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ORIGINAL RESEARCH

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

Hiroaki Yokoyama, MD; Futoshi Yamanaka, MD; Koki Shishido, MD; Tomoki Ochiai, MD; Shohei Yokota, MD; Noriaki Moriyama, MD; Yusuke Watanabe, MD; Shinichi Shirai, MD; Norio Tada, MD; Motoharu Araki, MD; Fumiaki Yashima, MD; Toru Naganuma, MD; Hiroshi Ueno, MD; Minoru Tabata, MD; Kazuki Mizutani, MD; Kensuke Takagi, MD; Masanori Yamamoto, MD; Shigeru Saito, MD; Kentaro Hayashida, MD; on behalf of the OCEAN-TAVI investigators;

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 vAlvular 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[1,2]—is affected by cardiac load. Therefore, these measurements of cardiac performance can sometimes lead

Correspondence to: Futoshi Yamanaka, MD, Department of Cardiology and Catheterization Laboratories, Shonan Kamakura General Hospital, Okamoto 1370-1, Kamakura City 247:8533, Japan. E-mail: futoshi-yamanaka@nifty.com

†A complete list of the OCEAN-TAVI investigators can be found in the Appendix at the end of the article.

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CLINICAL PERSPECTIVE

What Is New?

- Ventricular-arterial coupling has not yet been estimated in patients who underwent transcatheter aortic valve replacement .
- The arterial elastance to end-systolic elastance ratio (left ventricular end-systolic volume/stroke volume) is a noninvasively assessed index that reflects ventricular-arterial coupling status.
- A higher arterial elastance to end-systolic elastance ratio calculated with echocardiography at discharge after TAVR is associated with adverse clinical outcomes during midterm follow-up, and arterial elastance to end-systolic elastance ratio provides an incremental association with clinical outcomes over clinical indices and left ventricular ejection fraction.

What Are the Clinical Implications?

- Ventricular-arterial coupling may be a useful idea for understanding the balance between the left ventricular function and the arterial system in patients who underwent transcatheter aortic valve replacement .
- Ventricular-arterial coupling may be helpful to understand the effects of structure heart disease interventions on hemodynamics in depth.

Nonstandard Abbreviations and Acronyms

AS	aortic valve stenosis
Ea/Ees	arterial elastance to end-systolic elastance ratio
LVESP	left ventricular end-systolic pressure
LVESV	left ventricular end-systolic volume
OCEAN-TAVI	Optimized transCathEter vAlvular iNtervention
PG	pressure gradient
PV	pressure volume
SBP	systolic blood pressure
SV	stroke volume
SW	stroke work
TAVR	transcatheter aortic valve replacement
VAC	ventricular-arterial coupling

to misinterpreted results,[3] indicating the need for another index that is independent of cardiac load. 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]).[4] VAC is an important element of cardiac energy efficiency for the process of delivering blood from the heart to the arterial system.[5,6] Considering a load-independent physiological method to assess VAC, a noninvasive tool using echocardiography has been recently developed.[5] End-systolic ventricular elastance (Ees) is a minimally load-independent index of LV myocardial contractility.[5,6] 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.[7]

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 Medtronoic EvolutR (Medtronic) prosthesis at 14 collaborating high-volume centers in Japan.[8] 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 contractility[3,10,11]; 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-diastole[5] (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 energy.[16] 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]

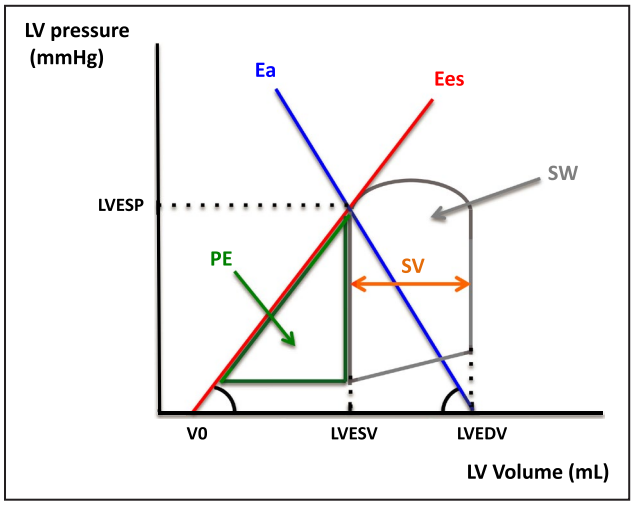

Figure 1. Schematic presentation of ventricular-arterial coupling on the pressure-volume relationship.
End-systolic elastance (Ees) represents the slope of the end-systolic pressure-volume relationship (ESPVR), where ESP denotes end-systolic pressure. V0 is the left ventricular (LV) volume at the point where ESPVR crosses the end-systolic pressure of 0 mm Hg. Effective arterial elastance (Ea) represents the negative slope connecting the pressure-volume loops between the end-systolic point and the point on the volume axis at end-diastole. LVEDV indicates left ventricular end-diastolic volume; LVESP, left ventricular end-systolic pressure; LVESV, left ventricular end-systolic volume; PE, potential energy; SV, stroke volume; and SW, stroke work.

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.[9] 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.[19]

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

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 (6.5)	27 (8.9)	38 (12.8)	22 (7.2)	0.037
Laboratory test						
BNP, pg/mL	255.00 [118.00–539.67]	173.40 [90.00–369.80]	170.30 [86.00–368.05]	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 (modified 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 (modified 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 (modified 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, cm^2/m^2	0.44 [0.37–0.52]	0.47 [0.40–0.54]	0.45 [0.38–0.52]	0.43 [0.36–0.51]	0.43 [0.34–0.50]	0.002
Mean PG, mm Hg	47.50 [38.00–61.00]	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.

Table 2. Post-TAVR Echocardiographic Data of the Overall Population and Classified Population Along Ea/Ees Quartiles

	Overall	Group 1	Group 2	Group 3	Group 4	*P* Value
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
SV, mL	69.00 [55.52–82.68]	80.00 [69.00–93.00]	70.60 [59.30–81.00]	63.95 [51.08–78.30]	60.00 [44.00–74.00]	<0.001
PVL ≥moderate, n (%)	16 (1.2)	7 (2.0)	2 (0.6)	3 (0.9)	4 (1.2)	0.318
Indexed EOA, cm^2/m^2	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, mm Hg	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 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]	2.03 [1.75–2.30]	<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. EOA indicates effective orifice area; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PG, pressure gradient; PVL, paravalvular leak; SV, stroke volume; and TAVR, transcatheter aortic valve replacement.

mm Hg/mL), and there was a significant difference between the 4 groups (*P*<0.001). The overall median Ea 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 overall median Ea/Ees was 0.45 (0.07–7.16); the distribution of Ea/Ees for each group is illustrated in Figure S2. The group with the lower Ea/Ees 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 Ea/Ees with various clinical indices and echocardiographic parameters. There was a weak but statistically significant correlation of Ea/Ees 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 Ea/Ees and clinical indices, model 2 comprised Ea/Ees and postprocedural echocardiographic parameters, and model 3 included Ea/Ees and all indices included in models 1 and 2. The HR of Ea/Ees 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. Postprocedural Ea/Ees had a significant association with the primary end point during the midterm

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

	Overall	Group 1	Group 2	Group 3	Group 4	*P* Value
Postprocedural systolic BP, mm Hg	124.00 [112.00–135.00]	122.00 [110.00–136.00]	125.50 [114.00–134.25]	126.00 [114.00–136.00]	123.00 [112.00–135.00]	0.194
Postprocedural diastolic BP, mm Hg	61.00 [54.00–69.00]	60.00 [52.00–68.00]	62.00 [55.00–69.00]	61.00 [54.00–68.00]	62.00 [55.00–70.00]	0.068
Ea, mm Hg/mL	1.61 [0.49–19.72]	1.38 [0.49–3.73]	1.57 [0.77–6.30]	1.77 [0.74–4.60]	1.85 [0.99–19.72]	<0.001
Ees, mm Hg/mL	3.76 [0.23–18.59]	5.60 [2.44–18.59]	4.21 [2.19–16.80]	3.37 [1.52–8.58]	1.89 [0.23–11.30]	<0.001
Ea/Ees	0.45 [0.07–7.16]	0.26 [0.07–0.33]	0.39 [0.33–0.45]	0.54 [0.45–0.66]	0.91 [0.66–7.16]	<0.001
SW/PV area, %	81.55 [21.84–96.46]	88.62 [86.01–96.46]	83.83 [81.55–86.01]	78.69 [75.06–81.54]	68.64 [21.84–75.05]	<0.001

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.

follow-up after TAVR. Moreover, prognostic associations were assessed in a hierarchal 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 4. Midterm Clinical Outcomes of the Overall Population and Classified Population Along Ea/Ees Quartile

	Overall	Group 1		Group 2		Group 3		Group 4			
	No. (%)	No. (%)	No. (%)	vs Group 1		No. (%)	vs Group 1		No. (%)	vs Group 1		Overall *P* Value
				HR (95% CI)	*P* Value		HR (95% CI)	*P* Value		HR (95% CI)	*P* Value	
Primary end point												
Three-y 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	<0.001
Secondary end point												
Three-y all-cause death	247 (17.9)	47 (13.6)	59 (17.2)	1.23 (0.84–1.80)	0.295	63 (18.3)	1.27 (0.87–1.86)	0.210	78 (22.6)	1.71 (1.19–2.46)	0.003	0.022
Three-y cardiovascular death	89 (6.5)	13 (3.8)	21 (6.1)	1.58 (0.79–3.15)	0.198	26 (7.6)	1.89 (0.97–3.68)	0.060	29 (8.4)	2.29 (1.19–4.41)	0.013	0.07
Three-y hospitalization for heart failure	130 (9.4)	15 (4.3)	26 (7.6)	1.73 (0.92–3.27)	0.091	42 (12.2)	2.75 (1.53–4.96)	<0.001	47 (13.6)	3.31 (1.85–5.91)	<0.001	<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.

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[25] 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 [25]) 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 preprocedural valvuloarterial impedance was not associated with 2-year all-cause or cardiovascular mortalities among patients who underwent TAVR[26]; 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 lower LVESP and/or higher LVESV. Lindman et al[27] 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 LVESV, 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[28] observed

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

	Univariable Analysis			Multivariable-Adjusted Analysis								
				Model 1			Model 2			Model 3		
	HR	95% CI	*P* Value	HR (per 1-Unit Increase)	95% CI	*P* Value	HR (per 1-Unit Increase)	95% CI	*P* Value	HR (per 1-Unit Increase)	95% CI	*P* Value
Composite end point (n=199)	1.51	1.30–1.74	<0.001	1.58	1.25–1.98	<0.001	1.33	1.07–1.65	0.009	1.47	1.08–2.01	0.015

HR indicates hazard ratio; and TAVR, transcatheter aortic valve replacement.

Model 1: arterial elastance to end-systolic elastance ratio (Ea/Ees) and clinical variables (age, sex, New York Heart Association class III/IV, Society of Thoracic Surgeons score, Clinical Frail Score, albumin, brain natriuretic peptide, estimated glomerular filtration rate, hemoglobin, β-blockers, diuretics, statin, chronic obstructive pulmonary disease, dyslipidemia, peripheral arterial disease, prior coronary artery bypass grafting, situation of procedure, atrial fibrillation, and left bundle branch block.

Model 2: Ea/Ees and postprocedural echocardiographic variables (E/e', transcatheter heart valve mean pressure gradient, transcatheter heart valve peak velocity, systolic pulmonary artery pressure, left atrium diameter, and left ventricular outflow tract-velocity time integral).

Model 3: Ea/Ees and the indices combining model 1 and model 2.

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.[7] Chirinos[7] 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

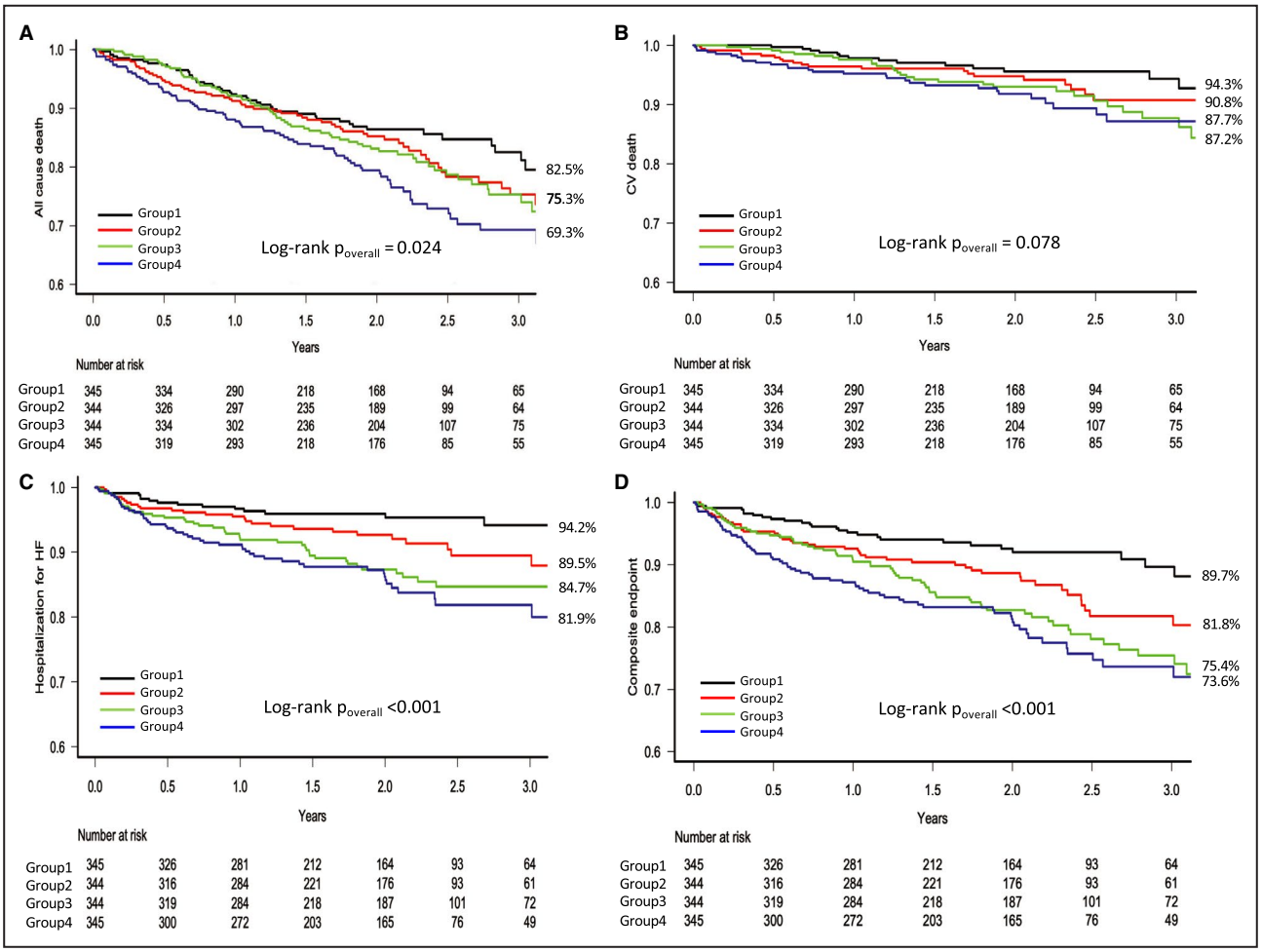

Figure 2. Midterm clinical outcomes in quartile groups according to post–transcatheter aortic valve replacement ventricular-arterial coupling.
(**A**) All-cause mortality, (**B**) cardiovascular (CV) death, (**C**) hospitalization for heart failure (HF), and (**D**) composite events of cardiovascular death and hospitalization for HF.

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

OCEAN-TAVI Investigators

Keio University School of Medicine, Tokyo, Japan: Kentaro Hayashida, Makoto Tanaka, Hikaru Tsuruta, Hiromu Hase, Nobuhiro Yoshijima, Tetsuya Saito, Sosuke Myojin, Yusuke Kobari, Toshinobu Ryuzaki, Tatsuo Takahashi, Shinichi Goto, Shohei Imaeda, Yuta Konami, Shingo Sakata, Taku Inohara, Yoshinori Katsumata. Toyohashi Heart Center, Toyohashi, Japan: Masanori Yamamoto, Mitsuru Sago, Tatsuya Tsunaki, Yuya Adachi, Ryo Yamaguchi, Kazuki Shimizu, Yutaka Koyama, Tetsuro Shimura. Nagoya Heart Center, Nagoya, Japan: Satoshi Tsujimoto, Ai Kagase, Toshihiro Kobayashi, Kenichi Shibata, Takahiro Tokuda, Tokuya Sakakura, Ryoutaku Kawahata, Hiroto Nishio.

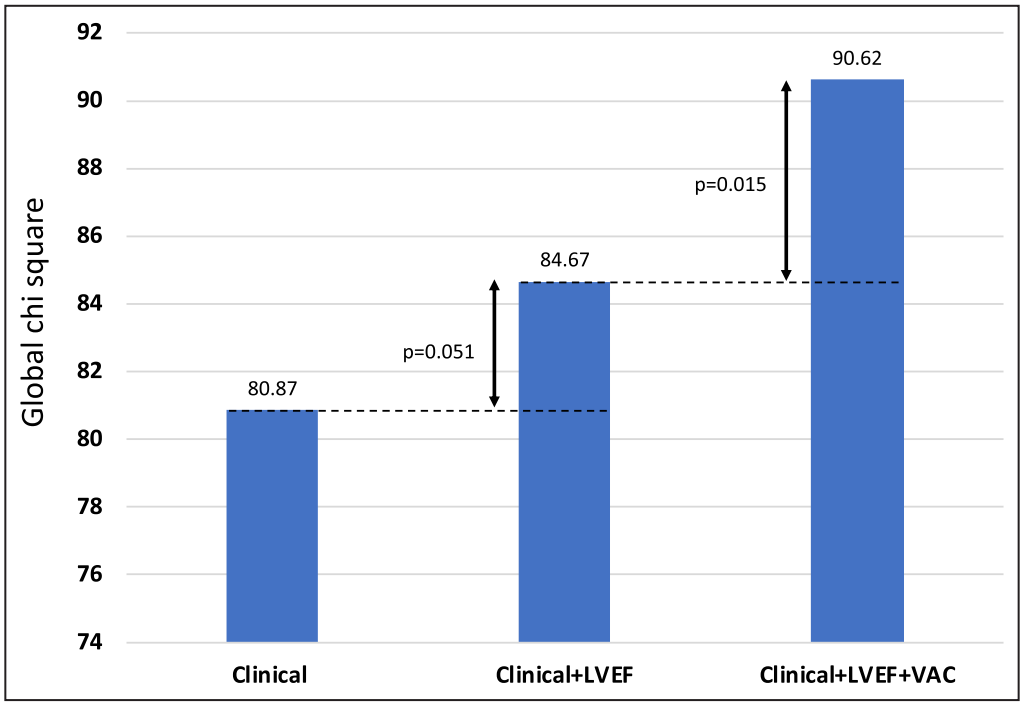

Figure 3. Incremental prognostic value of ventricular-arterial coupling (VAC) over clinical indices and postprocedural left ventricular ejection fraction (LVEF).
Clinical indices: the same clinical indices in model 1 of multivariable-adjusted analysis (Table 5).

Kokura Memorial Hospital, Kitakyushu, Japan: Shinichi Shirai, Masaomi Hayashi, Akihiro Isotani, Tomohiro Kawaguchi, Yoshio Arai, Tomohiko Taniguchi, Kenichi Ishizu, Shimpei Fujioka, Shintaro Mori, Takashi Morinaga, Masato Fukunaga, Hiroyuki Tabata, Kazuki Kitano. Teikyo University School of Medicine, Tokyo, Japan: Yusuke Watanabe, Yugo Nara, Hirofumi Hioki, Akihisa Kataoka, Hideyuki Kawashima, Fukuko Nagura, Makoto Nakashima, Hirosada Yamamoto, Nozomu Yukimitsu, Kazuya Sasaki, Shintaro Takamura, Taiga Katayama, Masaki Ito, Ruri Ishibashi, Junichi Nishikawa, Yosei Iseki, Takahiro Nomura, Yasuyuki Tsuchida, Kento Kito, Misako Fujii, Ayumi Harada, Yasuki Koyano. New Tokyo Hospital, Chiba, Japan: Toru Naganuma, Satoru Mitomo, Hirokazu Onishi, Hiroyoshi Kawamoto. Saiseikai Yokohama-City Eastern Hospital, Yokohama, Japan: Masahiro Yamawaki, Yohsuke Honda, Kenji Makino, Takahide Nakano, Chinatsu Yamada, Yasunori Iida. Sendai Kousei Hospital, Sendai, Japan: Norio Tada, Masaki Miyasaka, Yusuke Enta, Takashi Matsumoto, Masaki Nakashima, Yoshiko Munehisa, Arata Inoue, Kazunori Ishii, Takehiro Nomura, Makoto Saigan, Suguru Hirose. Shonan Kamakura General Hospital, Kamakura, Japan: Futoshi Yamanaka, Koki Shishido, Tomoki Ochiai, Shingo Mizuno, Noriaki Moriyama, Tsuyoshi Yamabe, Shigeru Hattori, Hiroaki Yokoyama, Shohei Yokota, Hirokazu Miyashita. Tokyobay Urayasuichikawa Medical Center, Chiba, Japan: Minoru Tabata, Kotaro Obunai, Masahiko Noguchi, Nahoko Kato, Hayato Morimura, Joji Ito, Makio Murahsi, Hidewo Amano, Shinsuke Kotani, Yuta Azumi. Toyama University School of Medicine, Toyama, Japan: Hiroshi Ueno, Nobuyuki Fukuda, Mitsuo Sobajima, Hiroshi Onoda, Hiroyuki Kuwahara, Shuhei Tanaka, Yohei Ueno, Kazuaki Fukahara, Toshio Doi, Shigeki Yokoyama, Teruhiko Imamura, Ryuichi Ushijima, Akira Oshima, Yuki Hida. Osaka City University Hospital, Osaka, Japan: Kazuki Mizutani. Saiseikai Utsunomiya Hospital, Tochigi, Japan: Fumiaki Yashima, Hiroaki Nishida, Kenichi Hashizume, Koji Ueno, Koki Ikebata, Masatoshi Oono, Kiwamu Sudo, Takesi Mori, Erito Huruse. Ogaki Municipal Hospital, Gifu, Japan: Kensuke Takagi.

ARTICLE INFORMATION

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Affiliations

Department of Cardiology, Shonan Kamakura General Hospital, Kamakura, Japan (H.Y., F. Yamanaka, K.S., T.O., S.Y., N.M., S. Saito.); Department of Cardiology, Teikyo University School of Medicine, Tokyo, Japan (Y.W.); Department of Cardiovascular Medicine, Kokura Memorial Hospital, Kitakyushu, Japan (S. Shirai); Department of Cardiology, Sendai Kousei Hospital, Sendai, Japan (N.T.); Department of Cardiology, Saiseikai Yokohama City Eastern Hospital, Yokohama, Japan (M.A.); Department of Cardiology, Saiseikai Utsunomiya Hospital, Utsunomiya, Japan (F. Yashima); Department of Cardiology, New Tokyo Hospital, Matsudo, Japan (T.N.); Department of Cardiovascular Medicine, Toyama University Hospital, Toyama, Japan (H.U.); Department of Cardiovascular Surgery, Tokyobay Urayasu Ichikawa Medical Center, Urayasu, Japan (M.T.); Department of Cardiovascular Medicine, Osaka City University Hospital, Osaka, Japan (K.M.); Department

of Cardiology, Ogaki Municipal Hospital, Ogaki, Japan (K.T.); Department of Cardiology, Nagoya Heart Center, Nagoya, Japan (M.Y.); Department of Cardiology, Toyohashi Heart Center, Toyohashi, Japan (M.Y.); Department of Cardiology, Keio University School of Medicine, Tokyo, Japan (K.H.); and Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan (F. Yamanaka, T.N.).

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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. Dr Araki, Dr Tabata, Dr Takagi, and Dr Hayashida are clinical proctors of Edwards Lifesciences. Dr Ueno is a clinical proctor for Medtronic. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S6
Figures S1–S5

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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 (69.2)	272 (78.8)	249 (72.4)	234 (68.0)	198 (57.4)	<0.001
BSA, m^2	1.40 [1.30, 1.53]	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 Ⅲ/Ⅳ, n (%)	708 (51.4)	152 (44.1)	168 (48.8)	176 (51.2)	212 (61.4)	<0.001
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]	0.006
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
Beta blocker, n (%)	477 (34.6)	107 (31.0)	105 (30.5)	135 (39.2)	130 (37.7)	0.027
Diuretic, n (%)	717 (52.0)	154 (44.6)	158 (45.9)	186 (54.1)	219 (63.5)	<0.001
Statin, n (%)	548 (39.8)	140 (40.6)	135 (39.2)	151 (43.9)	122 (35.4)	0.146
Cardiac risk factor						
Hypertension, n (%)	1037 (75.3)	257 (74.5)	264 (76.7)	262 (76.2)	254 (73.6)	0.762
Dyslipidemia, n (%)	565 (41.0)	144 (41.7)	139 (40.4)	147 (42.7)	135 (39.1)	0.788
Diabetes mellitus, n (%)	297 (21.6)	75 (21.7)	64 (18.6)	66 (19.2)	92 (26.7)	0.041
Past medical history						
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
Previous PMI, n (%)	99 (7.2)	20 (5.8)	21 (6.1)	28 (8.1)	30 (8.7)	0.355
All stroke, n (%)	178 (12.9)	39 (11.3)	47 (13.7)	43 (12.5)	49 (14.2)	0.676
Peripheral arterial disease, n (%)	182 (13.2)	35 (10.1)	44 (12.8)	52 (15.1)	51 (14.8)	0.194
COPD, n (%)	223 (16.2)	50 (14.5)	59 (17.2)	48 (14.0)	66 (19.1)	0.218
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 (6.5)	27 (8.9)	38 (12.8)	22 (7.2)	0.037
Left bundle branch block, n (%)	46 (3.8)	5 (1.8)	9 (2.9)	11 (3.6)	21 (6.9)	0.008
Laboratory test						
BNP, pg/ml	255.00 [118.00, 539.67]	173.40 [90.00, 369.80]	170.30 [86.00, 368.05]	259.40 [121.90, 488.00]	490.55 [270.25, 934.25]	<0.001
Hemoglobin, g/dl	11.20 [10.12, 12.40]	11.30 [10.30, 12.50]	11.40 [10.20, 12.50]	11.10 [10.17, 12.22]	11.20 [10.00, 12.40]	0.307
Albumin, g/dl	3.80 [3.50, 4.10]	3.80 [3.50, 4.10]	3.90 [3.60, 4.10]	3.80 [3.50, 4.10]	3.70 [3.30, 4.00]	<0.001
eGFR, ml/min/1.73 m^2	51.00 [37.83, 65.30]	54.70 [41.90, 68.11]	53.15 [40.00, 67.27]	49.75 [37.27, 64.03]	48.52 [34.00, 60.28]	<0.001
Pre-procedural BP						
Systolic BP, mmHg	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, mmHg	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
Pre-procedural echocardiographic data						
Systolic LV diameter, mm	61.00 [54.00, 69.00]	60.00 [52.00, 68.00]	62.00 [55.00, 69.00]	61.00 [54.00, 68.00]	62.00 [55.00, 70.00]	0.068
Diastolic LV diameter, mm	43.30 [40.00, 48.00]	41.00 [38.00, 44.00]	42.40 [40.00, 46.00]	44.00 [40.00, 48.00]	49.00 [44.00, 53.00]	<0.001
LVEF (modified 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 (modified 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 (modified 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
Left atrial diameter, mm	41.90 [37.00, 46.30]	40.00 [36.00, 45.00]	41.00 [36.95, 45.20]	42.00 [38.00, 47.00]	43.60 [39.00, 48.00]	<0.001
RWT	0.53 [0.46, 0.60]	0.57 [0.50, 0.65]	0.54 [0.48, 0.60]	0.53 [0.46, 0.60]	0.47 [0.39, 0.54]	<0.001
LVOT-VTI, cm	21.50 [17.73, 25.76]	23.54 [19.60, 27.90]	22.02 [19.00, 27.04]	21.37 [18.12, 25.40]	18.40 [15.00, 22.67]	<0.001
Stroke volume, 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
Systolic pulmonary artery pressure, mmHg	30.00 [25.00, 37.00]	29.50 [25.00, 36.00]	30.00 [25.00, 36.00]	30.00 [25.00, 36.00]	31.90 [25.00, 41.00]	0.28
AR ≥ moderate, n (%)	125 (9.1)	25 (7.3)	20 (5.8)	32 (9.3)	48 (13.9)	0.001
AVA, cm^2	0.63 [0.51, 0.75]	0.66 [0.52, 0.77]	0.63 [0.52, 0.73]	0.62 [0.51, 0.74]	0.62 [0.50, 0.74]	0.154
Indexed AVA, cm^2/m^2	0.44 [0.37, 0.52]	0.47 [0.40, 0.54]	0.45 [0.38, 0.52]	0.43 [0.36, 0.51]	0.43 [0.34, 0.50]	0.002
Mean PG, mmHg	47.50 [38.00, 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 PG, mmHg	82.00 [65.30, 104.00]	82.25 [67.00, 101.93]	84.60 [67.97, 107.55]	85.20 [68.00, 107.32]	74.60 [58.70, 95.00]	<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
E/e'	19.90 [15.05, 25.60]	19.70 [14.90, 25.40]	19.25 [15.29, 24.20]	20.70 [15.41, 26.09]	20.50 [14.88, 27.60]	0.309

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; Group4: 0.666 < Ea/Ees. AR = aortic valve regurgitation; AVA = aortic valve area; BMI = body mass index; BP = blood pressure; BSA = body surface area; BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting; 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; 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 (%)						0.472
Trans-femoral	1177 (85.4)	306 (88.7)	297 (86.3)	286 (83.1)	288 (83.5)	
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 (62.6)	193 (55.9)	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	1303 (94.6)	328 (95.1)	330 (95.9)	331 (96.2)	314 (91.0)	
Urgent	64 (4.6)	17 (4.9)	13 (3.8)	10 (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; Group4: 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 [69.00, 93.00]	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, 38.08]	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, cm^2	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, cm^2/m^2	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]	2.03 [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; Group4: 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

	ρ	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	-0.087	<0.001
Peak PG	-0.098	<0.001
Systolic LV diameter	0.469	<0.001
Diastolic LV diameter	0.428	<0.001
LVEF	-0.593	<0.001
LVESV	0.618	<0.001
LVEDV	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
LVEF	-0.742	<0.001
LVESV	0.794	<0.001
LVEDV	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.

Table S5. Multivariable-adjusted Cox hazard analysis in detail

Model 1				Model 2			
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	0.961-1.020	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							
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				

Model 3							
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	0.937	E/e'	0.9986	0.974-1.023	0.910
Clinical Frail Score	1.153	0.970-1.371	0.107	Peak velocity	0.5202	0.145-1.865	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	1.686	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	0.840-1.126	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	0.757-2.161	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	1.522	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:

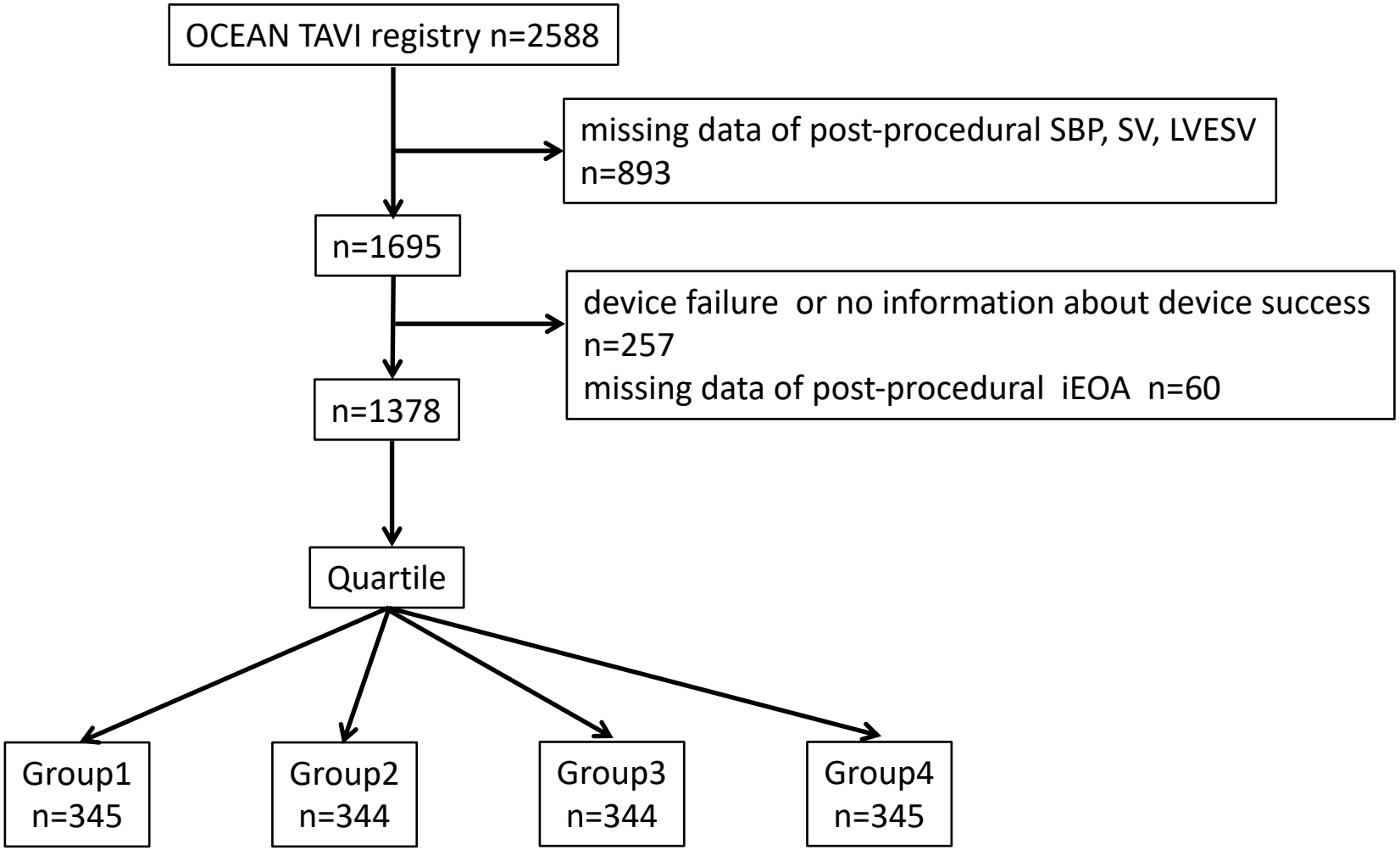
Figure S1. Patient selection flow chart. SBP: systolic blood pressure, SV: stroke volume, ESV: end-systolic volume, iEOA: indexed effective orifice area, PPM: patient-prosthesis mismatch.

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.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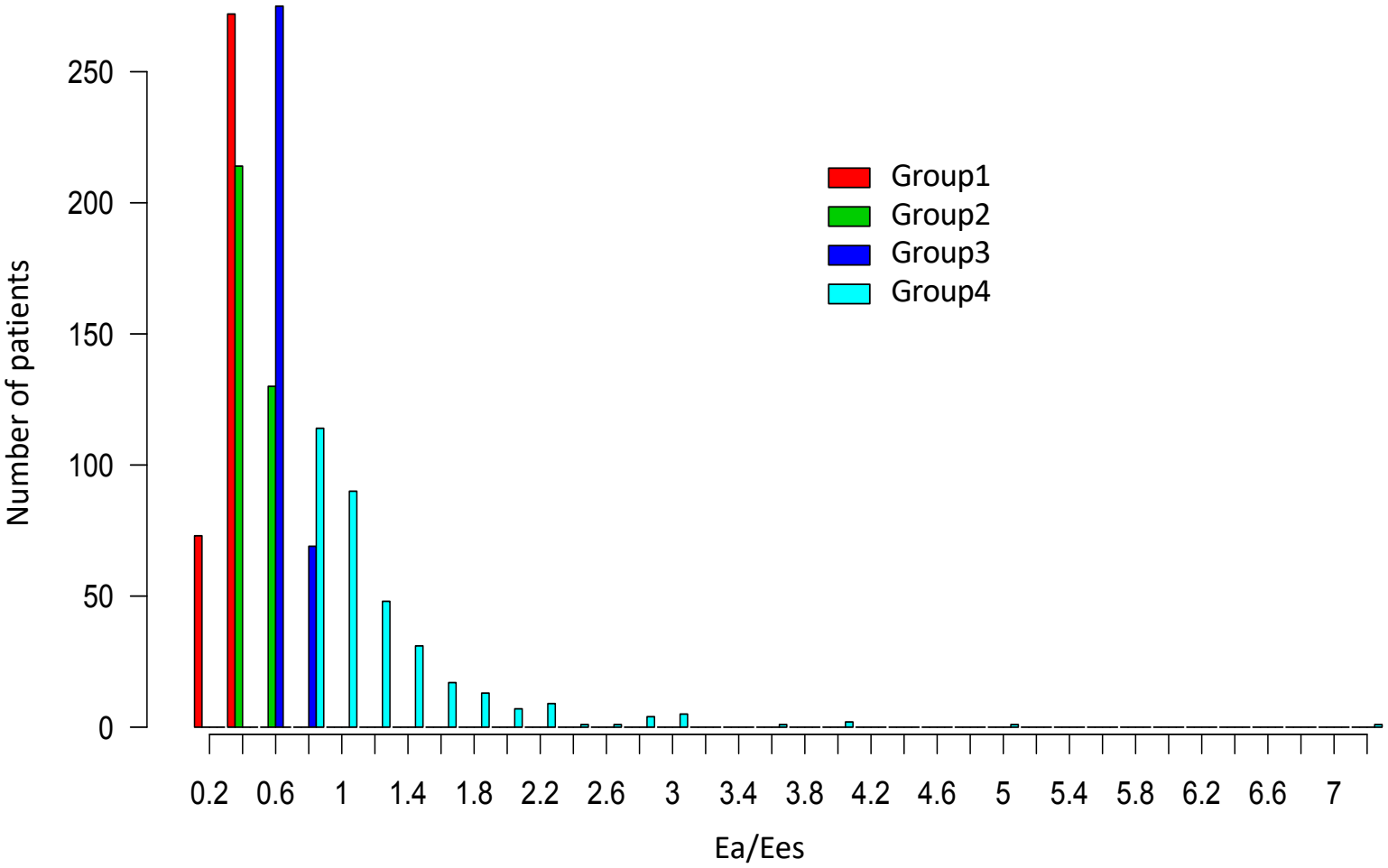
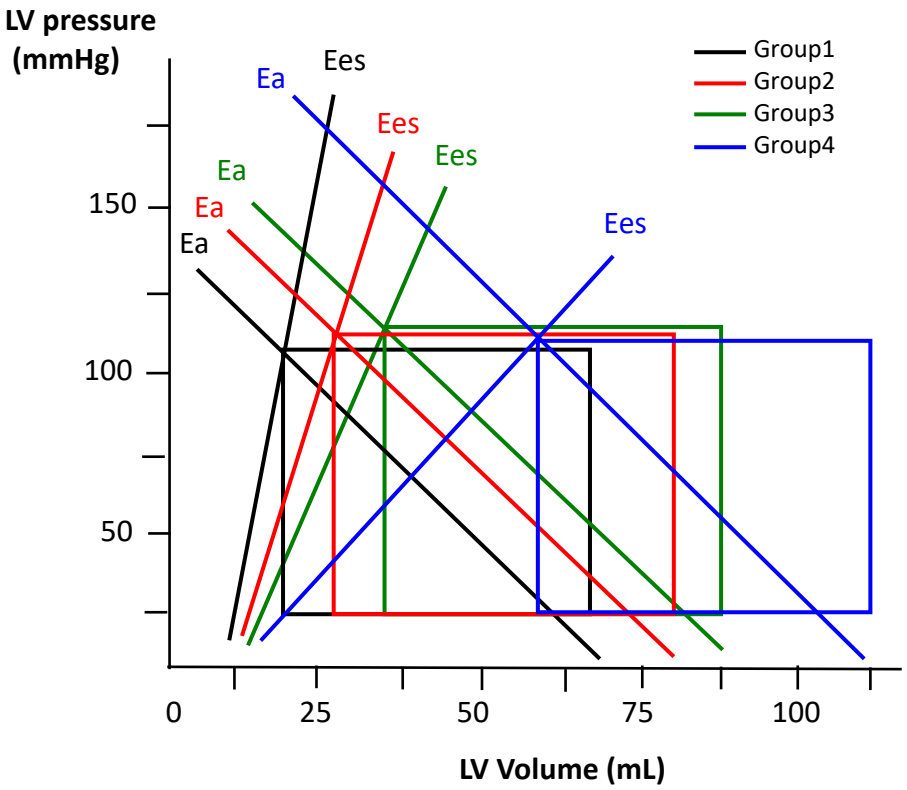
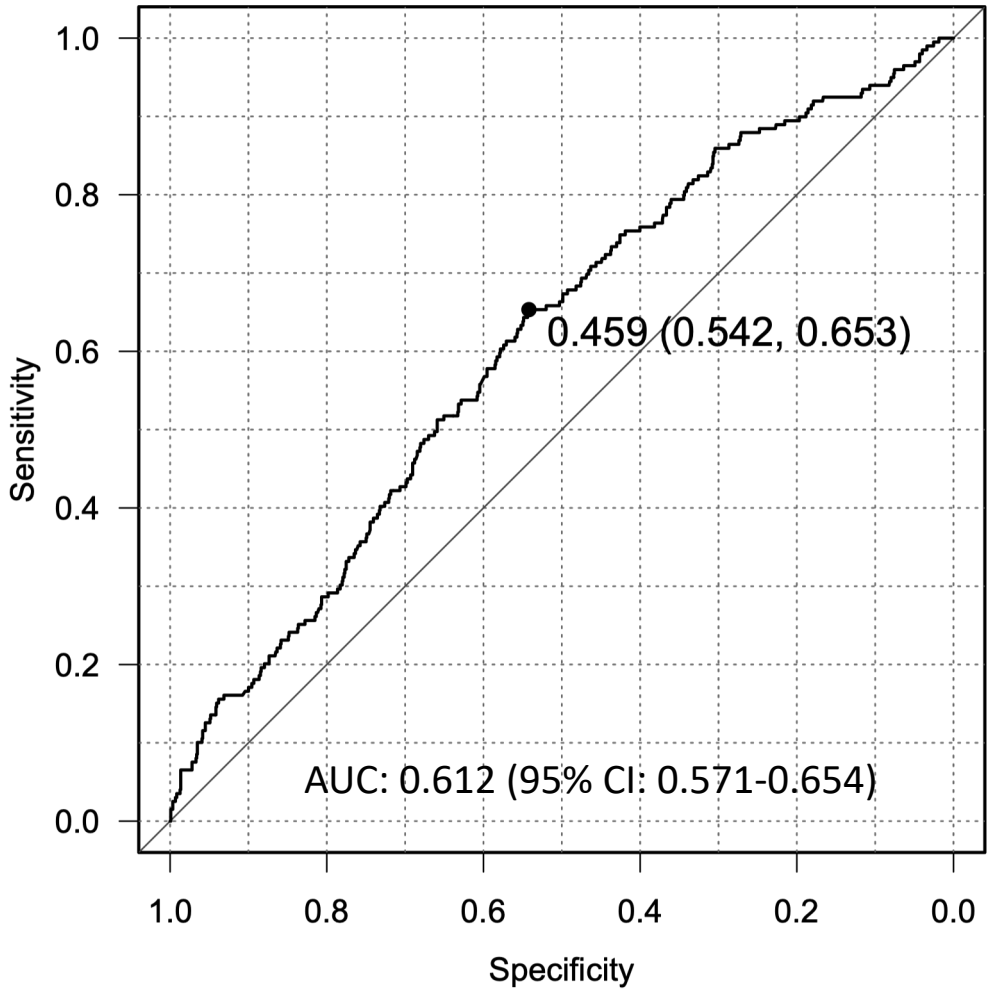
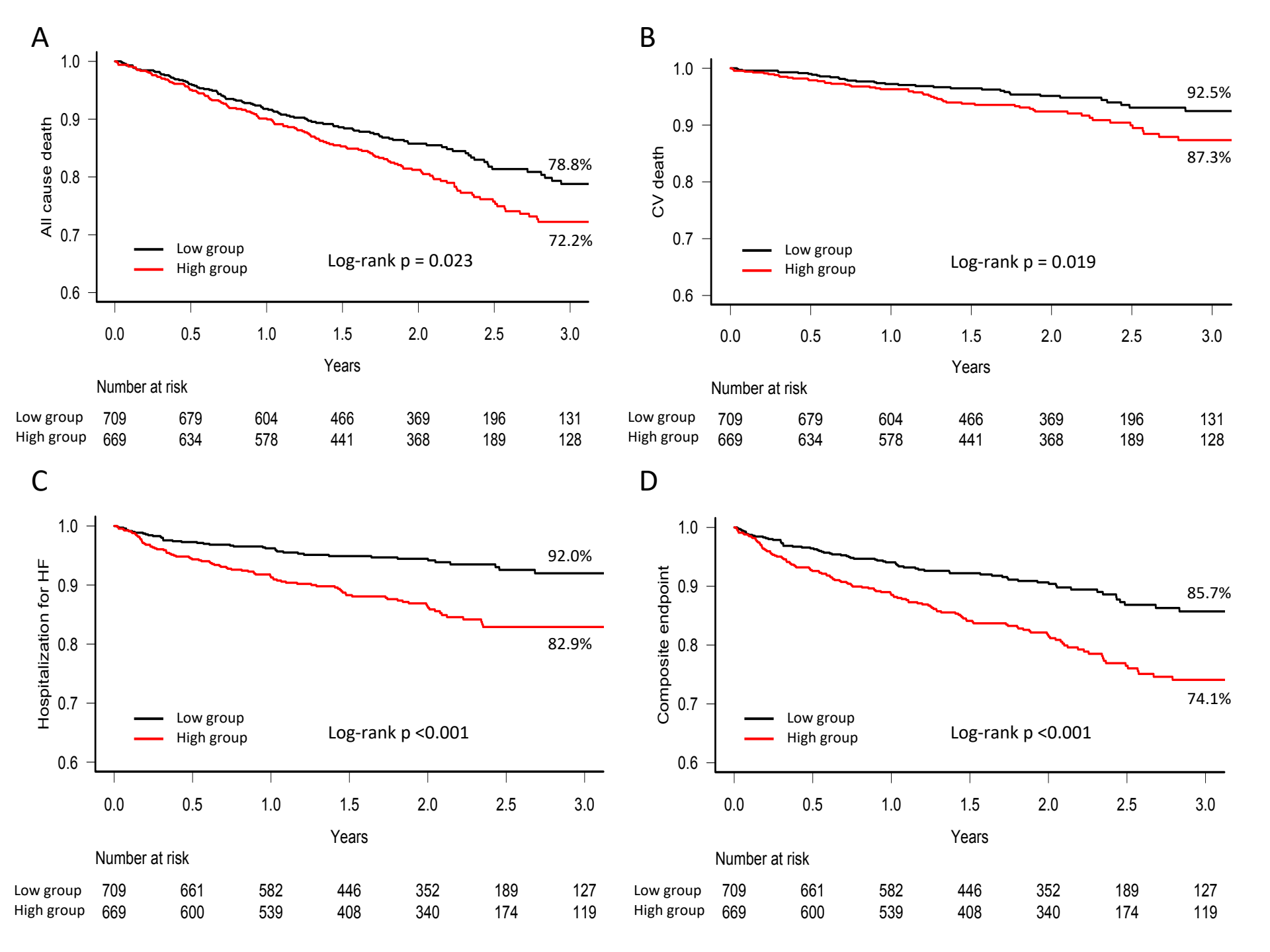
n=893
n=1695
device failure or no information about device success
n=257
missing data of post-procedural iEOA n=60
n=1378
Quartile
Group1
n=345
Group2
n=344
Group3
n=344
Group4
n=345


Number of patients
250
200
150
100
50
0
Group1
Group2
Group3
Group4
0.2
0.6
1
1.4
1.8
2.2
2.6
3
3.4
3.8
4.2
4.6
5
5.4
5.8
6.2
6.6
7
Ea/Ees

	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




1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.459 (0.542, 0.653)
AUC: 0.612 (95% CI: 0.571-0.654)
1.0
0.8
0.6
0.4
0.2
0.0
Specificity


A
All cause death
1.0
0.9
0.8
0.7
0.6
78.8%
72.2%
Low group
High group
Log-rank p = 0.023
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Years
Number at risk
Low group 709 679 604 466 369 196 131
High group 669 634 578 441 368 189 128
B
CV death
92.5%
87.3%
Low group
High group
Log-rank p = 0.019
Years
Number at risk
Low group 709 679 604 466 369 196 131
High group 669 634 578 441 368 189 128
C
Hospitalization for HF
92.0%
82.9%
Low group
High group
Log-rank p <0.001
Years
Number at risk
Low group 709 661 582 446 352 189 127
High group 669 600 539 408 340 174 119
D
Composite endpoint
85.7%
74.1%
Low group
High group
Log-rank p <0.001
Years
Number at risk
Low group 709 661 582 446 352 189 127
High group 669 600 539 408 340 174 119