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Transcatheter aortic valve replacement outcomes in Japan: Optimized CathEter vAlvular iNtervention (OCEAN) Japanese multicenter registry

Masanori Yamamoto [a,b,*], Yusuke Watanabe [c], Norio Tada [d], Toru Naganuma [e], Motoharu Araki [f], Futoshi Yamanaka [g], Kazuki Mizutani [h], Minoru Tabata [i], Hiroshi Ueno [j], Kensuke Takagi [k], Akihiro Higashimori [l], Shinichi Shirai [m], Kentaro Hayashida [n], , on behalf of theOCEAN-TAVI investigators

[a] Department of cardiology, Toyohashi Heart Center, Toyohashi, Japan
[b] Department of cardiology, Nagoya Heart Center, Nagoya, Japan
[c] Department of cardiology, Teikyo University School of Medicine, Tokyo, Japan
[d] Department of cardiology, Sendai Kosei Hospital, Sendai, Japan
[e] Department of cardiology, New Tokyo Hospital, Chiba, Japan
[f] Department of cardiology, Saiseikai Yokohama City Eastern Hospital, Yokohama, Japan
[g] Department of cardiology, Shonan Kamakura General Hospital, Kanagawa, Japan
[h] Department of Cardiovascular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan
[i] Department of Cardiovascular Surgery, Tokyo Bay Urayasu-Ichikawa Medical Center, Chiba, Japan
[j] Toyama University Hospital, Toyama, Japan
[k] Ogaki Municipal Hospital, Gifu, Japan
[l] Kishiwada Tokushukai Hospital, Osaka, Japan
[m] Department of cardiology, Kokura Memorial Hospital, Kokura, Japan
[n] Department of cardiology, Keio University School of Medicine, Tokyo, Japan

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ABSTRACT

Objectives: We aimed to assess real-world clinical outcomes of transcatheter aortic valve replacement (TAVR) in Japan.
Background: Data are limited concerning procedural safety and valve performance following TAVR in Japanese. A program by an on-site proctor and procedure screening system was applied during TAVR introduction.
Methods: We consecutively enrolled 1613 patients who underwent TAVR using data from the Optimized CathEter vAlvular iNtervention (OCEAN) Japanese registry, which consists of 14 centers. Baseline characteristics and procedural outcomes including combined early 30-day non-safety, and mortality rates were assessed among 4 groups, divided into quartiles (Q1-Q4).
Results: Most patients were women (70.4%), elderly (84.4 ± 5.1 years), and had a median Society of Thoracic Surgeons score of 6.7(4.7–9.5). The overall 30-day mortality, combined early non-safety, and cumulative 1-year mortality rates were 1.7%, 15.1%, and 11.3%, respectively. Thirty-day mortality was not affected by center experience differences divided into quartiles (1.0%, 2.0%, 2.5%, 1.5%, $p = 0.404$), whereas 30-day early safety was significantly improved (19.1%, 17.9%, 14.6%, 8.9%, $p < 0.001$). Thirty-day mortality was 0% under transfemoral on-site proctor. Cox-regression multivariate analysis revealed that male sex, clinical frailty scale, New York Heart Association class, creatinine, albumin, hemoglobin, liver disease, and non-transfemoral approach were independent predictive factors of increased midterm mortality risk.
Conclusions: Owning to the global supporting system in Japan, excellent early and midterm outcomes have been achieved to overcome the learning curve of the newly introduced TAVR procedure.

1. Introduction

Transcatheter aortic valve replacement (TAVR) has become an established option in patients with degenerative aortic stenosis (AS) considered to be inoperable or in those who have a high likelihood of requiring surgical aortic valve replacement (SAVR); the indications for the procedure have recently included an intermediate risk subset

* Corresponding author at: FESC Department of cardiology, Toyohashi Heart Center, 21-1 Gobudori, Oyamachyo, Toyohashi, Aichi 441-8530, Japan.
E-mail address: yamamoto@heart-center.or.jp (M. Yamamoto).

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[1–3]. Since October 2013, insurance programs in Japan consider TAVR as a therapeutic option for patients with AS. The number of TAVR centers and treated patients is rapidly increasing. Some reports have described TAVR outcomes in Japanese patients with ethnic and anatomical characteristics different from those in Western and other Asian countries [4–6]. However, the numbers of patients in these reports was low, and data are limited on the clinical outcomes of TAVR in a large Japanese cohort with specific anatomical features. In addition, a screening proctor program was applied when introducing the TAVR technique in Japan; the program aimed to minimize the learning curve and optimize patient selection. Growing experience, evidence, device improvements, and strict patient pre-screening are believed to make patient risk stratification more possible. In fact, a recent multicenter registry or national based data revealed significant improvement of clinical outcomes including early mortality rates ranging from 2.0–5.0% following TAVR [7–11]. To our knowledge, this is the first report from Japan presenting real-world clinical outcomes of TAVR in a large cohort of Japanese patients and assessing the use of a specific supportive system to overcome the learning curve of the newly introduced TAVR procedure.

2. Materials and methods

2.1. Study population

Between October 2013 and July 2016, 1613 patients were enrolled in the Optimized CathEter vAlvular iNtervention-transcatheter aortic valve implantation (OCEAN-TAVI) registry. The OCEAN-TAVI is an

Table 1
Baseline characteristics of study patients.

	Overall n = 1613	Q1 n = 404	Q2 n = 403	Q3 n = 403	Q4 n = 403	*p* value	*p* for trend
Baseline clinical characteristics							
Age, years	84.4 ± 5.1	84.4 ± 5.3	84.2 ± 5.0	84.5 ± 4.8	84.4 ± 5.3	0.84	0.59
Age group							
<80 years, n	232 (14.4%)	56 (13.9%)	69 (17.1%)	57 (14.1%)	50 (12.4%)		
80–84 years, n	532 (33.0%)	123 (30.4%)	129 (32.0%)	128 (31.8%)	152 (37.7%)	0.84	
85–89 years, n	635 (39.4%)	173 (42.8%)	149 (37.0%)	167 (41.4%)	146 (36.2%)		
≥90 years, n	214 (13.3%)	52 (12.9%)	56 (13.9%)	51 (12.7%)	55 (13.6%)		
Male, n	477 (29.6%)	115 (28.5%)	116 (28.8%)	119 (29.5%)	127 (31.5%)	0.78	0.33
Height, cm	149.8 ± 9.0	149.5 ± 9.0	149.8 ± 8.9	149.3 ± 9.0	150.4 ± 9.2	0.35	0.29
Weight, kg	49.8 ± 10.1	49.6 ± 9.8	49.8 ± 10.7	49.8 ± 10.0	50.0 ± 9.8	0.95	0.55
BSA, m^2	1.4 ± 0.17	1.4 ± 0.16	1.4 ± 0.17	1.4 ± 0.17	1.4 ± 0.17	0.66	0.31
BMI, kg/m^2	22.1 ± 3.6	22.1 ± 3.5	22.1 ± 3.7	22.3 ± 3.7	22.0 ± 3.5	0.80	1.0
BMI <20, n	466 (28.9%)	121 (30.0%)	120 (29.8%)	106 (26.3%)	119 (29.5%)	0.62	0.64
NYHA class, III or IV, n	813 (50.4%)	206 (51.0%)	201 (49.9%)	210 (52.1%)	196 (48.6%)	0.78	0.66
Logistic EuroSCORE, %	12.8 (8.3–21.6)	13.5 (9.0–23.5)	13.1 (8.4–20.5)	13.0 (7.9–22.8)	11.4 (7.5–19.7)	0.021	0.005
EuroSCORE II, %	3.8 (2.3–6.1)	4.0 (2.5–6.4)	3.6 (2.2–5.5)	3.9 (2.2–6.3)	3.6 (2.3–6.2)	0.26	0.61
STS score, %	6.7 (4.7–9.5)	6.9 (4.8–9.3)	6.7 (4.6–9.7)	6.7 (5.0–10.6)	6.3 (4.3–9.2)	0.14	0.72
<4%, n	274 (17.0%)	65 (16.1%)	73 (18.1%)	60 (14.9%)	76 (18.9%)		
4–8%, n	758 (47.0%)	195 (48.3%)	180 (44.7%)	188 (46.7%)	195 (48.4%)	0.49	0.43
>8%, n	581 (36.0%)	144 (35.6%)	150 (37.2%)	155 (38.5%)	132 (32.8%)		
Frailty components							
Peek grip strength (n = 1079), kg	12.0 ± 10.2	11.6 ± 9.9 (n = 269)	12.8 ± 10.2 (n = 281)	11.8 ± 10.2 (n = 267)	11.9 ± 10.4 (n = 262)	0.35	0.89
Albumin, g/dL	3.76 ± 0.49	3.85 ± 0.48	3.75 ± 0.46	3.68 ± 0.53	3.76 ± 0.49	<0.001	0.002
MMSE (n = 1111)	24.9 ± 4.6	25.1 ± 4.3 (n = 247)	25.0 ± 4.3 (n = 277)	24.8 ± 4.6 (n = 287)	24.8 ± 5.0 (n = 300)	0.79	0.33
CFS	4.0 ± 1.3	3.9 ± 1.2	3.9 ± 1.2	4.1 ± 1.3	4.1 ± 1.3	0.22	0.05
Preprocedural laboratory data							
BNP, pg/ml	225.8 (89.9–513.7)	267.0 (124.6–575.8)	229.3 (99.9–508.2)	215.4 (63.2–558.0)	210.9 (64.4–466.6)	<0.001	<0.001
Creatinine, mg/dL	1.0 ± 0.6	1.0 ± 0.4	1.0 ± 0.5	1.1 ± 0.6	1.0 ± 0.6	0.20	0.20
Estimated GFR, ml/min	51.9 ± 20.3	53.1 ± 21.0	53.6 ± 21.2	49.4 ± 18.9	51.4 ± 20.0	0.015	0.041
Hemoglobin, g/dL	11.2 ± 1.6	11.2 ± 1.6	11.2 ± 1.6	11.1 ± 1.6	11.3 ± 1.7	0.42	0.48
Comorbidities							
Peripheral artery disease, n	247 (15.3%)	73 (18.1%)	68 (16.9%)	56 (13.9%)	50 (12.4%)	0.095	0.013
Prior MI, n	116 (7.2%)	40 (9.9%)	29 (7.2%)	29 (7.2%)	18 (4.5%)	0.03	0.005
Prior PCI, n	431 (26.7%)	124 (30.7%)	103 (25.6%)	97 (24.1%)	107 (26.6%)	0.17	0.16
Prior CABG, n	120 (7.4%)	39 (9.7%)	30 (7.4%)	28 (6.9%)	23 (5.7%)	0.19	0.04
Prior BAV, n	317 (19.7%)	120 (29.7%)	75 (18.6%)	73 (18.1%)	49 (12.2%)	<0.001	<0.001
Prior stroke, n	231 (14.3%)	70 (17.3%)	52 (12.9%)	62 (15.4%)	47 (11.7%)	0.10	0.063
Diabetes mellitus, n	430 (26.7%)	111 (27.5%)	100 (24.8%)	105 (26.1%)	114 (28.3%)	0.69	0.71
Hypertension, n	1268 (78.6%)	309 (76.5%)	313 (77.7%)	321 (79.7%)	325 (80.6%)	0.47	0.11
Pulmonary disease, n	443 (27.5%)	106 (26.2%)	123 (30.5%)	106 (26.3%)	108 (26.8%)	0.47	0.80
Liver disease, n	52 (3.2%)	9 (2.2%)	13 (3.2%)	18 (4.5%)	12 (3.0%)	0.34	0.37
Active cancer, n	70 (4.3%)	18 (4.5%)	23 (5.7%)	17 (4.2%)	12 (3.0%)	0.32	0.35
Echocardiographic data							
LVEF, %	59.3 ± 13.0	60.7 ± 11.3	60.7 ± 14.1	57.8 ± 13.0	57.9 ± 13.1	<0.001	<0.001
AVA, cm^2	0.63 ± 0.17	0.62 ± 0.16	0.64 ± 0.16	0.64 ± 0.18	0.62 ± 0.18	0.35	0.69
Indexed AVA, cm^2/m^2	0.44 ± 0.12	0.44 ± 0.11	0.44 ± 0.12	0.45 ± 0.13	0.44 ± 0.13	0.53	0.97
Peak velocity, m/s	4.6 ± 0.80	4.6 ± 0.85	4.5 ± 0.79	4.5 ± 0.75	4.6 ± 0.80	0.12	0.71
Peak gradient, mmHg	86.1 ± 30.2	87.8 ± 30.9	85.1 ± 30.6	83.8 ± 28.5	87.7 ± 30.9	0.15	0.83
Mean gradient, mmHg	50.5 ± 18.0	51.4 ± 18.9	49.4 ± 16.8	49.9 ± 17.6	51.4 ± 18.8	0.26	0.93
AR ≥ moderate, n	155 (9.6%)	45 (11.1%)	43 (10.7%)	31 (7.7%)	36 (8.9%)	0.32	0.14
MR ≥ moderate, n	162 (10.0%)	41 (10.1%)	36 (8.9%)	45 (11.2%)	40 (9.9%)	0.77	0.82

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

ongoing, multicenter registry in 14 centers in Japan [6,12–14]. TAVR indications were determined individually based on the center. Surgical risk was defined using the logistic European System for Cardiac Operative Risk Evaluation (logistic-EuroSCORE), EuroSCORE II, and the Society of Thoracic Surgeons Predictive Risk of Mortality (STS) score. Information regarding the occurrence and/or causes of death was obtained from the treating hospital or by contacting the patient's family member(s). The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan defined the minimum requirement of TAVR education product before introducing this technique clinically. Briefly, patient screening was required for the first 25 cases with scheduled TAVR. A global onsite proctor supported the first 8 cases of transfemoral (TF) and non-TF TAVR for all centers. During the study period, the Edwards SAPIEN-XT (Edwards Lifesciences, Irvine, CA) balloon-expandable prosthesis was first introduced in Japan in October 2013. The Medtronic CoreValve Revalving System (Medtronic, Minneapolis, MN) self-expandable prosthesis was utilized starting in January 2016. Thereafter, the SAPIEN-3 (Edwards Lifesciences, Irvine, CA) balloon-expandable prosthesis was developed at the beginning of June 2016. To equalize the time course differences, we divided patients into 4 groups according to the TAVR experience in each center, using 4 quartiles. Regardless of the total center TAVR cases, groups were categorized into Experience 1 (first-quartile: n = 404), Experience 2 (second-quartile: n = 403), Experience 3 (third-quartile: n = 403), and Experience 4 (last-quartile: n = 403). In addition, to investigate the time course differences, we divided patients into 4 groups according to the TAVR date regardless of center number differences. Groups were also categorized into Time 1 (October 2013–November 2014: n = 403), Time 2 (November 2014–September 2015: n = 403), Experience 3 (September 2015–March 2016: n = 403), and Experience 4 (March 2016–July 2016: n = 404).

2.2. Data definition of TAVR procedure

Standard two-dimensional B mode and Doppler transthoracic echocardiography were performed prior to the procedure; the conventional parameters, including the degree of aortic regurgitation (AR), were measured as we previously presented [14]. Complications occurring during TAVR were evaluated according to the Valve Academic Research Consortium-2 (VARC-2) criteria [15]. The definition of cardiovascular mortality was also applied to VARC-2 criteria and included death due to cardiac causes, non-coronary vascular conditions such as stroke with neurological events, procedure-related aortic dissection, rupture, and other vascular diseases. The definition for 30-day early non-safety endpoint was a combination of all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury stage 2–3, coronary obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeated TAVR or SAVR at 30 days. Echocardiographic evaluation was performed at baseline prior to the TAVR procedure and at discharge. Prosthesis-patient mismatch (PPM) was determined by post-procedure echocardiography. PPM severity was defined according to the indexed effective orifice area (iEOA) of the prosthetic valve and is classified as follows: none or mild, >0.85 cm^2/m^2; moderate, 0.85–0.65 cm^2/m^2; severe, <0.65 cm^2/m^2. In patients with body mass index (BMI) <30 kg/cm^2, or 0.90–0.60 cm^2/m^2 (moderate) and <0.60 cm^2/m^2 (severe) in patients with BMI ≥30 kg/cm^2. PPM was also defined according to the VARC-2 criteria.

2.3. Statistical analysis

All statistical analyses were performed using IBM SPSS statistics v22 (SPSS, Inc., Chicago, Illinois, USA). Continuous variables are expressed as mean ± standard deviation and median with interquartile ranges. Differences were tested using the unpaired Student's *t*-test, one-way analysis of variance, or Kruskal–Wallis test depending on variable distribution. Baseline and procedural outcomes were compared between the TF and non-TF groups. The 30-day mortality and early non-safety were assessed according to TAVR experience and time course differences between Experience 1–4 and Time 1–4. The Kaplan–Meier method was used to estimate the cumulative incidence and differences were assessed with the log-rank test. The cumulative mortality rates were also compared among other subgroup focused on STS class (STS <4, STS 4–8, STS ≥8), approach route, and clinical frailty scale (CFS) score (CFS 1–3, CFS 4–6, CFS 7–9). 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

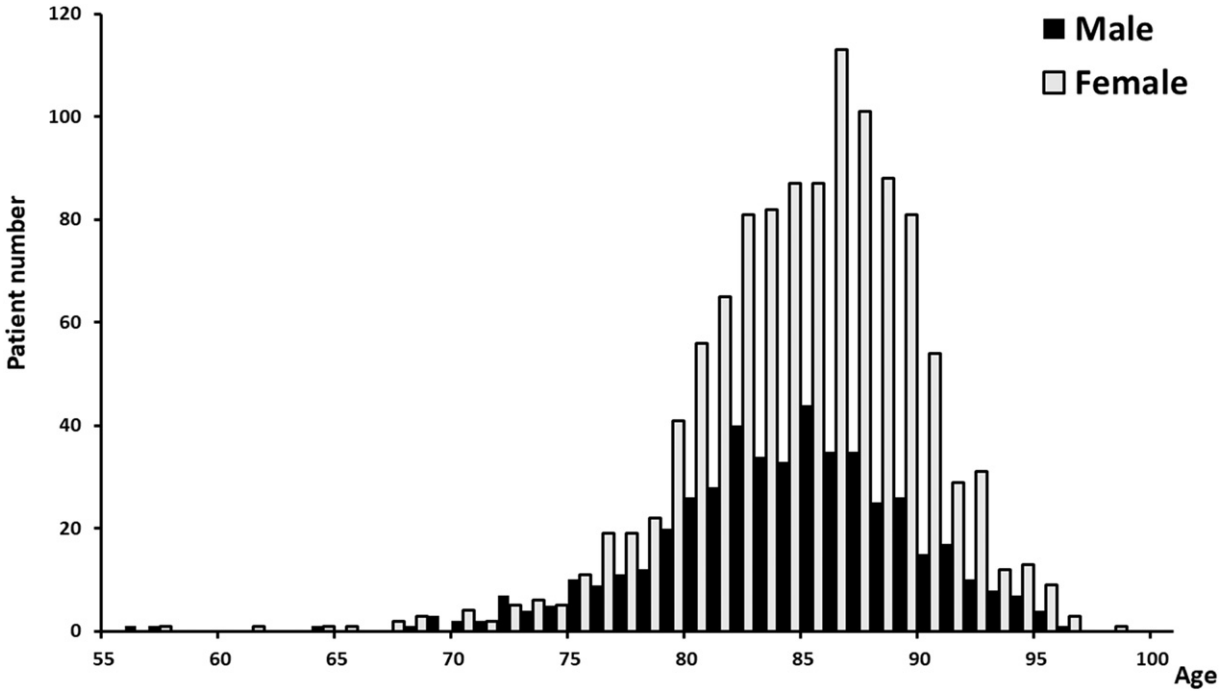

Fig. 1. Distribution of study patients' age for each sex.

with a univariate p value <0.05 in order to examine independent associations of midterm mortality. The statistical tests were all two-sided, and values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Demographics and baseline patient characteristics

The baseline characteristics of study patients are presented in Table 1. Overall age distribution in the entire cohort stratified by sex differences is illustrated in Fig. 1. The prevalence of men, peripheral artery disease, prior percutaneous coronary intervention, prior coronary artery bypass grafting, and prior stroke was higher in the non-TF group than in the TF group (all $p < 0.05$). There were differences in the body characteristics, creatinine, peak velocity, mean gradient between the 2 groups ($p < 0.05$). The all Logistic-EuroSCORE, EuroSCORE II and STS score were higher in the non-TF group (all $p > 0.05$).

3.2. Procedural variables and complications

Procedural variables and complications are shown in Table 2. Procedure time, fluoroscopy time, and dose of contrast media, total hospital length and duration of intensive care unit were significantly increased in the non-TF group than in the TF group (all $p < 0.05$). The non-femoral access rate significantly decreased across the 4 groups, which reflects the newly available SAPIEN-3 and CoreValve with smaller sheath sizes as access route than that of SAPIEN-XT (23.0%, 22.1%, 21.1%, and 15.6%; $p < 0.001$). Most of the annulus rupture cases were caused by using the SAPIEN-XT valve (87.5%, [n = 14/16]). The other causes were the balloon dilatation after CoreValve implantation and pre-dilatation of balloon valvuloplasty. The distributions of SAPIEN-XT, SAPIEN-3, and CoreValve were 82.3% (1328/1613), 8.7% (141/1613), and 8.9% (144/1613), respectively. In 1613 patients, 40 patients were excluded due to absence of iEOA data for the following reasons: conversion to SAVR (n = 10); death before post-procedural echocardiography (n = 16); unreliable data of echocardiography because of left ventricle obstruction or a poor image (n = 13); absence of valve implantation due to delivery failure (n = 1). Baseline and procedural characteristics of PPM in 3 categories (no PPM, moderate PPM, and severe PPM) are shown in Table 3. The overall incidence of moderate and severe PPM was 9.0% (141/1573) and 0.8% (12/1573), respectively. Body height, weight, and body surface area increased across the groups (all $p < 0.05$), although BMI was not different among the 3 groups ($p = 0.23$). The average annulus area showed significant differences among the 3 groups (no PPM: 396.8 ± 68.5 mm^2, moderate PPM: 370.8 ± 62.7 mm^2, severe PPM: 387.3 ± 69.5 mm^2, $p < 0.001$). The incidence of PPM seemed to be higher in SAPIEN-3 group, and smaller valve size such as 20–23 mm in both SAPIEN-XT/3 valve, whereas the prevalence of AR was higher in the CoreValve group.

Table 2
Procedural patient characteristics.

	Overall n = 1613	Q1 n = 404	Q2 n = 403	Q3 n = 403	Q4 n = 403	p value	p for trend
Procedural variables							
Non-elective procedure, n	71 (4.4%)	15 (3.7%)	21 (5.2%)	18 (4.5%)	17 (4.2%)	0.77	0.87
Procedure time, min	88.5 ± 47.7	101.7 ± 39.3	92.0 ± 44.9	87.2 ± 57.4	73.2 ± 42.7	<0.001	<0.001
Fluoroscopy time, min	20.8 ± 10.4	22.4 ± 10.1	19.8 ± 9.6	21.3 ± 12.2	19.8 ± 9.1	0.001	0.006
Contrast medium volume, ml	123.3 ± 60.1	141.1 ± 72.4	122.8 ± 53.4	121.6 ± 53.2	107.8 ± 54.7	< 0.001	< 0.001
Approach plan							
Local anesthesia, n	199 (12.3%)	7 (1.7%)	20 (5.0%)	61 (15.1%)	111 (27.5%)	<0.001	<0.001
Transfemoral approach, n	1283 (79.5%)	311 (77.0%)	314 (77.9%)	318 (78.9%)	340 (84.4%)	0.043	0.010
Non-transfemoral approach, n	330 (20.5%)	93 (23.0%)	89 (22.1%)	85 (21.1%)	63 (15.6%)		
Transapical approach, n	287 (17.8%)	85 (21.0%)	77 (19.1%)	73 (18.1%)	52 (12.9%)		
Transiliac approach, n	30 (1.9%)	7 (1.7%)	12 (3.0%)	8 (2.0%)	3 (0.7%)		
Transaortic approach, n	7 (0.4%)	1 (0.2%)	0 (0%)	3 (0.7%)	3 (0.7%)		
Transsubclavian approach, n	6 (0.4%)	0 (0%)	0 (0%)	1 (0.2%)	5 (1.2%)		
Valve type							
Edwards SAPIEN-XT, n	1328 (82.3%)	404 (100%)	401 (99.5%)	353 (87.6%)	170 (42.2%)		
Edwards SAPIEN3, n	141 (8.7%)	0 (0%)	0 (0%)	0 (0%)	141 (35.0%)	<0.001	<0.001
Medtronic CoreValve, n	144 (8.9%)	0 (0%)	2 (0.5%)	50 (12.4%)	92 (22.8%)		
Procedural complications							
Acute coronary obstruction, n	13 (0.8%)	5 (1.2%)	5 (1.2%)	3 (0.7%)	0 (0%)	0.16	0.035
Disabling stroke, n	27 (1.7%)	8 (2.0%)	8 (2.0%)	7 (1.7%)	4 (1.1%)	0.78	0.35
Acute kidney injury, n	150 (9.3%)	46 (11.4%)	50 (12.4%)	30 (7.4%)	24 (6.0%)	0.003	0.001
Major vascular complication, n	89 (5.5%)	27 (6.7%)	30 (7.4%)	20 (5.0%)	12 (3.0%)	0.027	0.008
Minor vascular complication, n	84 (5.2%)	17 (4.2%)	18 (4.5%)	25 (6.2%)	24 (6.0%)	0.47	0.16
Life-threatening/disabling bleeding, n	94 (5.8%)	35 (8.7%)	22 (5.5%)	26 (6.5%)	11 (2.7%)	0.004	0.001
Major bleeding, n	222 (13.8%)	53 (13.1%)	56 (13.9%)	66 (16.4%)	47 (11.7%)	0.27	0.81
Minor bleeding, n	189 (11.7%)	63 (15.6%)	56 (13.9%)	45 (11.2%)	25 (6.2%)	<0.001	<0.001
Cardiac tamponade, n	26 (1.6%)	8 (1.4%)	5 (1.2%)	7 (3.4%)	1 (1.7%)	0.20	0.27
2 valve implantation, n	21 (1.3%)	7 (1.7%)	4 (1.0%)	6 (1.5%)	4 (1.0%)	0.73	0.49
Annulus rupture, n	16 (1.0%)	4 (1.0%)	4 (1.0%)	7 (1.7%)	1 (0.2%)	0.21	0.50
Surgical conversion, n	20 (1.2%)	5 (1.2%)	6 (1.5%)	5 (1.2%)	4 (1.0%)	0.94	0.69
Post pacemaker implantation (n = 1498)	128 (8.5%)	18/376 (4.8%)	22/370 (5.9%)	41/375 (10.9%)	47/377 (12.5%)	<0.001	<0.001
Balloon-expandable valve, (n = 1366)	97 (7.1%)	18/376 (4.8%)	22/368 (6.0%)	28/329 (8.5%)	29/293 (9.9%)	0.042	0.005
Self-expandable valve (n = 132)	31 (23.5%)	0/0 (0%)	0/2 (0%)	13/46 (28.3%)	18/84 (21.4%)	0.50	0.62
Post AR none-trivial, n	1028 (64.5%)	253/399 (63.4%)	239/397 (60.2%)	256/397 (64.4%)	280/400 (70.0%)		
Post AR mild, n	548 (34.4%)	142/399 (35.6%)	155/397 (39.0%)	135/397 (34.0%)	116/400 (29.0%)	0.13	0.010
Post AR moderate, n	16 (1.0%)	4/399 (1.0%)	3/397 (0.8%)	5/397 (1.3%)	4/400 (1.0%)		
Post AR severe, n	1 (0.1%)	0/399 (0%)	0/397 (0%)	1/397 (0.3%)	0/400 (0%)		
Clinical outcomes							
Hospital stay after procedure, day	11.0 (7.0–16.0)	10.0 (7.0–15.8)	12.0 (8.0–17.0)	11.0 (7.0–17.0)	10.0 (7.0–15.0)	0.009	0.54
Intensive care unit stay, day	1.0 (1.0–3.0)	2.0 (1.0–3.0)	1.0 (1.0–3.0)	1.0 (1.0–3.0)	1.0 (1.0–2.0)	0.001	<0.001
30-day mortality, %	28 (1.7%)	4 (1.0%)	8 (2.0%)	10 (2.5%)	6 (1.5%)	0.40	0.49

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

Table 3
Baseline and procedural characteristics of PPM.

	No PPM	Moderate PPM	Severe PPM	*p* value	*p* for trend
Procedural variables, n = 1573					
Overall, n	1420/1573 (90.3%)	141/1573 (9.0%)	12/1573 (0.8%)		
Height, cm	149.6 ± 9.0	150.9 ± 9.1	153.7 ± 7.5	0.084	0.030
Weight, kg	49.7 ± 10.0	51.7 ± 10.2	52.8 ± 11.6	0.045	0.013
BSA, m^2	1.42 ± 0.17	1.46 ± 0.17	1.49 ± 0.16	0.038	0.011
BMI, kg/m^2	22.1 ± 3.6	22.6 ± 3.3	21.7 ± 4.8	0.23	0.24
Annulus size area by MDCT, mm^2	396.8 ± 68.5	370.8 ± 62.7	387.3 ± 69.5	<0.001	<0.001
Echocardiography variables, n = 1573					
AVA, cm^2	0.64 ± 0.17	0.59 ± 0.16	0.48 ± 0.13	<0.001	<0.001
Indexed AVA, cm^2/m^2	0.45 ± 0.11	0.41 ± 0.11	0.33 ± 0.09	<0.001	<0.001
Pre peak velocity, m/s	4.57 ± 0.80	4.48 ± 0.78	4.78 ± 0.50	0.25	0.46
Pre mean gradient, mmHg	50.6 ± 17.9	49.1 ± 18.0	55.4 ± 14.6	0.42	0.74
EOA, cm^2	1.76 ± 0.42	1.14 ± 0.16	0.85 ± 0.14	<0.001	<0.001
Indexed EOA, cm^2/m^2	1.24 ± 0.28	0.78 ± 0.05	0.58 ± 0.02	<0.001	<0.001
Post peak velocity, m/s	2.17 ± 0.41	2.41 ± 0.49	2.44 ± 0.42	<0.001	<0.001
Post mean gradient, mmHg	9.9 ± 3.7	12.8 ± 4.7	13.9 ± 5.0	<0.001	<0.001
Valve differences					
Edwards SAPIEN-XT, n = 1293	1181/1293 (91.3%)	103/1293 (8.0%)	9/1293 (0.7%)		
Edwards SAPIEN-3, n = 140	115/140 (82.1%)	24/140 (17.1%)	1/140 (0.7%)	0.007	0.001
Medtronic CoreValve, n = 140	124/140 (88.6%)	14 /140 (10.0%)	2/140 (1.4%)		
Valve size of Edwards SAPIEN-XT, n = 1293					
20 mm, n = 30	21/30 (70.0%)	8 (26.7%)	1/30 (3.3%)		
23 mm, n = 777	699/777 (90.0%)	73/777 (9.4%)	5/777 (0.6%)	<0.001	<0.001
26 mm, n = 433	409/433 (94.5%)	22/433 (5.1%)	5/433 (0.6%)		
29 mm, n = 53	52/53 (98.1%)	0	1/53 (1.9%)		
Valve size of Edwards SAPIEN-3, n = 140					
20 mm, n = 1	0	1/1 (100%)	0		
23 mm, n = 87	68/87 (78.2%)	18/87 (20.7%)	1/87 (1.1%)	0.18	0.020
26 mm, n = 46	14/46 (89.1%)	5/46 (10.9%)	0		
29 mm, n = 6	6/6 (100%)	0	0		
Valve size of Medtronic CoreValve, n = 140					
26 mm, n = 76	67/76 (88.2%)	8/76 (10.5%)	1/76 (1.3%)	0.97	0.92
29 mm, n = 64	57/76 (89.1%)	6/64 (9.4%)	1/64 (1.6%)		

Values are numbers (%) or mean ± SD. PPM, prosthesis patient mismatch; EOA, effective orifice area; MDCT, multidetector computed tomography, other abbreviations as in Table 1.

3.3. Combined 30-day early non-safety endpoint and 30-day mortality

The incidence of 30-day mortality is shown in Fig. 2. The overall 30-day mortality was 1.7% (28/1613). During the follow-up period, the 30-day mortality was not different based on center experience differences (Experience 1: 1.0% [4/404], Experience 2: 2.0% [8/403], Experience 3: 2.5% [10/403], Experience 4: 1.5% [6/403], $p = 0.40$) and time course differences (Time 1: 1.7% [7/403], Time 2: 2.5% [10/403], Time 3: 1.2% [5/403], Time 4: 1.5% [6/404], $p = 0.56$). The 30-day mortality was 0% (0/179) under on-site proctor in patients underwent TF-TAVR regardless of valve differences (SAPIEN-XT: 0% [0/112], and CoreValve: 0% [0/67], respectively), whereas the 30-day mortality of transapical TAVR using SAPIEN-XT was 4.7%. The incidence of combined early non-safety is shown in Fig. 3. The overall early combined non-safety was 15.1%. Early non-safety was significantly improved with the increased center experience (Experience 1: 19.1% [77/404], Experience 2: 17.9% [72/403], Experience 3: 14.6% [59/403], Experience 4: 8.9% [36/403], $p < 0.001$) and time course differences (Time 1: 18.4% [74/403], Time 2: 18.4% [74/403], Time 3: 15.4% [62/403], Time 4: 8.4% [34/404], $p < 0.001$). Under on-site proctor supports, the early non-safety was 9.8% in TF-TAVR using SAPIEN-XT, 11.9% in TF-TAVR using CoreValve, and 33.0% in transapical TAVR using SAPIEN-XT.

3.4. Cumulative 1-year mortality

The Kaplan-Meier curves showed that the cumulative 1-year all-cause, cardiovascular mortalities were 11.3% and 4.5% (Fig. 4A). Other subgroup analyses are shown in Fig. 4B–D. The cumulative 1-year mortality rates showed significant differences between the TF and non-TF groups (TF: 9.2% vs. non-TF: 19.4%; Log-rank test, $p < 0.001$). The cumulative 1-year mortality rates were similar in the STS <4 and STS 4–8 groups (7.3% vs. 7.2%); however, they were higher in the STS >8 group (18.2%). As a result, there were significant differences among the 3 groups stratified by STS score ($p < 0.001$). The cumulative 1-year mortality rates were significantly increased across the 3 CFS groups (CFS 1–3, 8.0% vs. CFS 4–6, 11.7% vs. CFS 7–9, 38.2%; $p < 0.001$).

3.5. Predictive factors of midterm mortality

All survived patients were clinically followed for at least 30 days. The median follow-up duration was 326 days (102.0–449.8). A total of 174 patients with all-cause death were identified during the follow-up period; 28 patients (16.1%) died within 30 days and the remaining 146 patients (83.9%) died beyond 30 days of the TAVR procedure. Cardiac death occurred in 39.1% (68/174) of patients and non-cardiac death in 60.9% (106/174). The Cox-regression analysis results for the association between all-cause mortality and clinical findings are presented in Table 4. Multivariate Cox regression indicated that men (HR: 1.48; 95% CI: 1.06–2.06; $p = 0.020$), CFS (HR: 1.49; 95% CI: 1.11–1.99; $p = 0.008$), New York Heart Association (NYHA) class III/IV (HR: 1.72; 95% CI: 1.11–2.40; $p = 0.002$), creatinine (HR: 1.43; 95% CI: 1.19–1.73; $p < 0.001$), albumin <3.5 (HR: 2.11; 95% CI: 1.52–2.93; $p < 0.001$), hemoglobin (HR: 0.84; 95% CI: 0.76–0.94; $p = 0.001$), liver disease (HR: 1.94; 95% CI: 1.03–3.68; $p = 0.041$), and non-TF approach (HR: 1.60; 95% CI: 1.13–2.26; $p = 0.007$) were independent predictors of midterm mortality.

4. Discussion

The current Japanese multicenter registry data firstly demonstrated acceptable early non-safety and mortality rates following TAVR at the initial adaption of a new technique in Japan using mainly a first-generation balloon-expandable device. Notably, the entire 30-day mortality rate was 1.7% and was not significantly influenced among differences in center experience and time course. Recent national based

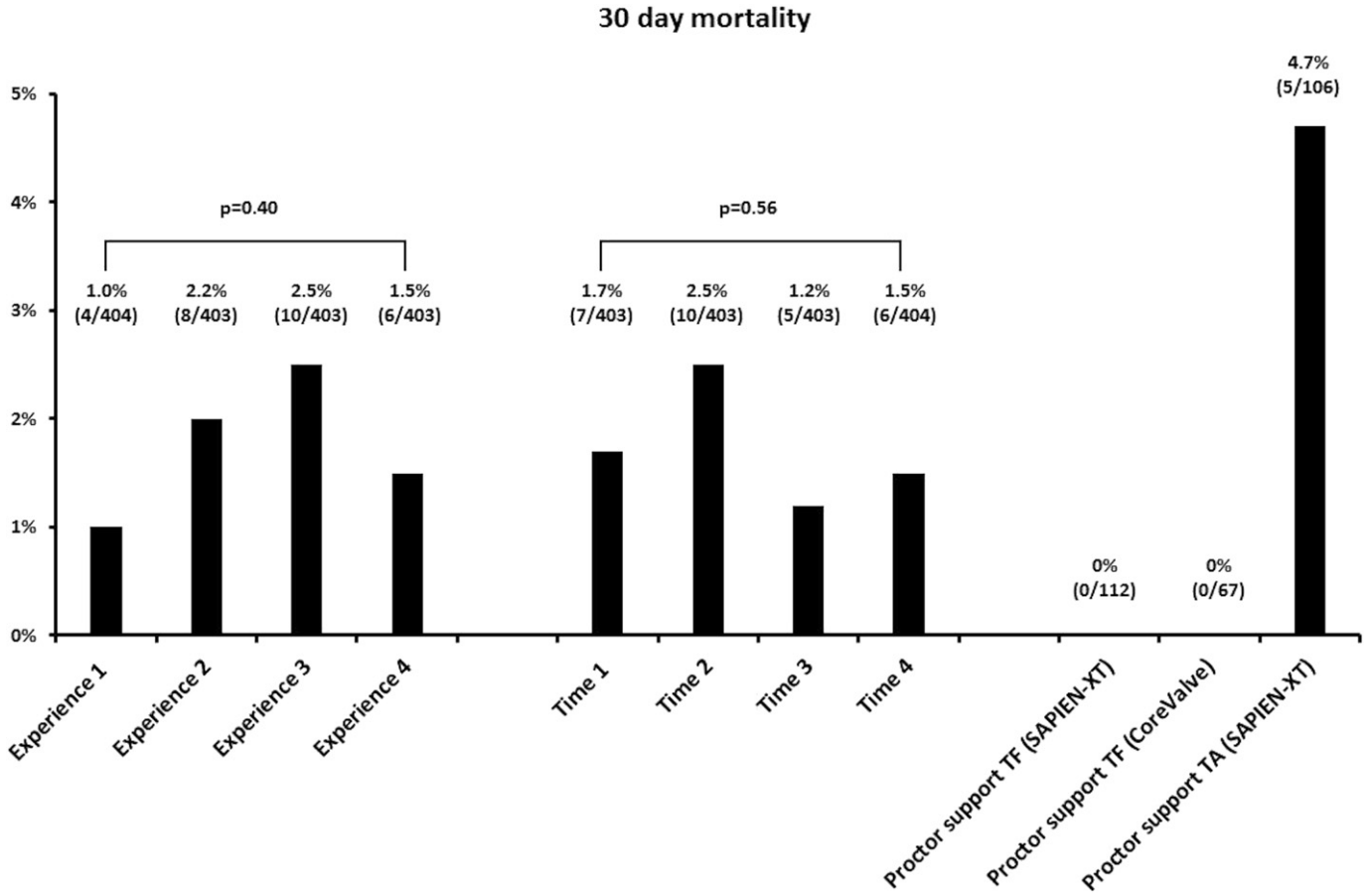

Fig. 2. Distributions of 30-day mortality among experience, procedure phase quartile, and proctor support TAVR. TF = transfemoral.

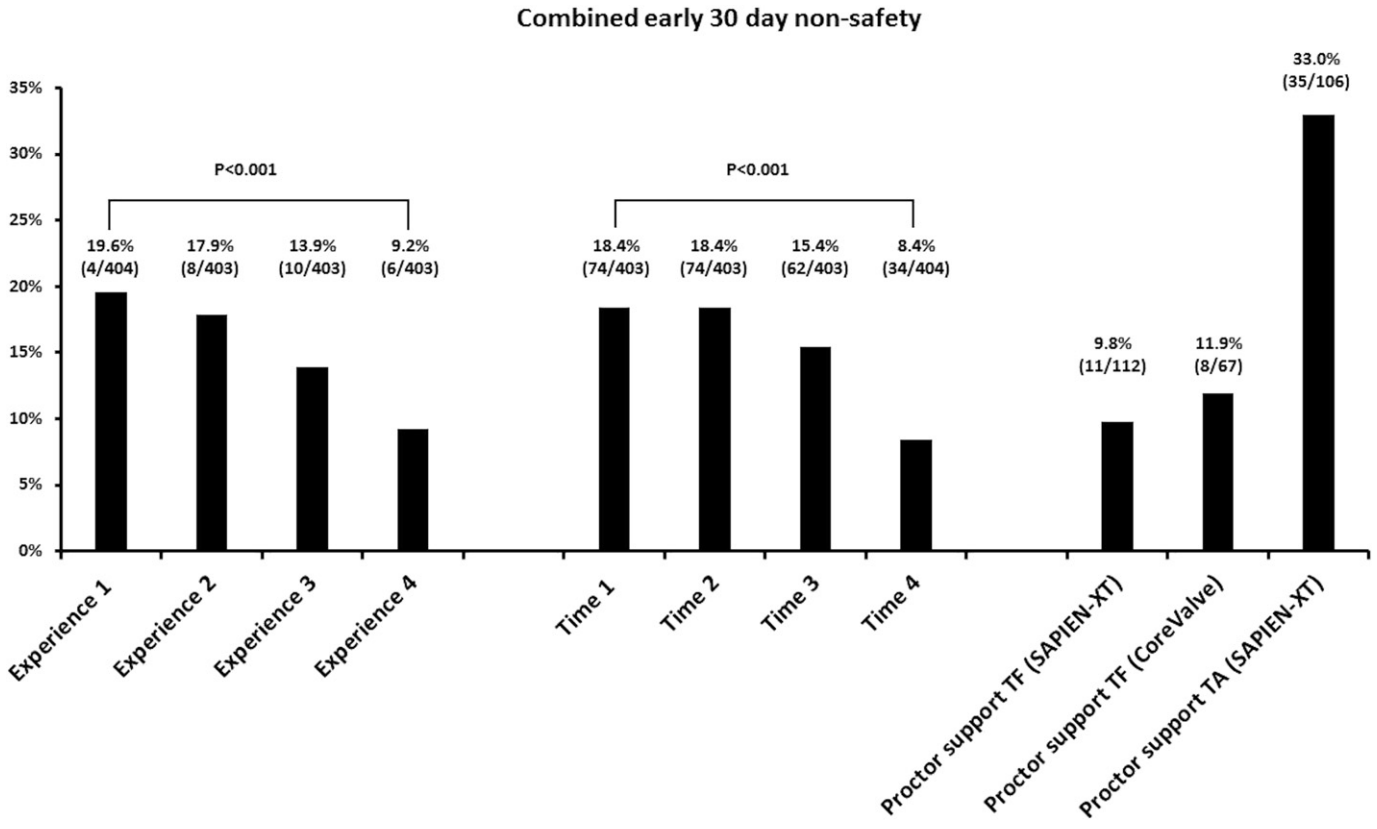

Fig. 3. Distributions of combined 30-day early non-safety among experience, procedure phase quartile, and proctor-supported TAVR. TF = transfemoral.

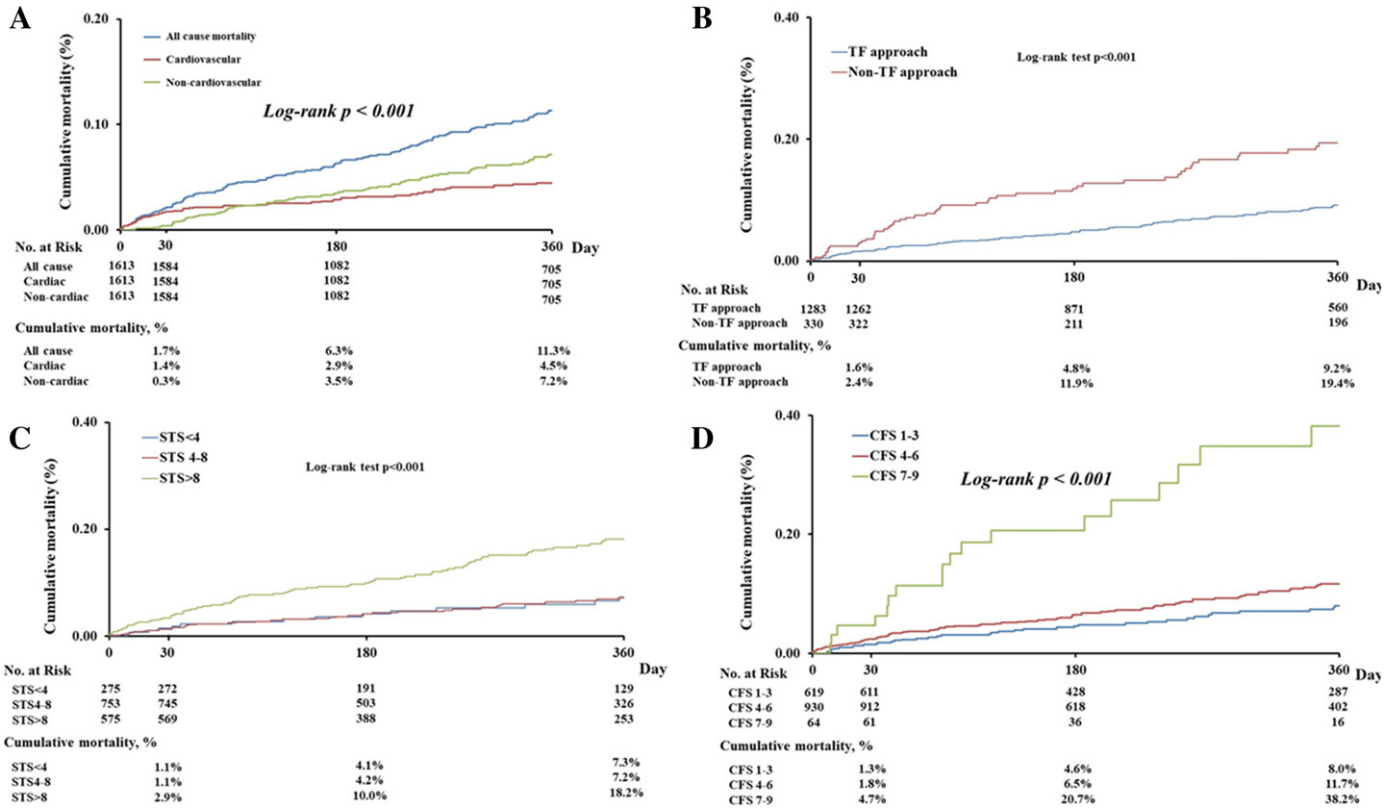

Fig. 4. Kaplan–Meier curves showing cumulative cardiovascular and non-cardiovascular mortality in the subgroups of approach routes, STS score, and CFS. TF = transfemoral, STS = Society of Thoracic Surgeons Predictive Risk of Mortality, CFS = clinical frailty scale.

data from the Transcatheter Valve Therapy (TVT), FRANCE 2, a large scale global registry of SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) 3, and Asian TAVR registry data revealed a significant improvement of 30-day mortality rates ranging from 10% to 2% with increasing TAVR procedure experience [7–10]. The current results are unique in that they contradict data from western countries and other Asia countries. As reported in our previous study, we believe this can be explained by applying a specific global supporting system before the introduction of the TAVR procedure in Japan [6]. In detail, online patient screening was mandatory for the first 25 cases with scheduled TAVR in each center. If the planning case was decided not suitable for TAVR due to anatomical features by the screening proctor, it was recommended to decline or postpone the procedure until the center gained more experience. PMDA defined the minimum requirement with the global on-site proctor supported the first 8 cases of TF and non-TF TAVR for all centers. Although an adequate number of cases supported by on-site proctor remain uncertain, the practice of the well-experienced operator will eradicate worries about a less experienced cardiac team. As a result, the 30-day mortality of TF cases under proctor was surprisingly maintained at 0%, minimizing the learning curve. However, the proctor-supported transapical TAVR was thought to be still challenging with relatively high 30-day mortality (4.7%) and combined early 30-day non-safety (33.0%). We should continue to seek an optimal planning and management method in patients scheduling transapical approach procedure.

The combined early non-safety and procedural complications were significantly decreased with the development of center experiences in agreement with TVT, FRANCE 2, SOURCE 3, and recent registry data [7–9,11]. A narrow access route was generally considered to be a cause of vascular complications in patients [16]. A small aortic valve complex close to the conduction node of the aortic annulus may increase the need of pacemaker implantation following TAVR. However, the results of combined early non-safety including vascular complications (5.5%) and pacemaker implantation rates (8.5%) were low. Specific complications such as coronary occlusion and annulus rupture were also very low rates as 0.8% and 1.0%, respectively. The feature of acute coronary occlusion was previously reported in our data [17]. Annulus rupture was mainly occurred in SAPIEN-XT valve, thus the complication rates were decreasing. These were comparable to previous western studies, as well as the Asian TAVR registry [7–11]. In addition, early non-safety in Experience 4 and Time 4 was 9.2% and 8.4%, owing to the next generation device in this quartile. The rates of the TF approach significantly increased in the later phase, which allowed the use of smaller-diameter sheaths with the new device. Especially with SAPIEN-3, the rate of major vascular complications decreased up to 2.8% and the combined early non-safety rate was 5.0% in this study (data not shown). Our study showed significant complication reduction using SAPIEN-3 compared with that of the use of other valves, which correlated with previous reports [9,10]. The OCEAN-TAVI registry is ongoing study involving several centers in Japan. The total volume and timing of the introduced TAVR procedure varied by center. In addition, the TAVR devices were also improved during the follow-up period in this study. When considering the complexity of the clinical scenarios, it is difficult to generalize the results of this study completely. Nonetheless, complication rates (combined early non-safety) showed significant reduction across Q1 to Q4 and T1 to T4. Both center experience and device technology are important for procedural safety improvements.

The cumulative 1-year mortality is 11.3% overall, 9.2% in TF, 7.2% in STS <4, and 7.3% in STS 4–8. Interestingly, we could not find any differences in the cumulative 1-year mortality rates between STS <4% (low risk) and STS 4–8 (intermediate risk). The midterm clinical outcomes were comparable to a previous intermediate risk study in Western and Asian populations [3,7–11]. We herein proved that men, CFS, NYHA class III/IV, creatinine, albumin <3.5, hemoglobin, liver disease, and non-TF approach were independent predictors of midterm mortality, although he prognostic value of STS score as traditional surgical risk

Table 4
Cox-regression analysis for the association between all-cause mortality and clinical findings.

	Univariate analysis			Multivariate analysis		
Explanatory variables	HR	95% CI	*p* value	HR	95% CI	*p* value
Adjusting factors						
Age (per 1 category increase)[a]	0.99	0.96–1.02	0.39	0.88	0.99–1.04	0.13
Men (for Women)	1.42	1.03–1.95	0.032	1.48	1.06–2.06	0.020
BMI <20 (for BMI ≥20)	1.42	1.04–1.93	0.028	1.31	0.95–1.79	0.097
CFS (per 1 category increase)[a]	1.88	1.42–2.49	<0.001	1.49	1.11–1.99	0.008
STS (per 1.0 increase)	1.80	1.42–2.26	<0.001	1.00	0.99–1.02	0.68
Experience (quartile)	1.13	0.97–1.33	0.12	–		
NYHA class III/IV (for NYHA class I/II)	2.35	1.69–3.26	<0.001	1.72	1.11–2.40	0.002
Creatinine (per 1.0 mg/dL increase)	1.76	1.52–2.05	<0.001	1.43	1.19–1.73	<0.001
Albumin <3.5 (for albumin ≥3.5 g/dL)	3.26	2.41–4.40	<0.001	2.11	1.52–2.93	<0.001
Hemoglobin (per 1.0 g/dL increase)	0.74	0.67–0.81	<0.001	0.84	0.76–0.94	0.001
Peripheral artery disease	1.82	1.28–2.59	0.001	1.14	0.78–1.67	0.51
Prior MI	1.43	0.87–2.33	0.16	–		
Prior PCI	1.10	0.79–1.53	0.59	–		
Prior CABG	1.38	1.10–1.73	0.006	1.58	0.99–2.53	0.058
Prior stroke	1.42	0.96–2.11	0.076	–		
Diabetes mellitus	1.37	0.99–1.89	0.059	–		
Hypertension	1.13	0.78–1.65	0.52	–		
Pulmonary disease	1.51	1.10–2.07	0.011	1.37	0.99–1.89	0.053
Liver disease	2.59	1.40–4.78	0.002	1.94	1.03–3.68	0.041
Active cancer	1.26	0.71–2.21	0.43	–		
LVEF (per 1.0% increase)	1.00	0.99–1.01	0.63	–		
Non-TF (for TF)	1.92	1.40–2.64	<0.001	1.60	1.13–2.26	0.007

HR, hazard ratio; CI, confidence interval; other abbreviations as in Table 1.
[a] Categorized as age < 80, 80–84, 85–90, ≥90, CFS 1–3, 4–6, 7–9.

model was attenuated in the multivariate Cox-regression model. These were correlated with previous our study and other clinical investigations [13,18–21]. When considering TAVR indications, this information may be useful for risk stratification before TAVR.

Another clinical concern about TAVR valve function in the specific is small body, as seen in Asian cohorts. Moreover, knowing how the small valve performs in a small annulus is critically important when considering the valve-in-valve strategy that mainly requires a small bioprosthesis. In this series, 8.7% patients developed moderate to severe PPM. In the balloon-expandable bioprosthesis, the incidence of PPM was decreased in the larger valve size group. Especially in the 29-mm balloon-expandable bioprosthesis, the incidence of PPM <2% was quite low. In contrast, the incidence of PPM between 26-mm and 29-mm self-expandable bioprostheses was similar at 10%. This may be informative when considered the selection of bioprosthesis regarding PPM avoidance. A previous report revealed that moderate–severe PPM was less frequently observed in a TAVI group than in a SAVR group, among patients with a small annulus, presumably due to the absence of a sewing ring in TAVR [22]. Several studies of SAVR in Japanese patients indicated that the incidence of moderate–severe PPM was 20–30%, which is higher than that observed in the TAVI cohort in this study [23,24]. The lower incidence of PPM in this study's cohort, as compared with that in previous studies, suggests that TAVI could represent a favorable approach to avoid PPM, particularly among patients with a small aortic annulus. Another clinical study suggested that TAVI could serve as a valuable alternative to SAVR to prevent PPM in patients with small aortic annulus [25]. We proved the effectiveness of TAVR valve with an extremely small native annulus [26]. However, the slight increased risk of moderate PPM of about 20% in patients receiving 20–23-mm SAPIEN-XT/3 valves should be noted. Although the prevalence of severe PPM is approximately 1.0%, even with 20–23-mm SAPIEN-XT/3 valves, long-term valve performance and prognostic value of PPM should be investigated in patients where a small TAVR valve is deployed should be investigated in future studies.

5. Limitations

Several study limitations should be addressed. Firstly, the OCEAN-TAVI registry is not a randomized study; thus, there were differences in the baseline clinical characteristics. In this study, subjects were divided into 4 groups according to experience and time course in each phase of the TAVR procedure. However, such comparison groups were thought to be arbitrary, not physiological and mechanistic classifications. Therefore, we should not overstate our conclusion and highlight the speculative subgroup analysis in this study. Given the very homogeneous Japanese population data, baseline characteristics such as small body size and higher proportion of women are characteristic compared with those of western countries. Race-specific differences might enhance the generalizability of clinical registry data. Secondly, pre-procedural evaluations, including MDCT or echocardiography, were performed separately in each study center; hence, inter-observer variability should be considered. This study primarily provides outcomes of the classical SAPIEN-XT device. Clarifying clinical TAVR data concerning the self-expandable CoreValve and next generation SAPIEN-3 were outside the scope of the present study. Such a limited therapeutic choice leads to the overutilization of the available device, which may result in unfavorable outcomes. Hence, further investigation with other devices in a larger study cohort is our future target. Lastly, we should not overstate the low 30-day mortality observed. The authors would like to highlight that considerable knowledge of screening methods, and tips and tricks of the TAVR procedure were gained from preceding Western experiences, although this is a great first step to consider for the safe introduction of a novel technique to minimize the learning curve.

6. Conclusion

The initial results of early and midterm clinical outcomes in Japan were excellent. The current global supporting system could achieve significant risk reduction of early mortality and safety with the development of center experiences. Although the generalization of this effective system to other centers remains uncertain, the results of this study may be a pivotal model when introducing new technology in the clinical field.

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