ORIGINAL RESEARCH

Patients Refusing Transcatheter Aortic Valve Replacement Even Once Have Poorer Clinical Outcomes

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***Background*—**Although transcatheter aortic valve replacement (TAVR) is the least invasive treatment for patients with symptomatic aortic stenosis, some patients hesitate to undergo the procedure. We investigated the clinical impact of treatment delay after patient refusal of TAVR.

***Methods and Results*—**We used the Japanese OCEAN (Optimized Catheter valvular intervention) regsitry data of 1542 patients who underwent TAVR. Refusal was defined as at least 1 refusal of TAVR at the time of informed consent. Patients were separated into 2 groups: refusal (28/1542, 1.8%) and non-refusal (1514/1542, 98.2%). We compared the baseline characteristics, procedural outcomes, and mortality rates between the groups. Additionally, data on reasons for refusal and those leading to eventually undergoing TAVR were collected. Age, surgical risk scores, and frailty were higher in the refusal group than in the non-refusal group ($P<0.05$ for all). Periprocedural complications did not differ between groups, whereas 30-day and cumulative 1-year mortality were significantly higher in the refusal group than in the non-refusal group (7.1% versus 1.3%, $P=0.008$ and 28.8% versus 10.3%, $P=0.010$, respectively). Multivariate Cox regression analysis revealed that TAVR refusal was an independent predictor of increased midterm mortality (hazard ratio: 3.37; 95% confidence interval: 1.52–7.48; $P=0.003$). The most common reason for refusal was fear (13/28, 46.4%), and the most common reason for changing their mind was worsening heart failure (21/28, 75.0%). All patients in the refusal group decided to undergo TAVR within 20 months (median: 5.5 months).

***Conclusions*—**Refusing TAVR even once led to poorer prognosis; therefore, this fact should be clearly discussed when obtaining informed consent. **(*J Am Heart Assoc*. 2018;7:e009195. DOI: 10.1161/JAHA.118.009195.)**

Key Words: Optimized Catheter Valvular Intervention • refusal • transcatheter aortic valve implantation • transcatheter aortic valve replacement • treatment delay

Aortic stenosis (AS) is a common cardiovascular disease that has a considerable impact on mortality and morbidity. According to recent Western guidelines, early invasive therapy is strongly recommended for symptomatic patients with severe AS because of their poor prognosis.[1,2] Based on the current low periprocedural mortality rates for isolated surgical aortic valve replacement (SAVR), earlier surgery for asymptomatic patients with severe AS has been

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Accompanying Table S1 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009195

*A complete list of the OCEAN-TAVI Investigators can be found in the Appendix at the end of the manuscript.

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Clinical Perspective

What Is New?

- We evaluated the influence of treatment delay on mortality after patient refusal of transcatheter aortic valve replacement (TAVR).
- Results of this study suggest an association between TAVR refusal and increasing early- to midterm mortality.
- TAVR refusal even once was an independent predictor of increased midterm mortality.

What Are the Clinical Implications?

- The present study showed refusal of TAVR is associated with poor clinical outcomes, even in patients who ultimately receive TAVR.
- Although patient's wishes and rights should be respected, it is important to explain that TAVR refusal is associated with worse prognosis.
- Whether this predominantly represents a causal relationship or is an association influenced by confounders needs to be further investigated.

increasingly advocated.[3–6] These studies suggest that early treatment of severe AS may improve the patient's prognosis. Despite these facts, previously published studies suggest that not all patients with indications for intervention undergo treatment.[7,8] There are 2 major reasons for this. First, elderly patients with severe AS are reluctant to undergo SAVR because of multiple comorbidities and perceived prohibitive operative risk. Second, patients sometimes refuse to undergo treatment on their own volition. These problems were believed to have been solved with the development of the less invasive transcatheter aortic valve replacement (TAVR) method. TAVR was designed as a new option for high-risk patients with severe AS who could not undergo SAVR.[9,10] However, the second problem remains, even in the TAVR era. There are still some patients who refuse TAVR, despite its minimally invasive nature and known survival benefits. Among these patients, some will eventually undergo TAVR because of aggravation of their symptoms or repeat hospitalizations for heart failure (HF). The treatment delay in this group of patients may negatively impact their prognosis. To the best of our knowledge, there are no studies on the prognosis of symptomatic patients with severe AS who delay treatment because of initial refusal of TAVR. This information would be useful for the development of an evidence-based informed consent form for the TAVR procedure, as well as further patient education. Therefore, we aimed to investigate the impact of this treatment delay on outcomes after TAVR using data from a Japanese multicenter registry.

Methods

Data and study materials will not be made available to other researchers for purposes of reproducing the results because of the terms of our data use agreements.

Patient Population

Between October 2013 and July 2016, 1613 patients were enrolled in the OCEAN (Optimized Catheter Valvular Intervention) registry. The OCEAN registry is an ongoing multicenter registry from 14 centers in Japan.[11–13] We initially excluded 71 patients who underwent urgent, emergent, and salvage TAVR. Therefore, the final sample included the remaining 1542 patients (Figure 1).

Patients were determined as adequate candidates for TAVR through the consensus of the individual centers and through discussions within the heart team when considering the surgical risks of those with multiple comorbidities. Surgical risk was considered according to the values of the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), EuroSCORE-II, and the Society of Thoracic Surgeons Predictive Risk of Mortality (STS) score. Patient frailty was considered according to serum albumin level, Mini Mental State Examination, and the Clinical Frailty Scale (CFS). The CFS is a semiquantitative tool that provides a generally accepted clinical definition of frailty, which can be easily measured (even by non-geriatricians).[14,15] According to the formula, the CFS ranges from 1 (very fit) to 9 (terminally ill). Clinical data, patient characteristics, laboratory data, echocardiographic data, procedural variables, length of hospital stay, and in-hospital and all-cause mortality rates were examined. Information on the occurrence and/or causes of death was obtained from the treating hospital or by calling the patient's family member(s).

This study was approved by all institutional review boards which participate in the OCEAN-TAVI registry. This trial was registered with the University Hospital Medical Information Network (no.: UMIN000020423).

TAVR Refusal

TAVR refusal was defined as at least 1 instance in which a patient was recommended the procedure by cardiologists and/or surgeons at each center, but independently refused the procedure for a certain reason. All patients eventually received the TAVR procedure during the follow-up period. The included study patients were separated into 2 groups as follows: patients who refused TAVR at least once (refusal group) and those who did not refuse TAVR (non-refusal group). Additionally, we identified the reason(s) for refusal and then the reason(s) for finally deciding to

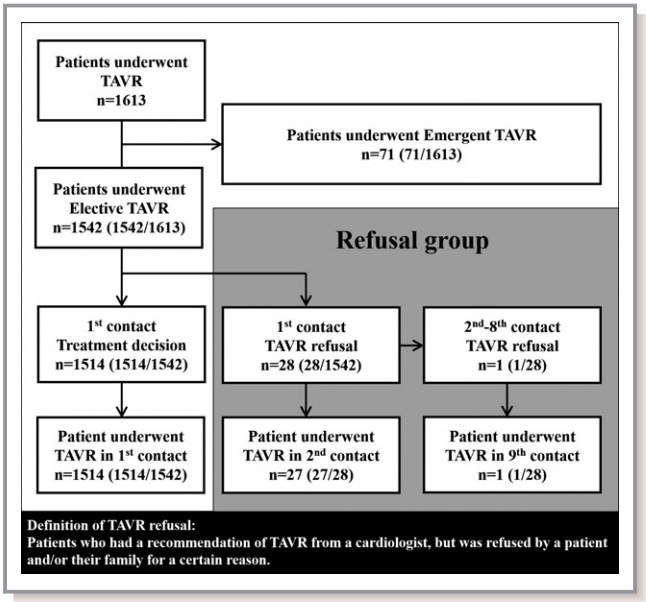

Figure 1. CONSORT patient flow chart and definitions of TAVR refusal. This study enrolled 1613 patients from the OCEAN-TAVI registry. Of these, 71 patients who underwent non-elective TAVR were excluded. The remaining 1542 patients were divided into the refusal group and the non-refusal group. TAVR indicates transcatheter aortic valve replacement.

undergo TAVR. The clinical course of these patients was also investigated.

TAVR Procedure and Data Definition

Detailed TAVR procedures were previously described.[11–13] The balloon-expandable Edwards Sapien-XT and Sapien-3 heart valves (Edwards Lifesciences, Irvine, CA, USA) and the self-expandable Medtronic CoreValve Revalving Systems (Medtronic, Minneapolis, MN, USA) are clinically approved for use in Japan. The size of the valve was mainly determined using multidetector computed tomography findings or echocardiography, based on the individual centers' examinations. Approach routes were chosen via the femoral artery first; if femoral access was inappropriate, the iliac artery, apical, subclavian, or direct aortic routes were considered. Procedural complications, including acute kidney injury, vascular complications, bleeding, and additional complications during TAVR, were evaluated according to the Valve Academic Research Consortium-2 criteria.[16]

Statistical Analysis

Statistical analyses except the Cox regression inference using the Firth correction were performed using IBM SPSS Statistics 22 (SPSS, Inc., Chicago, IL, USA). The Cox regression inference using the Firth correction was performed by the statistical software R (R Foundation for Statistical Computing, Vienna, Austria).[17] Continuous variables are expressed as mean±SD or as median with interquartile range, depending on the variable's distribution. Categorical data are expressed as percentages of the total. Comparisons between groups (refusal versus non-refusal) were made using chi-squared tests for categorical covariates, and one-way analysis of variance and the Mann–Whitney *U* test for continuous covariates, depending on the variable's distribution. The Kaplan–Meier method was used to estimate the cumulative incidence of mortality and differences were assessed using the log-rank test. Using a conventional sensitivity analysis for reducing the effect of immortal time bias, we compared the cumulative mortality between the non-refusal group and refusal group who finally decided to undergo TAVR with shorter duration of <5.5 months (median value of the period by which the refusal group underwent TAVR).

A univariate Cox regression analysis was performed to obtain the hazard ratio (HR) for midterm mortality during the follow-up period. Thereafter, a multivariate analysis was performed using the baseline clinical characteristics and other variables. We added Cox regression inference using the Firth correction to increase accuracy. Throughout statistical analysis, $P<0.05$ was considered statistically significant.

Results

Baseline Patient and Procedural Characteristics

Baseline patient characteristics are summarized in Table 1. Of the 1542 patients, 1.8% (n=28) were in the refusal group and 98.2% (n=1514) were in the non-refusal group.

Significant between-group differences were observed for age, CFS, levels of brain natriuretic peptide, as well as the number of patients with peripheral artery disease, moderate or severe mitral regurgitation, and left ventricular ejection fraction ($P<0.05$ for all). As a result, we observed significant differences in the Logistic EuroSCORE, EuroSCORE-II, and STS score between groups ($P<0.05$ for all).

Peri- and Post-Procedural Patient Characteristics

Peri- and post-procedural patient characteristics are shown in Table 2. The transfemoral approach was used in 1224 (79.4%) patients and non-transfemoral approaches were used in 318 (20.6%) patients. Significant differences were not detected between groups on transfemoral approach, use of local anesthesia, procedure time, and contrast volume use. Additionally, there were no significant differences between the refusal and non-refusal groups with respect to the number of patients with acute kidney injury (4 [14.3%] versus 129 [8.5%], respectively; $P=0.28$), major vascular complications (2 [7.1%] versus 76 [5.0%], respectively; $P=0.61$), and life-threatening/

disabling bleeding (2 [7.1%] versus 82 [5.4%], respectively; *P*=0.69). Despite these similarities, the length of stay in the intensive care unit was significantly longer in the non-refusal group than in the refusal group (2.0 [1.0–3.0] days versus 1.0 [1.0–2.25] day, respectively; *P*=0.009).

Clinical 30-Day and Cumulative 1-Year Mortality

Clinical 30-day follow-up data were obtained in all patients. The 30-day mortality rate was significantly higher in the refusal group compared with the non-refusal group (2 [7.1%] versus 19 [1.3%], respectively; *P*=0.008). TAVR refusal was significantly associated with increasing risk of 30-day mortality (HR: 5.85, 95% confidence interval: 1.36–25.1; *P*=0.018). Among the 1542 patients, 156 patients died (refusal group: n=7; non-refusal group: n=149); of these, 123 died within 1 year. The median follow-up of this registry was 288.0 days (range, 111.0–472.3 days). Kaplan–Meier analysis of cumulative all-cause mortality is presented in Figure 2. Cumulative 1-year all-cause mortality rate was 28.8% in the refusal group and 10.3% in the non-refusal group. Kaplan–Meier curves also indicated a significantly higher cardiovascular mortality rate in the refusal group than in the non-refusal group (Figure 3A). On the contrary, non-cardiovascular mortality was not significantly different between 2 groups (Figure 3B). A subgroup analysis of cumulative mortality was described between the 14 patients in the refusal group, excluding those with >5.5 months after initial TAVR refusal (median, 2.0 months) and 1514 patients in the non-refusal group. Even in this analysis, there was a similar poor all-cause mortality rate of patients in the refusal group (Figure S1).

Prognostic Value of Initial TAVR Refusal After the Procedure

Results of the Cox regression analysis for the association between midterm mortality and clinical findings are presented in Table 3. In the univariate analysis, HRs for TAVR refusal, body mass index <20 kg/m^2, STS score, New York Heart Association class III/IV, CFS, albumin <3.5 mg/dL, creatinine, hemoglobin, prior coronary artery bypass grafting, diabetes mellitus, peripheral artery disease, pulmonary disease, liver disease, and non-transfemoral approach were associated with increasing midterm mortality. The multivariate Cox regression model indicated that TAVR refusal, age, male sex, New York Heart Association class III/IV, CFS, albumin <3.5 mg/dL, creatinine, hemoglobin, prior coronary artery bypass grafting, pulmonary disease, and non-transfemoral approach were independent predictors of midterm mortality. The multivariate Cox regression inference using the Firth correction also showed refused TAVR as an independent predictor of midterm mortality (Table S1).

Detailed Information for the Refusal Group

In the refusal group, 27 of 28 patients refused TAVR once, and 1 patient refused TAVR 8 times. The shortest period from TAVR refusal to TAVR procedure was 1 month, and the longest was 20 months (median, 5.5 months). Seven of 28 patients died during the follow-up period, and 4 of those patients died from cardiac death. The reason for refusing TAVR and then finally deciding to undergo TAVR are shown in Figure 4A and 4B. The most common reason for refusing TAVR was that the patients were afraid of undergoing the procedure, which accounted for 46.4% of all reasons. The second most common reason was that patients felt that the symptoms were tolerable (28.6%). These 2 reasons accounted for 75.0% of all reasons. Conversely, the most common reason why patients finally decided to undergo TAVR was worsening HF, which accounted for 75.0% (Figure 4B). Figure 5 shows the change in the time course of patient numbers from initial TAVR refusal to undergoing the TAVR procedure. Four of five patients with severe AS, but without worsening symptoms, changed their minds and received TAVR within 4 months after initial refusal; this was because of persuasion from the patients' families and medical staff. Conversely, the number of patients who decided to undergo TAVR because of worsening AS symptoms steadily increased over time. Finally, all patients decided to undergo TAVR within 20 months after the initial refusal. Figure 6 shows the 1-year cumulative mortality of patients in the refusal group. There seemed to be a difference in cumulative mortality between those who decided to undergo TAVR without AS symptom worsening and those with AS symptom worsening, although no statistical difference was detected, which was likely because of the relatively small sample size (0% versus 33.9%, respectively; *P*=0.24).

Discussion

Based on the results of this observational study, initial TAVR refusal was associated with increasing risk of early- and midterm mortality in patients with symptomatic severe AS. Even though the patients ultimately received TAVR, the cumulative 1-year mortality was 28.8% in the refusal group. This rate was thought to be higher than those in general TAVR cohorts from previous pivotal investigations.[9,10,18,19] Moreover, most deaths in the refusal group occurred within 6 months after treatment. This finding suggests a disadvantage from treatment delay and a short time window for patients to undergo the TAVR procedure. Therefore, patients with severe AS should be encouraged to undergo TAVR early, if clinically required for AS treatment. However, because of the small sample size and the unique study proportion, definitive conclusions were not provided from this study. The

Table 1. Baseline Characteristics of Study Patients

	Refusal (n=28)	Non-Refusal (n=1514)	*P* Value
Baseline clinical characteristics			
Age, y	87.3±3.6	84.3±5.1	0.002
Male, n	8 (28.6%)	452 (29.9%)	0.88
Height, cm	147.8±9.8	149.9±9.0	0.24
Weight, kg	47.1±8.4	50.0±10.2	0.13
BSA, m^2	1.4±0.2	1.4±0.2	0.15
BMI, m^2	21.5±2.9	22.2±3.6	0.35
BMI <20, n	9 (32.1%)	434 (28.7%)	0.69
NYHA class I, n	2 (7.1%)	61 (4.0%)	0.66
NYHA class II, n	11 (39.3%)	716 (47.3%)	
NYHA class III, n	13 (46.4%)	673 (44.5%)	
NYHA class IV, n	2 (7.1%)	64 (4.2%)	
NYHA class, III or IV	15 (53.6%)	733 (48.4%)	0.59
Logistic EuroSCORE, %	18.9 (13.3–29.7)	12.3 (7.8–19.9)	<0.001
EuroSCORE II, %	4.4 (3.1–6.5)	3.6 (2.2–5.8)	0.002
STS score, %	8.8 (6.9–13.4)	6.3 (4.4–8.9)	<0.001
STS <4%	0 (0.0%)	273 (18.0%)	<0.001
STS 4% to 8%	9 (32.1%)	729 (48.2%)	
STS >8%	19 (67.9%)	512 (33.8%)	
Frailty components			
Albumin, g/dL	3.8±0.5	3.8±0.5	0.84
Albumin <3.5, n	5 (17.9%)	336 (22.2%)	0.58
MMSE (n=1111)	24.3±3.7 (n=18)	25.0±5.1 (n=1052)	0.53
Clinical Frailty Scale	4.5±1.5	3.9±1.2	0.02
Preprocedural laboratory data			
BNP, pg/mL	430.4 (173.0–961.6)	241.7 (113.2–504.2)	0.03
Creatinine, mg/dL	1.2±0.7	1.0±0.6	0.10
Hemoglobin, g/dL	11.3±1.8	11.2±1.6	0.94
Comorbidities			
Peripheral artery disease, n	8 (28.6%)	223 (14.7%)	0.04
Prior MI, n	1 (3.6%)	102 (6.7%)	0.51
Prior PCI, n	6 (21.4%)	403 (26.6%)	0.54
Prior CABG, n	2 (7.1%)	112 (7.4%)	0.96
Prior stroke, n	6 (21.4%)	211 (13.9%)	0.26
Diabetes mellitus, n	7 (25.0%)	399 (26.4%)	0.87
Hypertension, n	21 (75.0%)	1197 (79.1%)	0.60
Pulmonary disease, n	11 (39.3%)	413 (27.3%)	0.16
Liver disease, n	1 (3.6%)	48 (3.2%)	0.91
Active cancer, n	1 (3.6%)	74 (4.9%)	0.75
Echocardiographic data			
LVEF, %	54.7±15.6	62.3±12.1	0.001
AVA, cm^2	0.58±0.15	0.64±0.17	0.09
Indexed AVA, cm^2/m^2	0.42±0.09	0.45±0.12	0.25
Peak velocity, m/s	4.5±1.0	4.6±0.8	0.80
Peak gradient, mm Hg	85.0±37.0	86.1±29.8	0.84
Mean gradient, mm Hg	49.9±21.0	50.4±17.8	0.87
AR ≥ moderate, n	1 (3.6%)	145 (9.6%)	0.28
MR ≥ moderate, n	8 (28.6%)	132 (8.7%)	<0.001

Values are numbers (%) or mean±SD. AR indicates aortic regurgitation; AVA, aortic valve area; BMI, body mass index; BNP, B-type natriuretic peptide; BSA, body surface area; CABG, coronary artery bypass grafting; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricle ejection fraction; MI, myocardial infarction; MMSE, Mini Mental State Examination; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS score, Society of Thoracic Surgeons Predictive Risk of Mortality.

HR for TAVR refusal itself was significant, and the confidence interval was broad in this study. Therefore, TAVR refusal itself may be a risk, on average, but it is difficult to evaluate quantitatively to what extent TAVR refusal is associated with worse prognosis. However, the most important point was to convey to patients the fact that refusing TAVR may adversely impact prognosis. The rate of TAVR refusal in this study was lower than that reported in prior surgical cohorts.[7,8] However, in this registry, the patients in the refusal group were a highly selected cohort because most of them were introduced from medical practitioners to receive TAVR procedure. This point is completely different from previous surgical cohorts. It is therefore inappropriate to compare the TAVR refusal rate between our cohort and prior surgical cohorts.[7,8] In contrast to the previous surgical cohorts, the present study cohort eventually received the TAVR treatment; thus, this point is beyond our scope for this study.

Although the less invasive, catheter-based TAVR resolves the problem for patients with a high risk of SAVR or an inoperable state, patients still hesitate to undergo the TAVR procedure.[9,10] Two major reasons exist for refusing TAVR in the very elderly cohort. The first reason is fear of the TAVR procedure itself, and the other reason is that patients feel that

Table 2. Peri- and Post-Procedural Patient Characteristics and 30-Day In-Hospital Outcomes

	Refusal (n=28)	Non-Refusal (n=1514)	*P* Value
Procedural variables			
Procedure time, min	88.8±47.6	87.6±46.7	0.90
Fluoroscopy time, min	19.0±9.14	21.3±9.87	0.24
Contrast medium volume, mL	109.0±74.7	124.0±59.3	0.19
Approach route			
Transfemoral approach, n	19 (67.9%)	1205 (79.6%)	0.13
Non-transfemoral approach, n	9 (32.1%)	309 (20.4%)	
Trans-apical approach, n	8 (28.6%)	270 (17.6%)	
Trans-iliac approach, n	1 (3.6%)	28 (1.8%)	
Trans-aortic approach, n	0 (0.0%)	5 (0.3%)	
Trans-subclavian approach, n	0 (0.0%)	6 (0.4%)	
Balloon expandable valve, n	25 (89.3%)	1376 (90.9%)	0.77
Local anesthesia, n	3 (10.7%)	185 (12.2%)	0.81
Procedural complications			
Acute coronary obstruction, n	0 (0.0%)	12 (0.8%)	0.64
Disabling stroke, n	0 (0.0%)	24 (1.6%)	0.50
Acute kidney injury, n	4 (14.3%)	129 (8.5%)	0.28
Major vascular complication, n	2 (7.1%)	76 (5.0%)	0.61
Minor vascular complication, n	2 (7.1%)	78 (5.2%)	0.64
Life threatening/ disabling bleeding, n	2 (7.1%)	82 (5.4%)	0.69
Major bleeding, n	3 (10.7%)	202 (13.3%)	0.69
Minor bleeding, n	2 (7.1%)	174 (11.5%)	0.47
Cardiac tamponade, n	0 (0.0%)	26 (1.7%)	0.48
2valve implantation, n	1 (3.6%)	19 (1.3%)	0.28
Surgical conversion, n	1 (3.6%)	19 (1.3%)	0.28
Postprocedural pacemaker implantation (n=1432)	0/25 (0.0%)	122/1407 (8.7%)	0.30
Balloon expandable valve (n=1303)	0/23 (0.0%)	92/1280 (7.2%)	<0.001
Self-expandable valve (n=129)	0/2 (0.0%)	30/127 (23.6%)	
Post AR ≥ moderate, n	0 (0.0%)	16 (1.1%)	0.60
Clinical outcomes			
Hospital stay after procedure, day	12.5 (6.75–20.25)	11.0 (7.0–16.0)	0.31
Intensive care unit stay, day	1.0 (1.0–2.25)	2.0 (1.0–3.0)	0.009
30-day mortality, %	2 (7.1%)	19 (1.3%)	0.008

Values are numbers (%) or mean±SD. AR indicates aortic regurgitation.

AS symptoms are tolerable because of a typically low-activity level in daily life. The current study provoked the adverse outcomes of AS disease beyond TAVR procedure-related risks. In patients who feared and postponed scheduling TAVR, 75.0% of patients who initially refused TAVR were readmitted for worsening HF. Although we excluded non-elective cases of TAVR in the present study, some patients who were emergently admitted for worsening HF had to be treated under serious conditions. As shown in previous research, 30-day mortality of patients who underwent emergency TAVR was significantly higher than that of elective TAVR.[20] The results of the previous study and this study suggest that treatment delay may lead to worse and poor early- to midterm clinical outcomes.[8] We hypothesize that these differences were influenced by irreversible myocardial overload because of treatment delay of severe AS. In this study, left ventricle ejection fraction was lower in the refusal group. Worsening patient condition from myocardium overload causes worsening HF and reduces cardiac function.[21,22] Such overload of the myocardium may also lead to a higher risk of falling, decreased mobility, and decreased ability to perform basic activities of daily living, which, in turn, results in increased frailty.[23,24] In fact, in the refusal group, frailty status was relatively progressed compared with the non-refusal group. Patients in the refusal group might be faced with the dilemma of undergoing treatment or not, as these patients are more elderly within the TAVR cohort. As a result, patients in the refusal group were older than those in the non-refusal group. Therefore, progression of worsening condition at the time of the TAVR procedure not only affects early clinical adverse events, but also increases midterm mortality. However, taking into account the fact that the median follow-up was 5.5 months, the higher mean age might not be attributable solely to TAVR refusal. Unmeasurable confounders may also be underestimated or uncaptured in this study, and the relationship between patient refusal itself and poor midterm prognosis was not fully elucidated.

The determination of adequate timing for valve replacement in patients with AS is evolving in the literature. It has long been

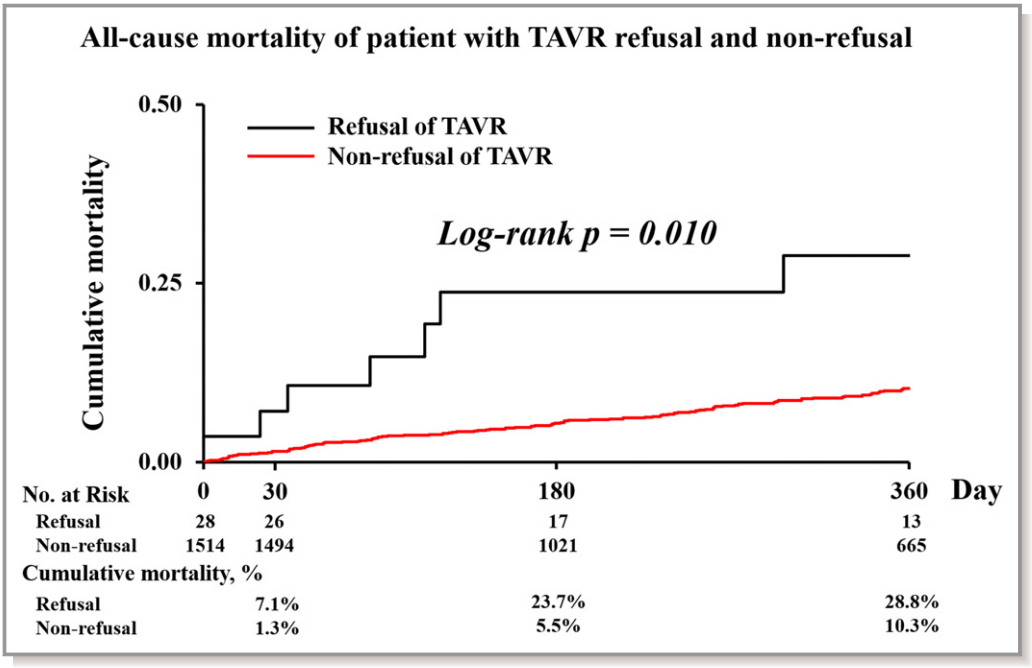

Figure 2. Kaplan–Meier analysis of all-cause mortality of patients in the refusal and non-refusal groups. The cumulative 1-year mortality rates were significantly higher in the refusal group than in the non-refusal group.

recognized that patients with symptomatic severe AS need to undergo SAVR.[25,26] Although a watchful waiting approach is generally justified in asymptomatic patients with severe AS, there are still concerns about when such a strategy should occur.[27] Because improved surgical techniques have led to lower operative mortality and morbidity rates, earlier intervention has been increasingly advocated.[3–5] Another recent report revealed that an initial SAVR strategy in patients with asymptomatic severe AS was associated with a lower risk for all-cause mortality compared with a conservative watchful waiting approach.[6] Current guidelines recommend that patients with significantly calcified valves, rapid hemodynamic progression, and a positive exercise test are likely to benefit from early elective surgery.[1,2] An optimal management strategy is still under debate for patients who feel that their AS symptoms are controllable, whereas evidence is growing on early valve replacement for patients with severe AS, regardless of clinical symptoms. Our study also revealed that 82.1% of patients who initially refused TAVR changed their minds within 20 months. Interestingly, there were several patients who changed their mind and received TAVR in the earlier phase without AS symptom worsening. However, the number of patients who decided to undergo TAVR because of

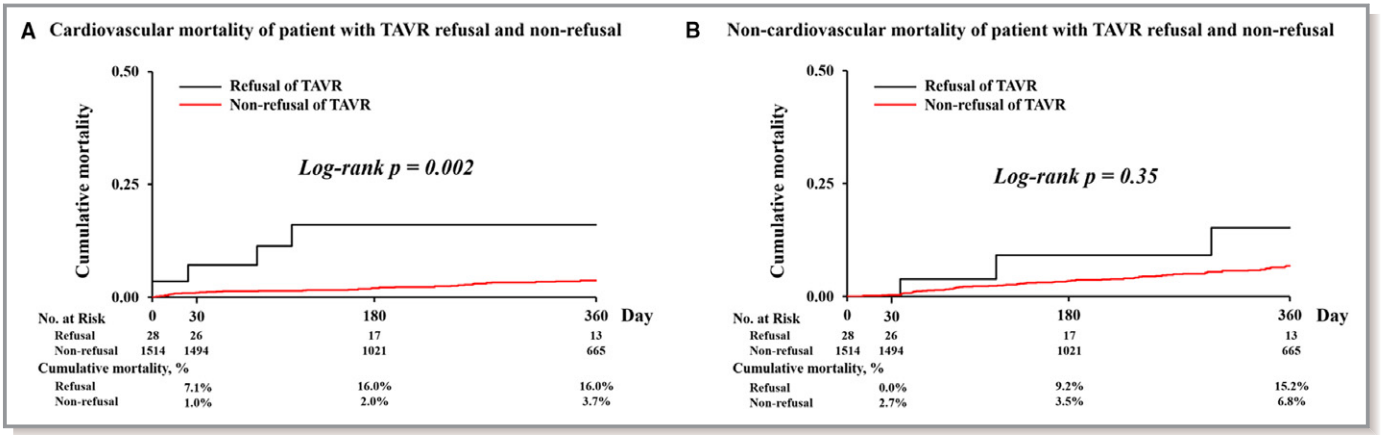

Figure 3. Kaplan–Meier curve showing cumulative (A>) cardiovascular mortality and (B) non-cardiovascular mortality in the refusal and non-refusal groups. A, The cumulative 1-year cardiovascular mortality rate was significantly higher in the refusal group than in the non-refusal group. B, The cumulative 1-year non-cardiovascular mortality rate was not significantly different between the groups.

Table 3. Cox Regression Analysis for the Association Between Midterm Mortality and Clinical Findings

	Univariate Analysis			Multivariate Analysis		
Variables	HR	95% CI	*P* Value	HR	95% CI	*P* Value
TAVR refusal	2.60	1.22 to 5.55	0.014	3.37	1.52 to 7.48	0.003
Adjusting factors						
Age (per 1 y increase)	0.99	0.96 to 1.02	0.43	0.97	0.93 to 1.00	0.035
Male (for female)	1.35	0.97 to 1.87	0.077	1.52	1.03 to 2.24	0.035
BMI <20 (for BMI ≥20)	1.39	1.00 to 1.93	0.048	1.18	0.83 to 1.69	0.35
STS score (per 1.0% increase)	1.05	1.03 to 1.06	<0.001	1.01	0.98 to 1.04	0.57
NYHA class III/IV (for I/II)	2.17	1.56 to 3.02	<0.001	1.70	1.18 to 2.44	0.004
Clinical frailty scale (per 1 grade increase)	1.32	1.17 to 1.48	<0.001	1.17	1.01 to 1.35	0.033
BNP (per 1.0 pg/mL increase)	1.00	1.00 to 1.00	0.059	1.00	1.00 to 1.00	0.76
Albumin <3.5 (for albumin ≥3.5)	3.27	2.38 to 4.51	<0.001	2.36	1.64 to 3.40	<0.001
Creatinine (per 1.0 mg/dL increase)	1.72	1.47 to 2.01	<0.001	1.34	1.07 to 1.68	0.010
Hemoglobin (per 1.0 g/dL increase)	0.76	0.68 to 0.84	<0.001	0.83	0.74 to 0.93	0.001
Prior MI	1.50	0.91 to 2.48	0.12	1.12	0.62 to 2.01	0.71
Prior PCI	1.18	0.84 to 1.65	0.35	1.03	0.69 to 1.53	0.88
Prior CABG	1.97	1.23 to 3.16	0.005	1.81	1.07 to 3.09	0.028
Prior stroke	1.26	0.83 to 1.92	0.28	0.92	0.58 to 1.45	0.72
Diabetes mellitus	1.51	1.09 to 2.10	0.014	1.12	0.77 to 1.63	0.56
Hypertension	1.27	0.85 to 1.90	0.25	1.05	0.69 to 1.60	0.83
Peripheral artery disease	1.99	1.40 to 2.84	<0.001	1.16	0.76 to 1.76	0.50
Pulmonary disease	1.47	1.06 to 2.04	0.022	1.47	1.03 to 2.10	0.036
Liver disease	2.57	1.35 to 4.89	0.004	1.60	0.74 to 3.48	0.24
Active cancer	1.14	0.58 to 2.23	0.70	1.19	0.56 to 2.53	0.66
LVEF (per 1.0% increase)	0.99	0.98 to 1.01	0.21	1.01	0.99 to 1.02	0.52
Non-transfemoral (for transfemoral)	2.09	1.51 to 2.91	<0.001	1.76	1.19 to 2.58	0.004

BMI indicates body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; LVEF, left ventricle ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS score, Society of Thoracic Surgeons Predictive Risk of Mortality; TAVR, transcatheter aortic valve replacement.

worsening of AS symptoms steadily increased over time, which was because of the progression of clinical symptom associated with severe AS. AS is a definitive progressive disease, yet TAVR continues to be postponed until AS symptoms progress to the point that patients have to undergo TAVR. Additionally, in this study, those who decided to undergo TAVR without AS symptom worsening had a lower cumulative mortality rate than those with AS symptom worsening (0% versus 33.9%). Therefore, further patient education might allow an optimal pathway for patient care.

Limitations

Several study limitations should be addressed. First, the present study was based on a Japanese multicenter registry, which consists of a relatively large number of patients; however, only 28 patients were in the refusal group, and this made difficulties in the statistical analysis. Although, as we mentioned in the discussion section, the HR for TAVR refusal itself was significant, the confidence interval was broad. Therefore, TAVR refusal itself may be a risk, on average, but it is difficult to evaluate quantitatively to what extent TAVR refusal is associated with worse prognosis. Second, the explanation and expository writing for TAVR procedure differs among institutions and these differences may have affected refusal rate and the clinical outcomes. Third, the number of 30-day deaths (n=21, 1.4%) and deaths in the refusal group (n=7, 25%) were too small to analyze using the multivariate regression model. The results described above may have been different if we had been able to evaluate data for a larger number of events. Fourth, in this study, refusal for TAVR did not include those patients who refused TAVR indefinitely and

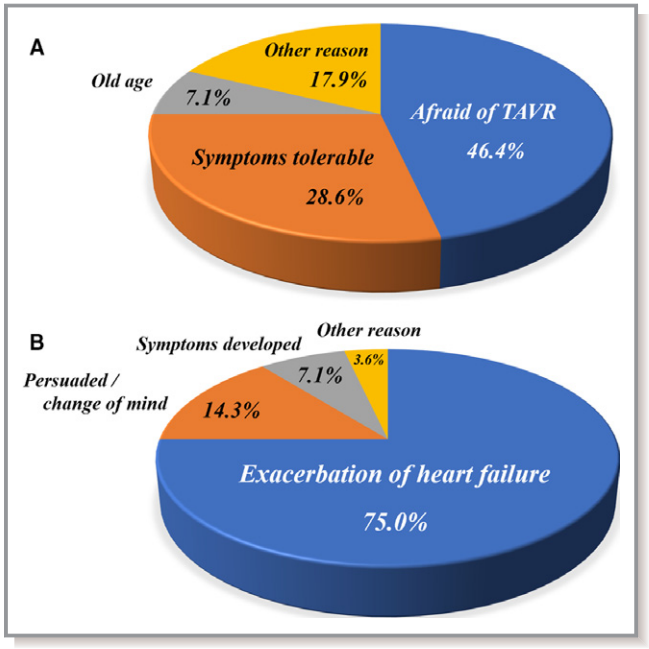

Figure 4. Distribution of reasons for (A) refusing TAVR and (B) eventually deciding to undergo TAVR after initial refusal in the refusal group. A, This pie chart summarizes the distribution of reasons for patient refusal of TAVR. B, This pie chart summarizes the distribution of reasons for eventually deciding to undergo TAVR after initial refusal. TAVR indicates transcatheter aortic valve replacement.

who were conservatively treated. Thus, the fate of patients who refused TAVR is unknown. In addition, this study did not include patients who died while awaiting the TAVR procedure.

These facts should be addressed as immortal bias of this study. Fifth, patients in the non-refusal group had an initial survival advantage because they underwent the procedure earlier, not because they "did not refuse" the procedure; this is another immortal bias of this study. We could not directly perform an investigation comparing patients who initially refused TAVR but later underwent the procedure to patients who did not refuse the procedure but underwent TAVR at the same time delay as the refusal group. For this reason, we performed a conventional sensitivity analysis with the aim of reducing the effect of immortal time bias. The results suggested that the cumulative survival rate in the TAVR refusal group was still poor. However, any statistical approaches were limited to minimize the immortal time bias because of our study design. Thus, we should not overstate our conclusions. Finally, since the target of this study was patients who refused to undergo the treatment, there is no analysis on patients for whom the TAVR procedure had to be postponed because of treatment of comorbidities or other reasons.

Conclusions

In this observational study, the sample size was too small to elucidate any definitive conclusions. However, the results suggest an association between TAVR refusal and increasing early- to midterm mortality; thus, decision-making regarding the indication of TAVR should be carefully completed. Moreover,

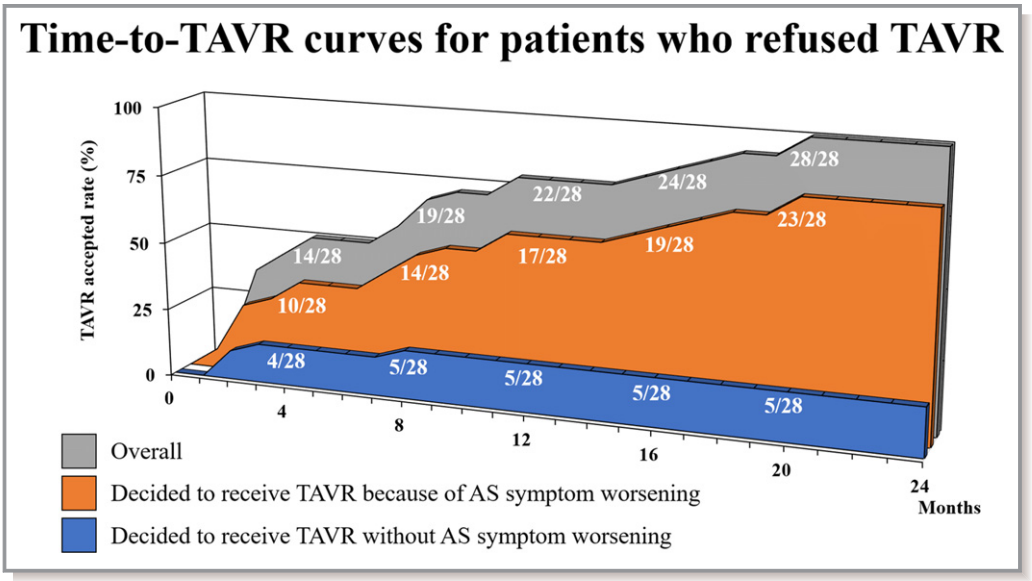

Figure 5. Time-to-TAVR curves for patients in the refusal group. The figure shows the change in the time course of patient numbers from initial TAVR refusal. All patients decided to undergo TAVR within 20 months after initial refusal (grey). Five of the 28 patients decided to undergo TAVR without AS symptom worsening within 8 months (blue). The number of patients who decided to undergo TAVR because of worsening AS symptoms steadily increased with time (orange). AS indicates aortic stenosis; TAVR, transcatheter aortic valve replacement.

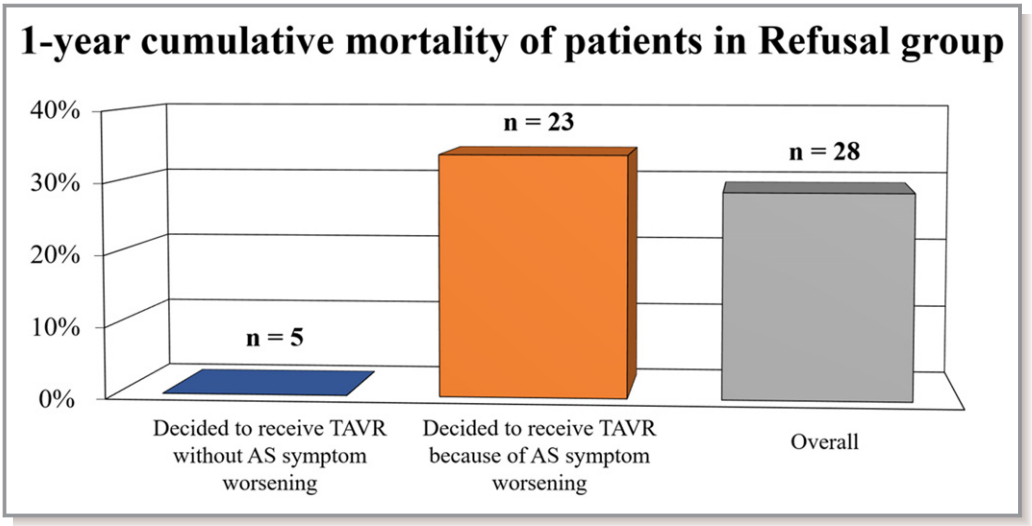

Figure 6. One-year cumulative mortality of patients in the refusal group. The cumulative 1-year all-cause mortality of patients who decided to undergo TAVR with AS symptom worsening (orange) was higher than that of patients who decided to undergo TAVR without AS symptom worsening (blue). AS indicates aortic stenosis; TAVR, transcatheter aortic valve replacement.

the present study's findings are also beneficial for patients who have difficulty deciding to undergo the TAVR procedure.

Appendix

The OCEAN-TAVI investigators are as follows: Kentaro Hayashida, Fumiaki Yashima, Taku Inohara, Yuki Kakefuda, Takahide Arai, Ryo Yanagisawa, Makoto Tanaka, Hiromu Hase, Nobuhiro Yoshijima, Tetsuya Saito, Hikaru Tsuruta, Takashi Kawakami, Yuichiro Maekawa, Kohno Takashi, Akihiro Yoshitake, Yasunori Iida, Masataka Yamazaki, Hideyuki Shimizu, Yoshitake Yamada, Masahiro Jinzaki, Yuji Itabashi, Mitsushige Murata, Michiyuki Kawakami, Shogo Fukui, Motoaki Sano, Tatsuo Takahashi, Hiroko Kato, Izumi Nakagawa-Tamura, Keiichi Fukuda belongs to Keio University School of Medicine, Tokyo, Japan; Masanori Yamamoto, Tetsuro Shimura, Seiji Kano, Soh Hosoba, Atsuko Kodama, Hirotomo Sato, Tomohiko Teramoto, Masashi Kimura, Mitsuru Sago, Tatsuya Tsunaki, Shoko Watarai, Masanao Tsuzuki, Keisuke Irokawa, Kazuki Shimizu, Etsuo Tsuchikane, Takahiko Suzuki belongs to Toyohashi Heart Center, Aichi, Japan; Ai Kagase, Yutaka Koyama, Toshihiro Kobayashi, Kenichi Shibata, Yasuhide Okawa belongs to Nagoya Heart Center, Aichi, Japan; Norio Tada, Masaki Miyasaka, Yusuke Enta, Yukiko Mizutani, Arata Inoue, Kazunori Ishii belongs to Sendai Kousei Hospital, Miyagi, Japan; Toru Naganuma, Hiroyoshi Kawamoto, Hirokazu Onishi, Satoru Mitomo, Sunao Nakamura belongs to New Tokyo Hospital, Chiba, Japan; Motoharu Araki, Masahiro Yamawaki, Yasunari Sakamoto, Yosuke Honda, Kenji Makino, Yui Akatsu belongs to Saiseikai Yokohama City Eastern Hospital, Kanagawa, Japan; Futoshi Yamanaka, Koki Shishido, Tomoki Ochiai, Tsuyoshi Yamabe, Kenichiro Noguchi, Shigeru Saito belongs to Shonan Kamakura General Hospital, Kanagawa, Japan; Shinichi Shirai, Akihito Isotani, Masaomi Hayashi, Norihiko Kamioka, Mizuki Miura, Takashi Morinaga, Tomohiro Kawaguchi, Mariko Yano, Michiya Hanyu, Yoshio Arai, Hideki Tsubota, Masafumi Kudo, Yuki Kuroda belongs to Kokura Memorial Hospital, Fukuoka, Japan; Kazuki Mizutani, Mana Nakao, Tsukasa Okai, Keiko Kajio belongs to Osaka City General Hospital, Osaka, Japan; Minoru Tabata, Kentaro Shibayama, Masahiko Noguchi, Kotaro Kobunai, Nahoko Kato, Shun Watanabe, Makoto Hiono belongs to Tokyo Bay Urayasu-Ichikawa Medical Center, Chiba, Japan; Hiroshi Ueno, Hiroshi Onoda, Hiroyuki Kuwahara belongs to Toyama University Hospital, Toyama, Japan; Kensuke Takagi belongs to Ogaki Municipal Hospital, Gifu, Japan; Akihiro Higashimori belongs to Kishiwada Tokushukai Hospital, Osaka, Japan; Yusuke Watanabe, Akihisa Kataoka, Hitofumi Hioki, Yugo Nara, Hideyuki Kawashima, Fukuko Nagura, Makoto Nakashima, Kazuya Sasaki, Junichi Nishikawa, Tomoki Shimokawa, Tadanori Harada, Taiga Katayama, Nozomu Yukimitsu, Shintaro Takamura, Hirosada Yamamoto, Ken Kozuma belongs to Teikyo University School of Medicine, Tokyo, Japan.

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Disclosures

Drs Yamamoto, Tada, Naganuma, Araki, Shirai, Watanabe, and Hayashida are proctors for transfemoral-TAVI for the Edwards SAPIEN valve. Drs Koyama and Tabata are proctors for transapical-TAVI for the Edwards SAPIEN valve. Drs Yamamoto, Naganuma, Shirai, and Watanabe are proctors for transfemoral TAVI for the Medtronic CoreValve. The remaining authors have no disclosures to report.

References

1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM III, Thompson A. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e1159–e1195.
2. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791.
3. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111:3290–3295.
4. Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. *Ann Thorac Surg*. 2006;82:2116–2122.
5. Kang DH, Park SJ, Rim JH, Yun SC, Kim DH, Song JM, Choo SJ, Park SW, Song JK, Lee JW, Park PW. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation*. 2010;121:1502–1509.
6. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Miyake M, Mitsuoka H, Kato M, Hirano Y, Matsuda S, Nagao K, Inada T, Murakami T, Takeuchi Y, Yamane K, Toyofuku M, Ishii M, Minamino-Muta E, Kato T, Inoko M, Ikeda T, Komasa A, Ishii K, Hotta K, Higashitani N, Kato Y, Inuzuka Y, Maeda C, Jinnai T, Morikami Y, Sakata R, Kimura T; CURRENT AS Registry Investigators. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2015;66:2827–2838.
7. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24:1231–1243.
8. Bouma BJ, van Den Brink RB, van Der Meulen JH, Verheul HA, Cheriex EC, Hamer HP, Dekker E, Lie KI, Tijssen JG. To operate or not on elderly patients with aortic stenosis: the decision and its consequences. *Heart*. 1999;82:143–148.
9. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607.
10. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198.
11. Yamamoto M, Shimura T, Kano S, Kagase A, Kodama A, Sago M, Tsunaki T, Koyama Y, Tada N, Yamanaka F, Naganuma T, Araki M, Shirai S, Watanabe Y, Hayashida K. Prognostic value of hypoalbuminemia after transcatheter aortic valve implantation (from the Japanese Multicenter OCEAN-TAVI Registry). *Am J Cardiol*. 2017;119:770–777.
12. Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, Tsuchikane E, Suzuki T, Otsuka T, Kohsaka S, Tada N, Yamanaka F, Naganuma T, Araki M, Shirai S, Watanabe Y,Hayashida K; OCEAN-TAVI Investigators. Impact of the clinical frailty scale on outcomes after transcatheter aortic valve replacement. *Circulation*. 2017;135:2013–2024.
13. Kano S, Yamamoto M, Shimura T, Kagase A, Tsuzuki M, Kodama A, Koyama Y, Kobayashi T, Shibata K, Tada N, Naganuma T, Araki M, Yamanaka F, Shirai S, Mizutani K, Tabata M, Ueno H, Takagi K, Higashimori A, Otsuka T, Watanabe Y, Hayashida K. Gait speed can predict advanced clinical outcomes in patients who undergo transcatheter aortic valve replacement: insights from a Japanese Multicenter Registry. *Circ Cardiovasc Interv*. 2017;10:e005088.
14. Faculty of Medicine, Geriatric Medicine Research, Dalhousie University. Research/Projects, Clinical Frailty Scale ©. Updated July 15, 2015. Available at: http://geriatricresearch.medicine.dal.ca/clinical_frailty_scale.htm. Accessed August 12, 2018.
15. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173:489–495.
16. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB; Valve Academic Research Consortium-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg*. 2013;145:6–23.
17. The Comprehensive R Archive Network. Available at: http://cran.r-project.org/. Accessed July 10, 2018.
18. Schymik G, Lefèvre T, Bartorelli AL, Rubino P, Treede H, Walther T, Baumgartner H, Windecker S, Wendler O, Urban P, Mandinov L, Thomas M, Vahanian A. European experience with the second-generation Edwards SAPIEN XT transcatheter heart valve in patients with severe aortic stenosis: 1-year outcomes from the SOURCE XT Registry. *JACC Cardiovasc Interv*. 2015;8:657–669.
19. Linke A, Wenaweser P, Gerckens U, Tamburino C, Bosmans J, Bleiziffer S, Blackman D, Schäfer U, Müller R, Sievert H, Søndergaard L, Klugmann S, Hoffmann R, Tchétché D, Colombo A, Legrand VM, Bedogni F, lePrince P, Schuler G, Mazzitelli D, Eftychiou C, Frerker C, Boekstegers P, Windecker S, Mohr FW, Woitek F, Lange R, Bauernschmitt R, Brecker S; ADVANCE study Investigators. Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. *Eur Heart J*. 2014;35:2672–2684.
20. Frerker C, Schewel J, Schlüter M, Schewel D, Ramadan H, Schmidt T, Thielsen T, Kreidel F, Schlingloff F, Bader R, Wohlmuth P, Schäfer U, Kuck KH. Emergency transcatheter aortic valve replacement in patients with cardiogenic shock due to acutely decompensated aortic stenosis. *EuroIntervention*. 2016;11:1530–1536.
21. Gheorghiade M, De Luca L, Fonarow GC, Filippatos G, Metra M, Francis GS. Pathophysiologic targets in the early phase of acute heart failure syndromes. *Am J Cardiol*. 2005;96:11G–17G.
22. Brown ML, Pellikka PA, Schaff HV, Scott CG, Mullany CJ, Sundt TM, Dearani JA, Daly RC, Orszulak TA. The benefits of early valve replacement in asymptomatic patients with severe aortic stenosis. *J Thorac Cardiovasc Surg*. 2008;135:308–315.
23. Uchmanowicz I, Kuśnierz M, Wleklik M, Jankowska-Polańska B, Jaroch J, Łoboz-Grudzień K. Frailty syndrome and rehospitalizations in elderly heart failure patients. *Aging Clin Exp Res*. 2018;30:617–623.
24. Rodríguez-Pascual C, Paredes-Galán E, Ferrero-Martínez AI, Gonzalez-Guerrero JL, Hornillos-Calvo M, Menendez-Colino R, Torres-Torres I, Vilches-Moraga A, Galán MC, Suarez-Garcia F, Olcoz-Chiva MT, Rodríguez-Artalejo F. The frailty syndrome is associated with adverse health outcomes in very old patients with stable heart failure: a prospective study in six Spanish hospitals. *Int J Cardiol*. 2017;236:296–303.
25. Ross J Jr, Braunwald E. Aortic stenosis. *Circulation*. 1968;38:61–67.
26. Schwarz F, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel HC, Schmitz W, Kübler W. The effect of aortic valve replacement on survival. *Circulation*. 1982;66:1105–1110.
27. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343:611–617.

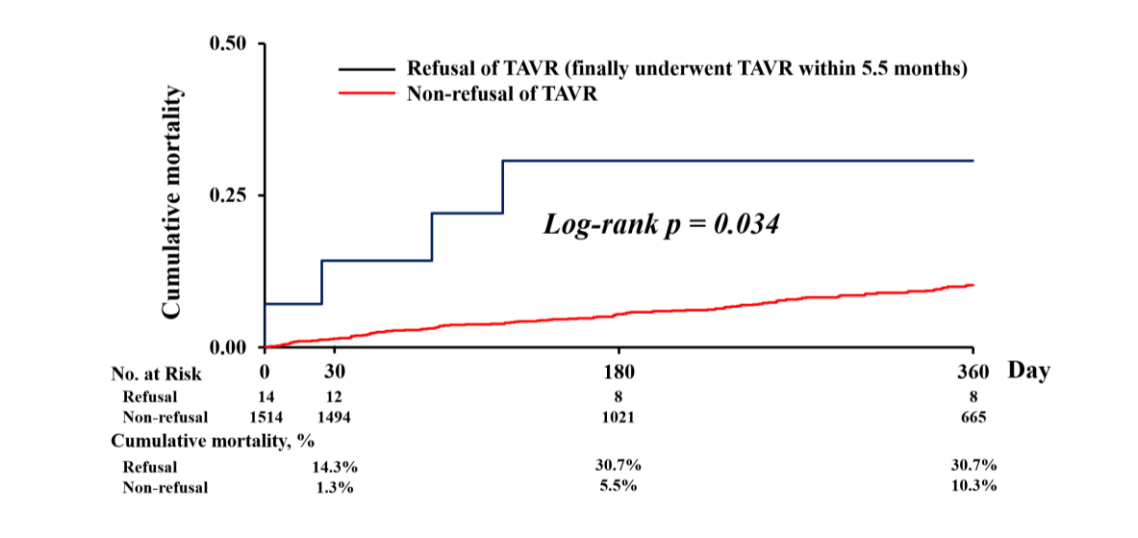
SUPPLEMENTAL MATERIAL

Table S1. The multivariate Cox regression inference using the Firth correction.

	Multivariate analysis Cox regression (Firth correction)		
Variables	HR	95% CI	p value
TAVR refusal	3.56	1.51-7.23	0.006
Adjusting factors			
Age (per 1 year increase)*	0.96	0.93-1.00	0.032
Male (for female)	1.52	1.03-2.22	0.037
BMI <20 (for BMI ≥20)	1.19	0.83-1.68	0.35
STS score (per 1.0 % increase)	1.01	0.98-1.04	0.52
NYHA class III/IV (for I/II)	1.69	1.18-2.43	0.004
Clinical frailty scale (per 1 grade increase)	1.17	1.01-1.34	0.034
BNP (per 1.0 pg/ml increase)	1.00	1.00-1.00	0.84
Albumin <3.5 (for albumin ≥3.5)	2.35	1.63-3.38	<0.001
Creatinine (per 1.0 mg/dL increase)	1.35	1.07-1.66	0.013
Hemoglobin (per 1.0 g/dL increase)	0.83	0.74-0.93	0.001
Prior MI	1.14	0.62-1.98	0.67
Prior PCI	1.03	0.69-1.52	0.87
Prior CABG	1.84	1.06-3.04	0.032
Prior stroke	0.94	0.58-1.44	0.77
Diabetes mellitus	1.12	0.77-1.62	0.54
Hypertension	1.03	0.69-1.60	0.88
Peripheral artery disease	1.15	0.75-1.74	0.50
Pulmonary disease	1.47	1.02-2.09	0.038
Liver disease	1.68	0.73-3.37	0.21
Active cancer	1.26	0.56-2.47	0.55
LVEF (per 1.0% increase)	1.00	0.99-1.02	0.54
Non-transfemoral (for transfemoral)	1.77	1.20-2.58	0.005

HR; hazard ratio, CI; confidence interval. TAVR, transcatheter aortic valve replacement; BMI, body mass index; STS score, Society of Thoracic Surgeons Predictive Risk of Mortality; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricle ejection fraction.

Figure S1. All- cause mortality of patients with TAVR refusal (finally underwent TAVR within 5.5 months) and non-refusal.



TAVR, transcatheter aortic valve replacement