85.4) | 306 (88.7) | 297 (86.3) | 286 (83.1) | 288 (83.5) | 0.472   |
| Trans-apical                        | 161 (11.7) | 32 (9.3)  | 36 (10.5) | 48 (14.0) | 45 (13.0) |         |
| Direct aorta                        | 8 (0.6)  | 2 (0.6)   | 2 (0.6)   | 0 (0.0)   | 4 (1.2)   |         |
| Trans-subclavian                    | 11 (0.8)  | 1 (0.3)   | 4 (1.2)   | 3 (0.9)   | 3 (0.9)   |         |
| Trans-iliac                         | 21 (1.5)  | 4 (1.2)   | 5 (1.5)   | 7 (2.0)   | 5 (1.4)   |         |
| Prosthesis, n (%)                   |         |         |         |         |         | <0.001  |
| Sapien XT                           | 863 (62.0) | 193 (55.5) | 209 (60.8) | 246 (71.5) | 215 (62.3) |         |
| Sapien 3                            | 338 (24.5) | 119 (34.5) | 82 (23.8)  | 65 (18.9)  | 72 (20.9)  |         |
| Corevalve                           | 112 (8.1)  | 18 (5.2)   | 36 (10.5)  | 21 (6.1)   | 37 (10.7)  |         |
| EvolutR                             | 65 (4.7)  | 15 (4.3)   | 17 (4.9)   | 12 (3.5)   | 21 (6.1)   |         |
| Prosthesis type, n (%)              |         |         |         |         |         | 0.004   |
| Balloon-expandable device          | 1201 (87.2) | 312 (90.4) | 291 (84.6) | 311 (90.4) | 287 (83.2) |         |
| Self-expanding device               | 177 (12.8) | 33 (9.6)   | 53 (15.4)  | 33 (9.6)   | 58 (16.8)  |         |
| Procedure situation, n (%)         |         |         |         |         |         | 0.007   |
| Elective                            | 1383 (94.6) | 328 (95.1) | 330 (95.9) | 331 (96.2) | 314 (91.0) |         |
| Urgent                              | 64 (4.6)  | 17 (4.9)   | 13 (3.8)   | 16 (2.9)   | 24 (7.0)   |         |
| Emergent                            | 11 (0.8)  | 0 (0.0)    | 1 (0.3)    | 3 (0.9)    | 7 (2.0)    |         |
| Days from TAVR to discharge         | 10.00 [7.00, 15.00] | 8.00 [6.00, 12.00] | 9.00 [7.00, 15.00] | 10.50 [7.00, 15.00] | 12.00 [8.00, 17.75] | <0.001 |

Values are n (%) or median [interquartile range]. Group 1: Ea/Ees < 0.326; Group 2: 0.326 ≤ Ea/Ees ≤ 0.453; Group 3: 0.453 ≤ Ea/Ees ≤ 0.666; Group 4: 0.666 < Ea/Ees. TAVR = transcatheter aortic valve replacement.
Table S3. Post-TAVR echocardiographic data in detail

|                         | Overall | Group 1 | Group 2 | Group 3 | Group 4 | P value |
|-------------------------|---------|---------|---------|---------|---------|---------|
| **Systolic LV diameter**, mm | 27.80 [25.00, 31.80] | 25.00 [23.00, 27.00] | 26.90 [25.00, 29.00] | 28.45 [26.08, 31.52] | 34.60 [29.00, 40.00] | <0.001 |
| **Diastolic LV diameter**, mm | 43.60 [40.00, 48.00] | 41.20 [38.00, 44.55] | 43.00 [40.00, 46.00] | 44.00 [41.00, 48.00] | 48.00 [43.00, 53.00] | <0.001 |
| **LVEF (modified Simpson or Teich)**, % | 63.00 [54.92, 67.80] | 68.00 [65.00, 74.10] | 66.00 [62.00, 69.20] | 62.00 [56.00, 65.00] | 48.10 [40.00, 55.40] | <0.001 |
| **LVESV (modified Simpson or Teich)**, mL | 29.40 [22.10, 42.88] | 20.00 [16.20, 24.00] | 26.70 [22.50, 31.85] | 33.75 [27.00, 42.12] | 59.30 [42.20, 75.90] | <0.001 |
| **LVEDV (modified Simpson or Teich)**, mL | 83.10 [65.57, 104.93] | 65.90 [52.10, 80.40] | 80.00 [65.00, 92.15] | 87.95 [70.40, 107.50] | 112.10 [86.00, 135.30] | <0.001 |
| **Left atrial diameter**, mm | 42.00 [38.00, 46.10] | 41.00 [37.00, 45.00] | 41.00 [37.00, 45.00] | 42.00 [38.00, 47.00] | 44.00 [39.00, 48.00] | <0.001 |
| **RWT** | 0.52 [0.23, 1.64] | 0.56 [0.38, 1.64] | 0.52 [0.29, 1.06] | 0.51 [0.33, 1.22] | 0.47 [0.23, 1.25] | <0.001 |
| **LVOT-VTI, cm** | 23.00 [19.00, 27.22] | 26.00 [22.78, 30.02] | 24.02 [20.70, 27.25] | 22.90 [19.23, 27.00] | 19.00 [16.00, 23.00] | <0.001 |
| **Stroke volume, mL** | 69.00 [55.52, 82.68] | 80.00 [60.00, 92.00] | 70.60 [59.30, 81.00] | 63.95 [51.08, 78.30] | 60.00 [44.00, 74.00] | <0.001 |
| **Systolic pulmonary artery pressure, mmHg** | 30.75 [25.00, 38.00] | 32.00 [25.00, 38.00] | 30.00 [23.90, 38.00] | 31.00 [25.00, 38.00] | 30.00 [25.00, 37.00] | 0.327 |
| **PVL ≥ moderate, n (%)** | 16 (1.2) | 7 (2.0) | 2 (0.6) | 3 (0.9) | 4 (1.2) | 0.318 |
| **EOA, cm²** | 1.70 [1.48, 2.00] | 1.80 [1.57, 2.08] | 1.70 [1.46, 1.90] | 1.66 [1.40, 1.91] | 1.70 [1.49, 2.00] | <0.001 |
| **Indexed EOA, cm²/m²** | 1.20 [1.05, 1.39] | 1.28 [1.14, 1.47] | 1.19 [1.05, 1.35] | 1.15 [1.00, 1.33] | 1.18 [1.03, 1.36] | <0.001 |
| **Mean PG, mmHg** | 9.90 [7.40, 12.40] | 10.70 [8.30, 13.50] | 10.10 [8.00, 13.00] | 9.70 [7.10, 12.00] | 8.65 [6.00, 10.90] | <0.001 |
| **Peak PG, mmHg** | 19.36 [14.70, 24.20] | 21.16 [17.00, 26.42] | 20.20 [16.00, 25.55] | 19.00 [14.44, 23.20] | 16.30 [12.45, 21.16] | <0.001 |
| **Peak velocity, m/s** | 2.20 [1.91, 2.47] | 2.30 [2.05, 2.57] | 2.25 [1.98, 2.54] | 2.18 [1.90, 2.41] | 2.01 [1.75, 2.30] | <0.001 |
| **E/e'** | 20.10 [15.52, 26.38] | 20.40 [15.50, 26.40] | 19.00 [14.90, 25.36] | 20.57 [16.38, 25.92] | 19.95 [15.90, 27.14] | 0.098 |

Values are median [interquartile range] or n (%). Group 1: Ea/Ees < 0.326; Group 2: 0.326 ≤ Ea/Ees < 0.453; Group 3: 0.453 ≤ Ea/Ees < 0.666; Group 4: 0.666 < Ea/Ees. AR = aortic valve regurgitation; EOA = effective orifice area; LV = left ventricular; LVEF = LV ejection fraction; LVESV = LV end-systolic volume; LVEDV = LV end-diastolic volume; LVOT-VTI = LV outflow tract velocity time integral; PG = pressure gradient; PVL = para-valvular leak; RWT = relative wall thickness.
Table S4. Association of Ea/Ees with clinical and echocardiographic parameters by using Spearman’s rank correlations

| Parameter                                | \( \rho \)  | P value |
|------------------------------------------|--------------|---------|
| Clinical indices                         |              |         |
| BSA                                      | 0.099        | <0.001  |
| STS score                                | 0.153        | <0.001  |
| BNP                                      | 0.345        | <0.001  |
| eGFR                                     | -0.147       | <0.001  |
| Hemoglobin                               | -0.041       | 0.133   |
| Pre-procedural systolic BP               | -0.147       | <0.001  |
| Post-procedural systolic BP              | 0.004        | 0.878   |
| Pre-procedural diastolic BP              | -0.081       | 0.004   |
| Post-procedural diastolic BP             | 0.056        | 0.038   |
| Pre-procedural echocardiographic parameters |           |         |
| Indexed AVA                              | -0.105       | <0.001  |
| Peak velocity                            | -0.102       | <0.001  |
| Mean PG                                  | -0.097       | <0.001  |
| Peak PG                                  | -0.098       | <0.001  |
| Systolic LV diameter                     | 0.469        | <0.001  |
| Diastolic LV diameter                    | 0.428        | <0.001  |
| LV EF                                    | -0.593       | <0.001  |
| LV ESV                                   | 0.618        | <0.001  |
| LV EDD                                   | 0.477        | <0.001  |
| RWT                                      | -0.337       | <0.001  |
| Systolic pulmonary artery pressure       | 0.054        | 0.061   |
| E/e'                                     | 0.060        | 0.036   |
| LVOT-VTI                                 | -0.287       | <0.001  |
| Post-procedural echocardiographic parameters |        |         |
| Indexed EOA                              | -0.166       | <0.001  |
| Peak velocity                            | -0.244       | <0.001  |
| Mean PG                                  | -0.221       | <0.001  |
| Peak PG                                  | -0.246       | <0.001  |
| Systolic LV diameter                     | 0.554        | <0.001  |
| Diastolic LV diameter                    | 0.417        | <0.001  |
| LV EF                                    | -0.742       | <0.001  |
| LV ESV                                   | 0.794        | <0.001  |
| LV EDD                                   | 0.544        | <0.001  |
| RWT                                      | -0.290       | <0.001  |
| Systolic pulmonary artery pressure       | -0.035       | 0.231   |
| E/e'                                     | 0.043        | 0.138   |
| LVOT-VTI                                 | -0.407       | <0.001  |

BSA = body surface area; BNP = brain natriuretic peptide; eGFR = estimated glomerular filtration rate; EOA = effective orifice area; LV = left ventricular; LVEF = LV ejection fraction; LVESV = LV end-systolic volume; LVEDV = LV end-diastolic volume; LVOT-VTI = LV outflow tract-velocity time integral; PG = pressure gradient; RWT = relative wall thickness.
| Factor                        | HR    | 95% CI      | P value | Factor                        | HR    | 95% CI      | P value |
|-------------------------------|-------|-------------|---------|-------------------------------|-------|-------------|---------|
| Ea/Ees                        | 1.576 | 1.253-1.983 | <0.001  | Ea/Ees                        | 1.330 | 1.074-1.647 | 0.009   |
| Age                           | 1.026 | 0.989-1.064 | 0.178   | Systolic pulmonary artery pressure | 1.027 | 1.015-1.040 | <0.001  |
| Male                          | 1.417 | 0.969-2.073 | 0.072   | Left atrial diameter          | 1.032 | 1.007-1.058 | 0.012   |
| NYHA class III/IV             | 1.065 | 0.735-1.543 | 0.740   | E/e'                          | 1.004 | 0.985-1.023 | 0.706   |
| Clinical Frail Score          | 1.076 | 0.929-1.246 | 0.327   | Peak velocity                 | 0.600 | 0.233-1.550 | 0.292   |
| STS score                     | 0.994 | 0.970-1.020 | 0.663   | Mean PG                       | 1.019 | 0.921-1.127 | 0.715   |
| Pre-procedural electrocardiography |       |             |         | LVOT-VTI                     | 0.990 | 0.861-1.020 | 0.508   |
| Atrial fibrillation           | 1.618 | 1.118-2.341 | 0.011   |                               |       |             |         |
| Left bundle branch block      | 1.021 | 0.414-2.520 | 0.964   |                               |       |             |         |
| Pre-procedural medication     |       |             |         | Pre-procedural laboratory test |       |             |         |
| diuretics                     | 1.946 | 1.305-2.902 | 0.001   |                               |       |             |         |
| beta blocker                  | 1.336 | 0.945-1.887 | 0.101   |                               |       |             |         |
| statin                        | 0.751 | 0.497-1.137 | 0.177   |                               |       |             |         |
| Pre-procedural laboratory test|       |             |         |                               |       |             |         |
| BNP                           | 1.000 | 1.000-1.000 | 0.690   |                               |       |             |         |
| Albumin                       | 0.985 | 0.678-1.430 | 0.936   |                               |       |             |         |
| Hemoglobin                    | 0.938 | 0.833-1.057 | 0.292   |                               |       |             |         |
| eGFR                          | 0.993 | 0.983-1.003 | 0.147   |                               |       |             |         |
| Past medical history          |       |             |         |                               |       |             |         |
| dyslipidemia                  | 0.842 | 0.565-1.256 | 0.400   |                               |       |             |         |
| chronic obstructive pulmonary disease | 1.306 | 0.875-1.949 | 0.192   |                               |       |             |         |
| peripheral artery disease     | 1.441 | 0.927-2.239 | 0.104   |                               |       |             |         |
| previous CABG                 | 2.006 | 1.112-3.588 | 0.019   |                               |       |             |         |
| Procedure situation           | 1.613 | 0.952-2.734 | 0.076   |                               |       |             |         |
| Factor                      | HR  | 95% CI      | P value | Factor                      | HR  | 95% CI      | P value |
|-----------------------------|-----|-------------|---------|-----------------------------|-----|-------------|---------|
| Ea/Ees                      | 1.473 | 1.079-2.010 | 0.015   | Post-procedural echocardiography |     |             |         |
| Age                         | 1.027 | 0.982-1.073 | 0.247   | Systolic pulmonary artery pressure | 1.024 | 1.005-1.044 | 0.014   |
| Male                        | 1.809 | 1.124-2.911 | 0.015   | Left atrial diameter        | 1.014 | 0.980-1.050 | 0.420   |
| NYHA class III/IV           | 1.019 | 0.645-1.610 | 0.837   | E/e'                        | 0.9986 | 0.974-1.023 | 0.916   |
| Clinical Frail Score        | 1.153 | 0.970-1.371 | 0.107   | Peak velocity               | 0.5202 | 0.415-1.665 | 0.316   |
| STS score                   | 0.997 | 0.967-1.028 | 0.864   | Mean PG                     | 1.057 | 0.916-1.220 | 0.451   |
| Pre-procedural electrocardiography |     |             |         | LVOT-VTI                    | 0.9915 | 0.952-1.032 | 0.677   |
| Atrial fibrillation         | 1.316 | 0.786-2.203 | 0.296   |                             |     |             |         |
| Left bundle branch block    | 1.696 | 0.514-5.533 | 0.389   |                             |     |             |         |
| Pre-procedural medication   |     |             |         |                             |     |             |         |
| diuretics                   | 1.643 | 1.006-2.683 | 0.047   |                             |     |             |         |
| beta blocker                | 1.364 | 0.876-2.124 | 0.169   |                             |     |             |         |
| statin                      | 0.892 | 0.532-1.495 | 0.664   |                             |     |             |         |
| Pre-procedural laboratory test |     |             |         |                             |     |             |         |
| BNP                         | 1.000 | 0.999-1.000 | 0.245   |                             |     |             |         |
| Albumin                     | 0.862 | 0.507-1.466 | 0.583   |                             |     |             |         |
| Hemoglobin                  | 0.972 | 0.849-1.126 | 0.708   |                             |     |             |         |
| eGFR                        | 0.991 | 0.978-1.004 | 0.157   |                             |     |             |         |
| Past medical history        |     |             |         |                             |     |             |         |
| dyslipidemia                | 0.72  | 0.438-1.183 | 0.195   |                             |     |             |         |
| chronic obstructive pulmonary disease | 1.279 | 0.757-2.141 | 0.359   |                             |     |             |         |
| peripheral artery disease   | 1.113 | 0.647-1.913 | 0.699   |                             |     |             |         |
| previous CABG               | 2.263 | 1.184-4.324 | 0.013   |                             |     |             |         |
| Procedure situation         | 1.322 | 0.652-3.554 | 0.332   |                             |     |             |         |

The variables included in multivariable-adjusted analysis had p<0.10 in univariate analysis. HR = hazard ratio; CI = confidence interval; BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; LVOT-VTI = LV outflow tract-velocity time integral; NYHA = New York Heart Association; PG = pressure gradient; STS = Society of Thoracic Surgeons.
Table S6. Mid-term clinical outcomes in two groups according to cut-off value with ROC curve

|                      | Low group n=709                  | High group n=669                  | P value |
|----------------------|----------------------------------|-----------------------------------|---------|
| **Primary endpoint** |                                  |                                   |         |
| 3 years composite endpoint, n (%) / event free rate (95% CI) | 70 (9.9) / 85.7% (81.7-88.9) | 129 (19.3) / 74.1% (69.5-78.1) | <0.001  |
| **Secondary endpoint** |                                  |                                   |         |
| 3 years all cause death, n (%) / event free rate (95% CI) | 109 (15.4) / 78.8% (74.3-82.6) | 138 (20.6) / 72.2% (67.5-76.4) | 0.011   |
| 3 years cardiovascular death, n (%) / event free rate (95% CI) | 35 (4.9) / 92.5% (89.2-94.8) | 54 (8.1) / 87.3% (83.2-90.5) | 0.021   |
| 3 years hospitalization for heart failure, n (%) / event free rate (95% CI) | 41 (5.8) / 92.0% (88.9-94.3) | 89 (13.3) / 82.9% (79.1-86.1) | <0.001  |

CI = confidence interval. Cut-off value of Ea/Ees is 0.459, and AUC is 0.612.
Supplemental Figure Legends:

**Figure S1. Patient selection flow chart.** SBP: systolic blood pressure, SV: stroke volume, ESV: end-systolic volume, iEOA: indexed effective orifice area, PPM: patient-prosthesis mismatch.

**Figure S2. Distribution of ventricular-arterial coupling in each quartile.** VAC: ventricular-arterial coupling

**Figure S3. Schematic presentation of pressure-volume loops using every median value of the load parameters in quartile groups.** Black line: Group 1, Red line: Group 2, Blue line: Group 3, and Green line: Group 4. As the group number increases, the frame on pressure-volume field shifts to the right side.

**Figure S4. ROC curve of the primary endpoint by using ventricular-arterial coupling.** The cut-off value was 0.459, and AUC was 0.612. ROC: receiver operating characteristics; AUC: area under the curve.

**Figure S5. Mid-term clinical outcomes in two groups according to the cut-off value from ROC curve.** (A) all-cause mortality, (B) cardiovascular death, (C) hospitalization for HF, and (D) the primary endpoint of cardiovascular death and hospitalization for HF in the two groups according to the cut-off value of VAC calculated from ROC curve. HF: heart failure; ROC: receiver operating characteristics.
OCEAN TAVI registry n=2588

- n=1695
- missing data of post-procedural SBP, SV, LVESV n=893

- n=1378
- device failure or no information about device success n=257
- missing data of post-procedural iEOA n=60

Quartile

- Group1 n=345
- Group2 n=344
- Group3 n=344
- Group4 n=345
LV pressure (mmHg)

|                | Group1 n=345 | Group2 n=344 | Group3 n=344 | Group4 n=345 |
|----------------|--------------|--------------|--------------|--------------|
| Ea, mmHg/mL    | 1.38         | 1.57         | 1.77         | 1.85         |
| Ees, mmHg/mL   | 5.60         | 4.21         | 3.37         | 1.89         |
| Ea/Ees         | 0.26         | 0.39         | 0.54         | 0.91         |
| SW/PVA, %      | 88.62        | 83.83        | 78.69        | 68.64        |
| LVESV, mL      | 20.00        | 26.70        | 33.75        | 59.30        |
| LVEDV, mL      | 65.90        | 80.00        | 87.95        | 112.10       |
| LVESP, mmHg    | 109.80       | 112.95       | 113.40       | 110.70       |

LV Volume (mL)

- Black line: Group 1
- Red line: Group 2
- Green line: Group 3
- Blue line: Group 4
AUC: 0.612 (95% CI: 0.571-0.654)
