

# Medium and long-term prognosis of transcatheter aortic valve implantation from the perspective of left ventricular diastolic function

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## Abstract

**Background:** The effects of left ventricular (LV) diastolic function are well known in cardiac surgery, but unclear in transcatheter aortic valve implantation (TAVI). The objective of this study was to examine the association of preoperative LV diastolic function with medium to long-term outcomes of TAVI.

**Methods:** Eighty patients who underwent TAVI were classified into grades I, II and III based on preoperative LV diastolic function. Findings related to cardiovascular outcomes after TAVI were extracted retrospectively from clinical and echocardiographic data and relationships with diastolic function were examined.

**Results:** The average follow-up was 529 days (interquartile range [IQR] 358–741 days). Cardiovascular events occurred in 17 cases, including 6 deaths, and were significantly associated with Euro II score ( $p = 0.043$ ), albumin level ( $p = 0.026$ ), coronary artery disease (CAD) ( $p = 0.017$ ), and diastolic function ( $p < 0.001$ ). The 360-day event-free rates were 89.5%, 89.5% and 37.5% for grades I, II and III ( $p = 0.00013$ ). Median event-free survival (EFS) in grade III cases was 180 days. In a Cox proportional hazard model, LV diastolic dysfunction (hazard ratio [HR] 3.99, 95% confidence interval [CI] 1.35–11.80,  $p = 0.012$ ) and low albumin (HR 4.73, 95% CI 1.42–15.80,  $p = 0.012$ ) were significant independent predictors of reduced EFS.

**Conclusions:** Medium to long-term outcomes of TAVI were poorer in patients with deteriorated LV diastolic function, and outcomes in grade III cases were significantly worse than those in grade I and II cases. Preoperative LV diastolic function may be useful in prediction of outcomes after TAVI. (Cardiol J 2019; 26, 1: 29–35)

**Key words:** left ventricular diastolic function, aortic stenosis, transcatheter aortic valve implantation (TAVI), outcomes, prognosis, echocardiography

## Introduction

Some cases of aortic stenosis (AS) are inoperable due to underlying disease, severity and frailty [1–3]. In these cases, the increasingly common use of transcatheter aortic valve implantation (TAVI) may improve prognosis [1, 4]. An increase in AS-induced afterload causes reduced left ventricular (LV) compliance, and elevated LV end-diastolic

pressure causes reduced diastolic function, which are causes of a poor prognosis. TAVI reduces the transaortic gradient and relieves afterload, with a resultant improvement in systolic and diastolic function [1, 4–13]. However, the effects of LV diastolic dysfunction on prognosis after TAVI have not been examined. Therefore, the objective of this study was to analyze prognosis based on preoperative LV diastolic function in patients treated with TAVI.

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## Methods

### Patient population

A retrospective observational study was conducted in 80 patients who were diagnosed with severe AS and underwent TAVI at Teikyo University Hospital from February 2014 to August 2015. The exclusion criteria included shock, emergency surgery, chronic atrial fibrillation (AF), severe mitral annular calcification, moderate to severe mitral stenosis, and severe mitral regurgitation. Patient background, clinical findings and blood test results were retrieved from electronic medical records (EMRs) and anesthesia charts. Data were collected for age, gender, European System for Cardiac Operative Risk Evaluation II (Euro II) score [5], Logistic Euro (LogEuro) score, Society of Thoracic Surgery (STS) score [6], albumin level [7], renal function based on estimated glomerular filtration rate (eGFR), hypertension, diabetes, dyslipidemia, coronary artery disease (CAD) and percutaneous coronary intervention, chronic obstructive pulmonary disease, and New York Heart Association classification.

### Echocardiographic variables

The following echocardiographic findings were obtained from EMRs: LV ejection fraction (LVEF), E/e', septal e', lateral e', tricuspid regurgitation (TR) velocity, left atrial volume index (LAVI), pulmonary veins: systolic velocity/diastolic velocity ratio (S/D ratio) and time difference between duration of pulmonary vein flow and mitral inflow during atrial contraction (Ar-A duration). Echocardiography was performed following American Society of Echocardiography (ASE) guidelines [14, 15]. Preoperative LV diastolic dysfunction was classified into three grades (I, II, and III) based on 2016 ASE Recommendations for Evaluation of Left Ventricular Diastolic Function by Echocardiography [16]. For subjects at the borderline of grades I and II who were difficult to classify with the algorithm, left atrial pressure was assessed with LAVI, S/D ratio and Ar-A duration for classification into grades. Echocardiography in all subjects was performed by two cardiologists at our hospital. In all cases, echocardiography was performed once several days before TAVI subsequent to admission to hospital.

### Endpoints

The endpoints of the study were cardiovascular (CV) events during the follow-up period after discharge, and mortality. The incidences of

events on days 180, 360 and 540 were examined. The study was approved by the research ethics committee of the documented hospital. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Exacerbation of heart failure, shift to AF, pneumonia and events including conduction block.

### Statistical analysis

Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean  $\pm$  standard deviation and were compared by unpaired t test or one-way analysis of variance (ANOVA). Categorical variables are expressed as frequencies (percentages) and compared by the Fisher exact test. Time-to-event analysis was performed using the Kaplan-Meier method and compared between groups by log-rank test. Cox proportional hazards models with best subset regression were used to identify clinical and echocardiographic measurements that were significantly related to cardiac events or death during follow-up. A p value  $< 0.05$  was considered significant in all analyses.

## Results

### Patient characteristics

The preoperative patient background is shown in Table 1. The mean age was  $85.0 \pm 5.2$  years old and 77.5% of the subjects were female. Euro II, LogEuro and STS scores were  $5.9 \pm 4.6$ ,  $18.4 \pm 9.7$  and  $8.1 \pm 3.8$ , respectively, and LVEF, E/e' and LAVI were  $57.5 \pm 10.8\%$ ,  $21.8 \pm 8.6$  and  $63.5 \pm 25.1$  mL/m<sup>2</sup>, respectively. There were no significant differences in age, gender, Euro II, LogEuro, STS, albumin or underlying disease, except for eGFR, CV events, E/e' and LAVI, among patients with LV diastolic dysfunction of grades I, II, and III (Table 2).

### Grade classification

In preoperative echocardiography, LVEF, E/e', LAVI, S/D ratio and Ar-A duration, but not TR velocities, were measured in all subjects. The grade classification was performed based on the algorithm of the 2016 ASE Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography three subjects however, were difficult to classify and were placed into grade I or II (grade I: 2, grade II: 1) by assessing left

**Table 1.** Baseline characteristics of 80 patients in this study.

Variables	Overall (n = 80)	Event-free survival (n = 63)	Cardiovascular events (n = 17)	P
Age [years]	85.0 ± 5.2	85.3 ± 4.8	83.9 ± 6.3	0.3
Female	62 (77.5)	48 (76.2%)	14 (82.4%)	0.75
Euro II	5.9 ± 4.6	5.4 ± 4.2	7.9 ± 5.8	0.043
LogEuro	18.4 ± 9.7	17.8 ± 9.5	20.7 ± 10.3	0.28
STS	8.1 ± 3.8	7.9 ± 3.7	8.8 ± 4.2	0.36
Albumin	3.7 ± 0.5	3.7 ± 0.4	3.5 ± 0.6	0.026
eGFR	50.2 ± 17.0	51.0 ± 17.1	47.5 ± 16.6	0.46
Hypertension	60 (75%)	45 (71.4%)	15 (88.2%)	0.21
Diabetes mellitus	18 (22.5%)	15 (23.8%)	3 (17.6%)	0.75
Dyslipidemia	47 (58.8%)	37 (58.7%)	10 (58.8%)	1
Coronary artery disease	12 (15.0%)	6 (9.5%)	6 (35.2%)	0.017
Previous PCI	26 (32.5%)	18 (31.0%)	8 (36.4%)	0.16
COPD	13 (16.3%)	10 (15.8%)	3 (17.6%)	1
Class NYHA:				
I	None	None	None	
II	33 (41.3%)	29	4	
III	35 (43.8%)	27	8	
IV	12 (15.0%)	7	5	
Class NYHA III–IV	47 (58.8%)	34 (54.0%)	13 (76.5%)	0.11
Diastolic dysfunction:				
Grade I	19 (23.8%)	17	2	
Grade II	49 (61.3%)	41	8	
Grade III	12 (15.0%)	5	7	
LVEF	57.5 ± 10.8	57.9 ± 10.2	56.1 ± 13.1	0.55
E/e'	21.8 ± 8.6	22.3 ± 8.9	19.6 ± 7.1	0.29
LAVI	63.5 ± 25.1	61.0 ± 23.5	72.6 ± 28.5	0.093

Continuous variables are shown as mean ± standard deviation, and categorical variables as frequencies (%); Euro II — European System for Cardiac Operative Risk Evaluation Score II; LogEuro — Logistic Euro score; STS — Society of Thoracic Surgeons score; eGFR — estimated glomerular filtration rate; PCI — percutaneous coronary intervention; COPD — chronic obstructive pulmonary disease; NYHA — New York Heart Association; LVEF — left ventricular ejection fraction; LAVI — left atrial volume index

atrial pressure in accordance with LAVI, S/D and Ar-A duration.

### Complications during TAVI

Complications developing during TAVI included hemorrhage from a puncture site in 2 patients; femoral artery occlusion, oozing from the left ventricle after TAVI, mitral valve prolapse, cardiac tamponade after TAVI, right ventricular injury caused by a pacing wire, and stenosis due to calcified plaque in the entrance of the left coronary artery after TAVI in 1 patient and complete atrioventricular block after TAVI in 4 patients. No patients died during surgery and the follow-up survey after discharge from hospital was conducted in all subjects.

### Cardiovascular events

The average follow-up was 529 days (interquartile range [IQR] 358–741 days). Cardiovascular events during follow-up occurred in 17 of 80 subjects, and were exacerbated by heart failure in all 17 subjects. Of these subjects, 4 developed heart failure with AF. Onset of heart failure with AF was defined as CV events when NT-pro-B-type natriuretic peptide was higher during the observation of period after discharge than that at the time of discharge and the patients had clinical symptoms including dyspnea and pedal edema, consequently, they were diagnosed with AF-induced heart failure. Heart failure was the cause of death in all 6 subjects who died (grade I: 1, grade II: 5, grade III: 0).

**Table 2.** Baseline grades for severity of diastolic dysfunction.

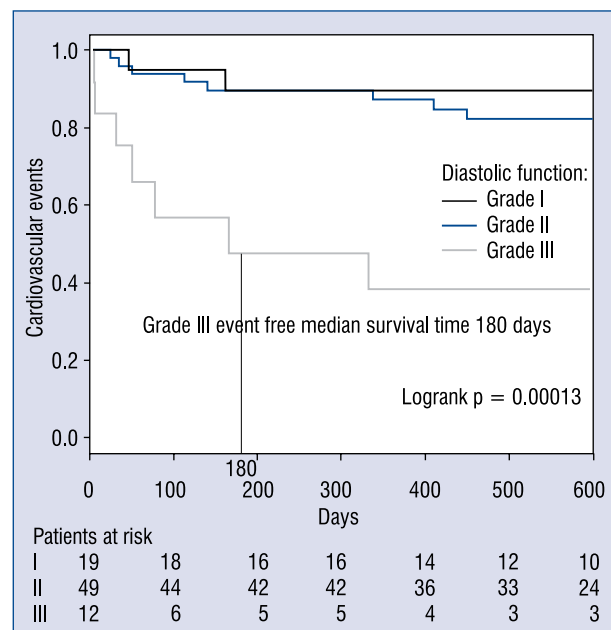
Variables	Grade I (n = 19)	Grade II (n = 49)	Grade III (n = 12)	P
Age [years]	85.9 ± 4.7	85.4 ± 4.7	82.2 ± 7.0	0.11
Female	13 (68.4%)	37 (75.5%)	12 (100%)	0.1
Euro II	5.8 ± 5.2	5.6 ± 4.1	7.3 ± 5.8	0.5
LogEuro	16.3 ± 8.4	19.3 ± 10.7	18.2 ± 6.9	0.53
STS	7.4 ± 3.1	8.3 ± 3.7	8.4 ± 5.2	0.69
Albumin	3.8 ± 0.3	3.7 ± 0.5	3.7 ± 0.6	0.73
eGFR	56.8 ± 19.0	49.8 ± 16.3	41.4 ± 12.2	0.044
Hypertension	14 (73.7%)	37 (75.5%)	9 (75.0%)	1
Diabetes mellitus	5 (26.3%)	12 (24.5%)	1 (8.3%)	0.51
Dyslipidemia	11 (57.9%)	27(55.1%)	9 (75.0%)	0.5
Coronary artery disease	3 (15.8%)	7 (14.3%)	2 (16.7%)	1
Previous PCI	7 (36.8%)	17 (34.7%)	2 (16.7%)	0.49
COPD	4 (21.1%)	9 (18.4%)	0 (0%)	0.29
Class NYHA III-IV	10 (52.6%)	26 (53.1%)	9 (75.0%)	0.4
Cardiovascular events	2 (10.5%)	8 (16.3%)	7 (58.3%)	< 0.001
LVEF	58.9 ± 7.8	57.3 ± 11.8	56.3 ± 11.3	0.78
E/e'	14.2 ± 4.8	23.9 ± 8.4	25.1 ± 6.9	< 0.001
LAVI	43.7 ± 13.8	65.3 ± 21.1	90.0 ± 29.5	< 0.001

Continuous variables are shown as mean ± standard deviation, and categorical variables as frequencies (%); Euro II — European System for Cardiac Operative Risk Evaluation Score II; LogEuro — Logistic Euro score; STS — Society of Thoracic Surgeons score; eGFR — estimated glomerular filtration; PCI — percutaneous coronary intervention; COPD — chronic obstructive pulmonary disease; NYHA — New York Heart Association; LVEF — left ventricular ejection fraction; LAVI — left atrial volume index

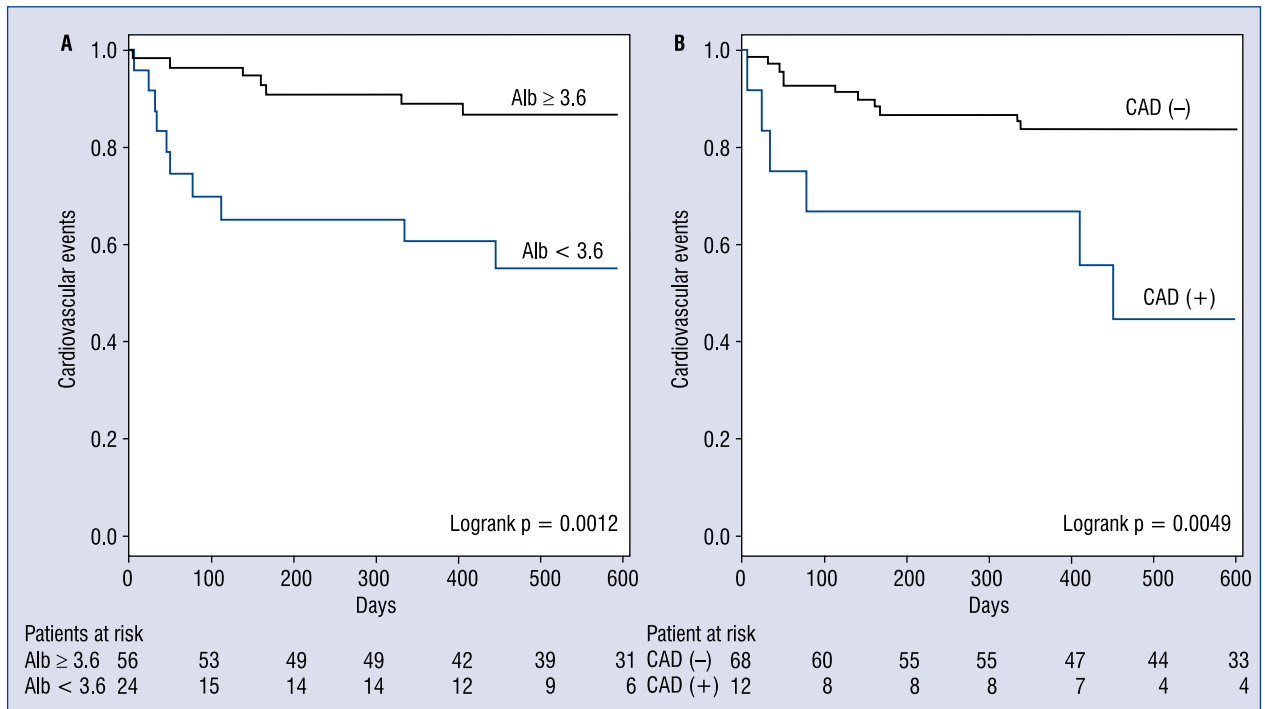
Non-CV events after discharge included pneumonia and 3-degree block (after 314 days) in 1 subject each and there were no deaths.

Some patients did not undergo echocardiography because they could not visit the hospital due to being elderly or having to travel a long distance, and some were excluded from follow-up due to CV events during follow-up after TAVI. In the survey of prognoses, no patient was lost to follow-up because prognoses were determined by interview when visiting the hospital or telephone calls to patients or their families.

Albumin (3.5 ± 0.6 vs. 3.7 ± 0.4 g/dL, p = 0.026), Euro II score (7.8 ± 5.8 vs. 5.4 ± 4.2, p = 0.043) and CAD (35.2% vs. 9.5%, p = 0.017) were significantly related to CV events (Table 1). In grades I, II and III, the 180-day event-free survival (EFS) rates were 89.5%, 89.5% and 46.9%, the 360-day EFS rates were 89.5%, 89.5% and 37.5%, and the 540-day EFS rates were 89.5%, 82.3% and 37.5%, respectively. In grade III cases, the median EFS was 180 days (Fig. 1) and the prognosis based on EFS rates which were significantly worse than for grades I and II (p = 0.00013). Events occurred more frequently in cases with lower albumin (< 3.6 vs. ≥ 3.6 g/dL, p = 0.0012), and CAD(+) vs. CAD(-), p = 0.0049; Fig. 2).



**Figure 1.** Kaplan-Meier event-free survival (EFS) rates for patients with diastolic function of grade I (n = 19), grade II (n = 49), and grade III (n = 12). The grade III median EFS time was 180 days. In grades I, II and III, the EFS rates were 89.5%, 89.5%, and 46.9% at 180 days; 89.5%, 89.5%, and 37.5% at 360 days; and 89.5%, 82.3%, and 37.5% at 540 days, respectively.



**Figure 2.** Kaplan-Meier event free survival rates for cases with (A) albumin (Alb) < 3.6 g/dL vs. ≥ 3.6 g/dL, (B) CAD(+) vs. CAD(-); CAD — coronary artery disease.

**Table 3.** Multivariate analysis of clinical and echocardiographic predictors of events.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Diastolic dysfunction	3.84 (1.66–8.84)	0.0016	3.99 (1.35–11.8)	0.012
Low albumin (< 3.6 g/dL)	4.36 (1.65–11.49)	0.0029	4.73 (1.42–15.8)	0.012
Coronary artery disease	3.78 (1.40–10.24)	0.0089		

CI — confidence interval; HR — hazard ratio

### Predictors of medium and long-term prognosis

In univariate analysis, LV diastolic dysfunction (hazard ratio [HR] 3.84,  $p = 0.0016$ ), low albumin (< 3.6 g/dL) (HR 4.36,  $p = 0.0029$ ), and CAD (HR 3.78,  $p = 0.0089$ ) were associated with CV events or mortality. In multivariate Cox regression analysis, LV diastolic dysfunction (HR 3.99,  $p = 0.012$ ) and low albumin (HR 4.73,  $p = 0.012$ ) were independent predictors of a poor outcome during the follow-up period (Table 3).

### Discussion

Technical improvements and advances in devices due to accumulated data have contributed

to better outcomes of TAVI; however, problems remain regarding preoperative evaluation and postoperative complications. In this study, the relationship between preoperative LV diastolic function and postoperative complications in patients treated with TAVI was investigated. Pre-diastolic function grade was found to be strongly associated that a higher grade of preoperative LV diastolic dysfunction and with poorer EFS. Especially, events in grade III cases which occurred earlier and at a higher incidence than those for grades I and II. A Cox proportional hazards model indicated that preoperative LV function is an independent risk factor for postoperative CV events. Preoperative LV diastolic dysfunction has been shown to affect EFS after CV surgery [17]. TAVI is a brief and

less invasive procedure that improves systolic and diastolic function at an earlier stage compared with surgical aortic valve replacement [4, 18]. The function of the LV system, including the left atrium, and right ventricular function recover early after TAVI and diastolic function is improved [4, 8], while AS-induced cardiac hypertrophy is improved over the medium to long-term, this further improves LV function [4, 13, 18, 19].

Albumin has been proposed to be a prognostic factor for postoperative mortality and complications [7, 20]. Yamamoto et al. [7] indicated that hypoalbuminemia was a predictor for mortality and complications after TAVI, and 30-day mortality was significantly higher in patients with albumin < 3.5 g/dL. The results of this study also showed that EFS after TAVI was significantly lower in subjects with albumin < 3.6 g/dL, which closely matches the results of Yamamoto et al. [7].

Of note is an algorithm proposed by Nagueh et al. [16] which was used for detection and severity classification of LV diastolic dysfunction into grades. This algorithm is simple to use for detection, but when the grade was difficult to determine because of the border zone (grade I or II), it was based on other echocardiographic findings, such as LAVI, S/D ratio and Ar-A duration. All subjects classified using other echocardiographic findings had no data for TR, due to a failure of TR velocity measurement. LAVI and S/D are related to mean left atrial pressure, and Ar-A duration is related to LV end-diastolic pressure [16]; therefore, increased left atrial pressure was assessed using these data and subjects were classified into grades I or II.

The most important finding in this study was that EFS rate in patients with preoperative LV diastolic dysfunction of grade III who were significantly worse than those in patients with grades I and II. The median event occurrence period was 180 days in grade III, which suggests that patients in grade III specially take care of follow-up after TAVI. Patients who complicate with CAD, which was found to be a risk factor in this study, may have further adverse outcomes. Use of TAVI has been slowly increasing, therefore some indices including LV diastolic function may be important for preoperative evaluation before TAVI.

### Limitations of the study

The major limitations of the study were the retrospective observational design and the inclusion of some subjects in whom detailed courses could not be followed for an extended period. The

guidelines for LV diastolic function did not allow for some subjects to be classified into a grade using the algorithm alone. These subjects were classified by estimating increased left atrial pressure using other indicators; however, the accuracy of this method is unclear and the assigned grade is uncertain. Detailed courses were not found in all EMRs because elderly patients could not undergo echocardiography or a full interview during the observational period. In echocardiography, detailed data were available before TAVI, whereas postoperative data collected during follow-up had many missing values because some patients could not undergo echocardiography due to their condition. Consequently, changes in the grade of LV diastolic function from prior to and after TAVI or postoperative echocardiographic findings in follow up could not be verified. There was no postoperative mortality in 6 subjects in grade III, showing no tendency for worsening of outcomes at a higher grade. However, the number of subjects was insufficient to evaluate the significance of mortality data. Euro II, LogEuro and STS scores were noted and used as indicators for preoperative risk assessment in CV surgery. In this study, significant differences in Euro II scores alone were found among cases with different LV diastolic dysfunction. Some studies indicate overestimation of these risk scores [21, 22], but it is unclear why only Euro II scores were significant in this study. However, it was noted that Euro II, LogEuro and STS scores are predictors of mortality risk after conventional CV surgeries, these scores may not be applicable to clinical status and performance of TAVI in extremely elderly patients.

### Conclusions

Postoperative events after TAVI occurred more frequently in patients with advanced preoperative LV diastolic dysfunction, as found after other CV surgery. Events in cases with grade III LV diastolic dysfunction occurred earlier and at a significantly higher incidence than those in grades I and II. Therefore, diastolic function may be a useful indicator for prediction of outcomes after TAVI. A large-scale prospective study is required to validate these findings. Present results show that postoperative outcomes after TAVI are influenced by several factors and these findings make the study particularly valuable in identifying patients who will benefit most from TAVI.

**Conflict of interest:** None declared

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