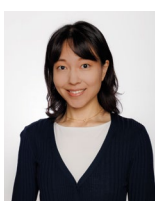


Differences between Japan and France in transcatheter aortic valve implantation: insights from the TOTO-TAVI study



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ABSTRACT

BACKGROUND: The number of transcatheter aortic valve implantation (TAVI) procedures is increasing worldwide. However, studies comparing regional differences remain scarce.

AIMS: This study aimed to compare clinical outcomes after TAVI between Japan and France using a database compiled from two large hospitals.

METHODS: The TOTO-TAVI study included patients who underwent TAVI in Japan and France. The primary endpoint was in-hospital death. Periprocedural safety outcomes and 3-year all-cause mortality were also evaluated. A subgroup analysis was performed to assess the independent TAVI risk for each country.

RESULTS: Among 6,967 patients who underwent TAVI between 2016 and 2024, 1,422 in Japan and 4,771 in France were included. Although patients in Japan showed a significantly smaller body size, a smaller aortic valve, and a higher operative risk than those in France, the in-hospital death rate was comparable between the two groups (0.6% vs 1.3%; $p=0.068$). The new pacemaker implantation rate was lower in Japan than in France. There was no significant difference in 3-year all-cause mortality between Japan and France (22.5% vs 23.5%, hazard ratio 0.678, 95% confidence interval: 0.114-4.033; $p=0.583$). For the subgroup analysis, there were no statistically significant independent risk factors for composite outcomes, including in-hospital death, stroke, and bleeding, in Japan; however, in France, female sex, higher body mass index, lower haemoglobin levels, previous coronary artery bypass grafting and cerebrovascular disease, bicuspid annulus, and general anaesthesia were independent risk factors.

CONCLUSIONS: Despite differences in patient backgrounds, in-hospital and 3-year mortality were comparable between Japan and France, suggesting that procedural safety and medium-term prognosis after TAVI were established regardless of procedural risks.

KEYWORDS: Asia; clinical outcomes; Europe; periprocedural risks; transcatheter aortic valve implantation

The excellent clinical outcomes of transcatheter aortic valve implantation (TAVI) for the short- to midterm are well established,¹⁻⁴ and the indications for TAVI are rapidly expanding to include younger and lower-risk patients with aortic stenosis.^{5,6} Therefore, the number of TAVI cases is increasing worldwide. Consequently, understanding the patient population and clinical characteristics of TAVI has become increasingly important. Recent studies, including a pivotal randomised controlled trial, have placed particular emphasis on patients with a small aortic annulus.⁷⁻⁹ This issue is particularly pertinent for the Asian population, who frequently have a small aortic annulus and are more likely to experience prosthesis-patient mismatch (PPM) and elevated transvalvular pressure gradients (PGs) when treated with TAVI.¹⁰⁻¹³ However, despite TAVI being performed using a common device system worldwide, studies evaluating regional differences in TAVI outcomes remain limited. Previous studies – initiated in Europe when TAVI was introduced – comparing early outcomes in Asia with those in Europe demonstrated that TAVI could be safely implemented even in smaller-framed Asians.^{14,15} Recently, however, TAVI devices have evolved, and treatment strategies are becoming established. As in the era anticipating the expansion of TAVI indications to broader populations, it will be crucial to develop treatment strategies informed by an understanding of regional differences. This study aimed to compare clinical outcomes after TAVI between Asia and Europe using the latest database from two large hospitals.

Methods

STUDY COHORT

The Tokyo-Toulouse-Transcatheter Aortic Valve Implantation (TOTO-TAVI) study is an ongoing prospective multicentre cohort study involving patients with aortic stenosis undergoing TAVI. This registry was conducted at Keio University Hospital (Tokyo, Japan) and at Clinique Pasteur (Toulouse, France). These two centres were among the hospitals that had the largest case numbers in each country. Data were collected from all consecutive patients undergoing TAVI for severe aortic stenosis using SAPIEN 3 (Japan, 2016-2023; France, 2016-2024), SAPIEN 3 Ultra (France, 2023-2024), SAPIEN 3 Ultra RESILIA (Japan, 2023-2024; all SAPIEN devices: Edwards Lifesciences), Evolut R (Japan, 2016-2019; France, 2016-2022), Evolut PRO (Japan, 2018-2021; France, 2017-2023), Evolut PRO+ (Japan, 2020-2023; France, 2021-2024), Evolut FX (Japan, 2022-2024; France, 2022-2024; all Evolut devices: Medtronic), Navitor (Japan, 2022-2024; France, 2022-2024), or Navitor Vision (Japan, 2024; both Navitor devices: Abbott) between May 2016 and October 2024 at two centres. The valves used in France included several devices not used in Japan (such as Myval [Meril Life Sciences] or ACURATE [Boston Scientific] series), which were excluded from analysis. Device selection was determined by each institutional Heart Team.

The baseline clinical, procedural, and follow-up data were prospectively captured and recorded in a dedicated database. All procedural complications were defined according to the Valve Academic Research Consortium (VARC)-3 criteria and were systematically collected.⁶ Patients undergoing valve-in-valve or transcatheter aortic valve (TAV)-in-TAV procedures were excluded from the current analysis. This study was

Impact on daily practice

The number of transcatheter aortic valve implantation (TAVI) procedures is increasing worldwide, but studies comparing regional differences remain scarce. The TOTO-TAVI study, which included patients who underwent TAVI in Japan and France, suggested that although patients in Japan showed a significantly smaller body size, a smaller aortic valve, and a higher operative risk than those in France, the in-hospital death rate was comparable between the two groups and there was no significant difference in 3-year all-cause mortality between Japan and France. This study suggests that procedural safety and medium-term prognosis after TAVI were established regardless of the procedural risks.

conducted in compliance with the principles of the Declaration of Helsinki. All patients provided informed consent for the use of their medical records for research purposes.

ENDPOINT DEFINITIONS

The primary endpoint of this study was in-hospital death in patients undergoing TAVI. Periprocedural safety outcomes, including in-hospital death, cardiovascular death, conversion to open surgery, coronary obstruction, disabling stroke, transient ischaemic attack, acute kidney dysfunction, major bleeding, minor bleeding, major vascular complication, minor vascular complication, new pacemaker implantation, and new onset of atrial fibrillation, were evaluated. Each outcome has been defined with reference to the VARC-3 definition.⁶ Three-year all-cause mortality was also evaluated. A subgroup analysis was performed to assess TAVI risks according to each country using multivariable analysis. The composite in-hospital outcomes included death, all strokes, and all bleeding after TAVI.

ECHOCARDIOGRAPHY AND LABORATORY TESTS

Transthoracic echocardiography and laboratory tests were performed before the procedure and at discharge after TAVI. PPM was categorised based on prosthesis effective orifice area (EOA) indexed to body surface area as severe (≤ 0.65 cm²/m²) or moderate (>0.65 cm²/m² to 0.85 cm²/m²) in the non-obese population, and as severe (≤ 0.55 cm²/m²) or moderate (>0.55 cm²/m² to 0.70 cm²/m²) in the obese population (those with a body mass index ≥ 30 kg/m²).¹⁶ Experienced echocardiographers analysed the results.

STATISTICAL ANALYSIS

Categorical variables are reported as frequencies and percentages, and differences were evaluated using the chi-square test or two-tailed Fisher's exact test. Continuous variables are presented as mean $\pm$ standard deviation or median with interquartile range (IQR) and were compared between groups using the two-sample t-test or the Mann-Whitney U test as appropriate. Multivariable logistic regression analyses were performed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the clinical endpoints. The regression model was constructed based on the 17 baseline variables that may have affected the study outcomes. The

variables included age, sex, body mass index, haemoglobin, New York Heart Association (NYHA) Class III or IV, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, atrial fibrillation, chronic pulmonary disease, chronic kidney disease, peripheral artery disease, previous coronary artery bypass grafting, previous cerebral vascular disease, left ventricular ejection fraction, bicuspid annulus, transfemoral approach, local anaesthesia, and self-expanding valves. All p-values were two-sided; a p-value<0.05 was considered statistically significant for all tests. For the analysis of 3-year all-cause mortality, the missing follow-up data were imputed using multiple imputation. After multiple imputation, the Cox regression model was used to calculate hazard ratios (HRs) and 95% CIs for the clinical endpoints. The model was constructed based on the 16 variables that could potentially affect study outcomes: age, sex, body mass index, haemoglobin, chronic kidney disease, chronic pulmonary disease, coronary artery disease, peripheral artery disease, NYHA Class III or IV, STS-PROM score, atrial fibrillation, left ventricular ejection fraction, annulus area, local anaesthesia, balloon-expandable or self-expanding valve, and severe PPM. All data analyses were performed using SPSS Statistics, version 29.0 (IBM).

Results

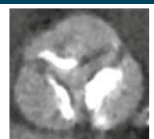
STUDY POPULATION AND BASELINE CHARACTERISTICS

Among 6,967 consecutive patients who underwent TAVI between May 2016 and October 2024 at Clinique Pasteur

and Keio University Hospital, 4,771 and 1,422 patients, respectively, met the inclusion criteria and were analysed (**Central illustration, Figure 1**). The baseline characteristics of the cohort are presented in **Table 1**. There were many significant differences in the background characteristics between Japan and France, including age (84.4 ± 5.5 years vs 83.4 ± 5.9 years), male sex (39.0% vs 54.0%), body mass index (22.5 ± 3.7 kg/m² vs 26.5 ± 5.0 kg/m²), body surface area (1.45 ± 0.18 m² vs 1.76 ± 0.22 m²), STS-PROM score (5.0 [IQR 3.5-7.8]% vs 3.6 [IQR 2.4-5.5]%), haemoglobin level (11.7 ± 1.6 g/dL vs 12.8 ± 1.6 g/dL), hypertension (72.7% vs 78.2%), haemodialysis (8.6% vs 1.4%), chronic pulmonary disease (8.9% vs 15.8%), chronic kidney disease (73.0% vs 49.7%), coronary artery disease (33.1% vs 42.2%), peripheral artery disease (8.9% vs 12.6%), the incidence of left bundle branch block (3.2% vs 10.6%), and history of percutaneous coronary intervention (19.4% vs 29.8%; p<0.001 for all comparisons). In echocardiographic evaluation before TAVI, comparing Japan and France, there were differences in aortic valve area (0.63 ± 0.18 cm² vs 0.80 ± 0.23 cm²), indexed aortic valve area (0.43 ± 0.12 cm²/m² vs 0.45 ± 0.14 cm²/m²), peak flow velocity (4.6 ± 0.71 m/s vs 4.2 ± 0.62 m/s), left ventricular ejection fraction ($62.4 \pm 10.5\%$ vs $59.1 \pm 11.9\%$), systolic pulmonary artery pressure (33.0 ± 10.8 mmHg vs 42.1 ± 11.0 mmHg; p<0.001 for all). In computed tomography assessment before TAVI, patients in Japan showed significantly smaller anatomy than those in France, including annulus area (399 ± 72 mm² vs 458 ± 94 mm²), annulus perimeter (22.9 ± 2.0 mm vs

Comparison of patient backgrounds and clinical outcomes of transcatheter aortic valve implantation in Asia and Europe.

6,967 patients underwent TAVI from May 2016 to October 2024
The TOTO-TAVI study



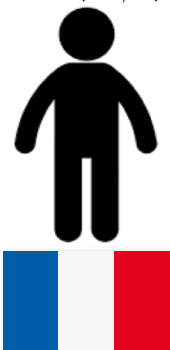
Aortic annulus area ≤ 430 mm²
69.3% vs 40.1%

Japan (N=1,422)

France (N=4,771)



Height (cm)
152 vs 164
Body weight (kg)
52 vs 72
Body surface area (m²)
1.45 vs 1.76
Vascular diameter (mm)
6.3 vs 8.3



Mortality (%)

Japan vs France

In-hospital

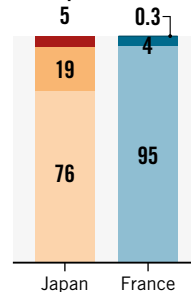
0.6 vs 1.3 p=0.068

3-year

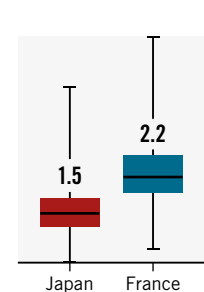
22.5 vs 23.5

HR 0.68, 95% CI: 0.11-4.0 p=0.22

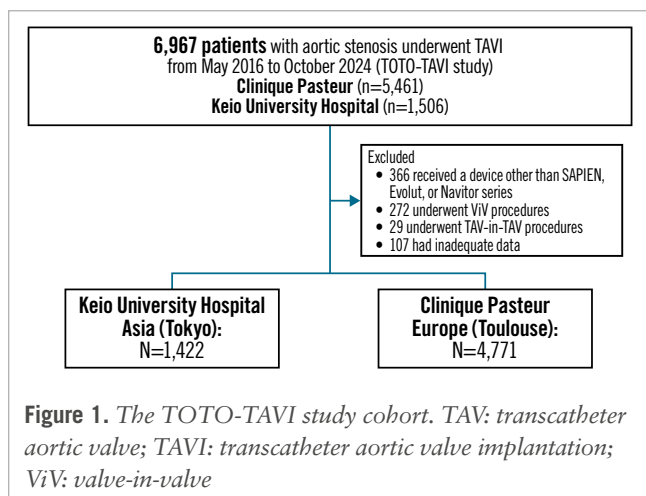
Prosthesis-patient mismatch (%)



Effective orifice area (cm²)



The short-term TAVI outcomes were favourable in both Japan and France, regardless of the differences in patient backgrounds



24.5±2.5 mm), minimum lumen diameter (right: 6.3±1.2 mm vs 8.3±1.7 mm, left: 6.1±1.2 mm vs 8.2±1.7 mm; $p<0.001$ for all comparisons).

PROCEDURAL CHARACTERISTICS AND ECHOCARDIOGRAPHIC OUTCOMES

Periprocedural characteristics are summarised in **Table 2** and **Figure 2**. The proportions of patients managed with the transfemoral approach and local anaesthesia were significantly higher in Japan than in France (transfemoral: 98.7% vs 97.8%; $p=0.041$; local anaesthesia: 97.8% vs 96.8%; $p=0.044$), though the differences were small. Differences in valve types showed a higher prevalence of balloon-expandable valves in Japan and self-expanding valves in France (SAPIEN: 79.0% vs 33.1%; Evolut: 15.5% vs 63.4%; Navitor: 5.5% vs 3.5%; $p<0.001$). Furthermore, based on anatomical differences in the aortic valve complex, the valve sizes used were significantly smaller in Japan compared with in France. Regarding the echocardiographic evaluations, patients in Japan had a significantly smaller EOA (1.53 ± 0.42 cm² vs 2.30 ± 0.59 cm²) and indexed EOA (1.05 ± 0.28 cm²/m² vs 1.31 ± 0.37 cm²/m²), resulting in a higher incidence of PPM (none: 74.3% vs 82.7%; moderate: 18.6% vs 3.6%; severe: 5.2% vs 0.3%; all $p<0.001$). The peak flow velocity and mean PG were also higher in patients in Japan than in France (peak flow velocity: 2.4 ± 0.50 m/s vs 2.0 ± 0.44 m/s; mean PG: 11.9 ± 5.3 mmHg vs 9.4 ± 4.2 mmHg; all $p<0.001$).

COMPLICATIONS AND CLINICAL OUTCOMES

Periprocedural complications and other clinical outcomes are shown in **Table 3**. The rate of in-hospital death, the primary endpoint, was comparable between patients in Japan and in France (0.6% vs 1.3%; $p=0.068$). The rates of cardiovascular death (0.2% vs 1.0%; $p=0.003$), major bleeding (1.3% vs 3.2%; $p<0.001$), new pacemaker implantation (7.9% vs 15.3%; $p<0.001$), and new onset of atrial fibrillation (1.5% vs 3.1%; $p=0.002$) were lower in Japan than in France. On the other hand, patients in Japan had a longer hospital stay than those in France (8 [IQR 6-13] days vs 6 [IQR 5-7] days; $p<0.001$), a lower haemoglobin level (10.3 ± 1.6 g/dL vs 11.4 ± 1.7 g/dL; $p<0.001$), and a higher incidence of minor bleeding (3.3% vs 2.2%; $p=0.017$). Between the two groups, there were no significant differences in other clinical

outcomes, including conversion to open surgery, coronary obstruction, disabling stroke, transient ischaemic attack, acute kidney dysfunction, and major and minor vascular complications.

RESULTS FOR BALLOON-EXPANDABLE AND SELF-EXPANDING VALVES SEPARATELY

The results of the comparison between Japan and France, separated into balloon-expandable valve procedures and self-expanding valve procedures, are summarised in **Supplementary Table 1** and **Supplementary Table 2**, respectively. Regarding the analysis results of echocardiography and computed tomography, the differences between Japan and France were similar to those observed in the overall cohort. The in-hospital outcomes were also largely similar to those of the overall cohort; however, regarding pacemaker implantation rates, Japan had a lower rate for balloon-expandable valves (5.3% vs 13.3%; $p<0.001$) and a higher rate for self-expanding valves (17.4% vs 15.3%; $p<0.001$), compared with France.

MEDIUM-TERM CLINICAL OUTCOMES

Three-year all-cause mortality is shown in **Figure 3**. There was no significant difference in 3-year all-cause mortality between Japan and France (22.5% vs 23.5%, HR 0.678, 95% CI: 0.114-4.033; $p=0.583$). The STS-PROM score was significantly associated with 3-year mortality (HR 1.034, 95% CI: 1.008-1.060; $p=0.014$). No other factors were significantly associated with the medium-term prognosis.

SUBGROUP ANALYSIS

Multivariable analysis was performed to identify independent predictors of composite in-hospital outcomes, including death, stroke, and bleeding after TAVI for each country (**Table 4**). In Japan, previous cerebral vascular disease and self-expanding valves tended to increase the risks, but these were not statistically significant. In France, higher body mass index (OR 0.970, 95% CI: 0.947-0.994; $p=0.015$), higher haemoglobin level (OR 0.826, 95% CI: 0.770-0.887; $p<0.001$), and local anaesthesia (OR 0.443, 95% CI: 0.246-0.797; $p=0.007$) were independently associated with reduced in-hospital death. In contrast, female sex (OR 1.310, 95% CI: 1.028-1.669; $p=0.029$), previous CABG (OR 1.868, 95% CI: 1.182-2.954; $p=0.007$), previous cerebral vascular disease (OR 1.717, 95% CI: 1.245-2.367; $p<0.001$), and bicuspid annulus (OR 1.825, 95% CI: 1.228-2.711; $p=0.003$) were associated with a higher probability of composite in-hospital outcomes.

Discussion

To the best of our knowledge, this study provides data on the patient backgrounds and clinical outcomes of the largest number of patients using the latest devices in Japan and France. The salient findings from the present analysis comparing patients in Japan and France are summarised as follows: (1) although there were many different aspects in patient backgrounds, in-hospital outcomes (death, disabling stroke, transient ischaemic attack, vascular complications, and surgical conversion) showed no significant differences. (2) The EOA was smaller in Japan than in France. (3) The incidence of PPM was significantly higher in Japan, although

Table 1. Baseline characteristics compared between Japan and France.

	Japan N=1,422	France N=4,771	p-value
Age, years	84.4±5.5	83.4±5.9	<0.001
Male sex	555 (39.0)	2,577 (54.0)	<0.001
Height, cm	152.5±9.3	164.5±9.0	<0.001
Weight, kg	52.5±10.9	72.0±15.5	<0.001
Body mass index, kg/m ²	22.5±3.7	26.5±5.0	<0.001
Body mass index ≥30 kg/m ²	44 (3.1)	980 (20.7)	<0.001
Body surface area, m ²	1.45±0.18	1.76±0.22	<0.001
STS-PROM score, %	5.0 (3.5-7.8)	3.6 (2.4-5.5)	<0.001
NYHA III or IV	375 (26.4)	1,295 (27.1)	0.004
Haemoglobin, g/dL	11.7±1.6	12.8±1.6	<0.001
Concomitant diseases			
Hypertension	1,033 (72.7)	3,718 (78.2)	<0.001
Diabetes mellitus	374 (26.4)	1,105 (23.2)	0.015
Dyslipidaemia	680 (48.0)	2,205 (46.3)	0.286
Haemodialysis	122 (8.6)	65 (1.4)	<0.001
Chronic pulmonary disease	126 (8.9)	749 (15.8)	<0.001
Chronic kidney disease	1,038 (73.0)	2,339 (49.7)	<0.001
Coronary artery disease	470 (33.1)	2,008 (42.2)	<0.001
Peripheral artery disease	127 (8.9)	598 (12.6)	<0.001
Carotid stenosis	75 (5.3)	363 (7.9)	0.001
Electrocardiogram			
Atrial fibrillation	301 (21.2)	956 (20.1)	0.39
LBBS	45 (3.2)	505 (10.6)	<0.001
RBBB	194 (13.7)	603 (12.7)	0.337
Previous history			
History of PCI	276 (19.4)	1,416 (29.8)	<0.001
History of CABG	49 (3.4)	223 (4.7)	0.012
History of cerebrovascular disease	106 (7.5)	415 (8.7)	0.143
Echocardiographic data			
Aortic valve area, cm ²	0.63±0.18	0.80±0.23	<0.001
Indexed aortic valve area, cm ² /m ²	0.43±0.12	0.45±0.14	<0.001
Peak flow velocity, m/s	4.6±0.71	4.2±0.62	<0.001
Aortic valve mean gradient, mmHg	48.8±17.0	47.1±13.7	0.497
Left ventricular ejection fraction, %	62.4±10.5	59.1±11.9	<0.001
Left ventricular ejection fraction <40%	68 (4.8)	440 (9.2)	<0.001
Systolic pulmonary artery pressure, mmHg	33.0±10.8	42.1±11.0	<0.001
Severe pulmonary hypertension	31 (2.2)	344 (7.2)	<0.001
Computed tomography			
Annulus area, mm ²	399±72	458±94	<0.001
Annulus area ≤430 mm ²	985 (69.3)	1,914 (40.1)	<0.001
Annulus perimeter, mm	22.9±2.0	24.5±2.5	<0.001
Bicuspid annulus	34 (2.4)	296 (6.2)	<0.001
Minimum lumen diameter (right), mm	6.3±1.2	8.3±1.7	<0.001
Minimum lumen diameter (left), mm	6.1±1.2	8.2±1.7	<0.001

Values are mean±standard deviation, median (interquartile range), or n (%). P-values are from Fisher's exact test (2x2 comparison), the chi-square test (nx2 comparisons), or t-tests (continuous parameters). CABG: coronary artery bypass grafting; LBBS: left bundle branch block; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; RBBB: right bundle branch block; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

Table 2. Procedural and echocardiographic outcomes.

	Japan N=1,422	France N=4,771	p-value
Procedural data			
Transfemoral	1,403 (98.7)	4,664 (97.8)	0.041
Contrast volume, mL	43±18	83±36	<0.001
Local anaesthesia	1,391 (97.8)	4,606 (96.8)	0.044
Predilatation	429 (30.2)	638 (13.5)	<0.001
Valve type			<0.001
SAPIEN 3 series	1,123 (79.0)	1,579 (33.1)	
Evolut series	221 (15.5)	3,027 (63.4)	
Navitor series	78 (5.5)	165 (3.5)	
Self-expanding valves	299 (21.0)	3,129 (66.9)	<0.001
Valve size			<0.001
20 mm	77 (5.4)	0 (0)	
23 mm	717 (50.4)	442 (9.3)	
25 mm	31 (2.2)	72 (1.5)	
26 mm	473 (33.3)	1,593 (33.4)	
27 mm	16 (1.1)	45 (0.9)	
29 mm	102 (7.2)	2,095 (43.9)	
34 mm	6 (0.4)	524 (11.0)	
Echocardiographic data			
Effective orifice area, cm ²	1.53±0.42	2.30±0.59	<0.001
Indexed effective orifice area, cm ² /m ²	1.05±0.28	1.31±0.37	<0.001
Peak flow velocity, m/s	2.4±0.50	2.0±0.44	<0.001
Mean pressure gradient, mmHg	11.9±5.3	9.4±4.2	<0.001
Prosthesis-patient mismatch			<0.001
None	1,056 (74.3)	3,948 (82.7)	
Moderate	265 (18.6)	171 (3.6)	
Severe	74 (5.3)	13 (0.3)	

Values are mean±standard deviation or n (%). P-values are from Fisher's exact test (2x2 comparison), the chi-square test (nx2 comparisons), or t-tests (continuous parameters).

the proportion of severe PPM was very low in both groups. 4) The rate of self-expanding valve use and the number of new pacemaker implants were both lower in Japan than in France. 5) There were no statistically significant independent risk factors for composite outcomes (in-hospital death, stroke, and bleeding) in Japan; on the other hand, in France, female sex, higher body mass index, lower haemoglobin, previous coronary artery bypass grafting and cerebrovascular disease, bicuspid annulus, and general anaesthesia were all independent risk factors. 6) There was no significant difference in 3-year all-cause mortality between Japan and France.

This study demonstrated regional differences in patient backgrounds and TAVI outcomes in a large-scale population. Despite significant differences in patient backgrounds, including comorbidities and aortic or vascular diameters, the current results showed that clinical outcomes after TAVI were favourable across both regions, including in-hospital death, complications, and 3-year mortality. These results suggest that TAVI procedures are establishing stable safety regardless of patient risks, such as body size or patient background. It

is noteworthy that the incidence of vascular complications remained unchanged despite the significantly smaller minimum femoral vessel diameter observed in Japanese patients. This is likely attributable to advances in TAVI device technology, enabling access with smaller sheaths and improvements in closure devices, allowing for safe performance of TAVI.

Despite patients' overall higher STS-PROM scores, careful patient management following TAVI may have ensured perioperative safety in Japan. Indeed, Japan showed significantly longer hospital stays than France. Given that most of the patients who underwent TAVI were aged and had various comorbidities, this suggests that ensuring postoperative safety requires management beyond cardiovascular events and necessitates a certain period of hospitalisation.

Furthermore, 3-year all-cause mortality was comparable between Japan and France. This finding suggests that the TAVI devices and procedures steadily improved patient prognosis regardless of valve sizes or regional differences. Although patients in Japan showed a significantly higher incidence of PPM compared with those in France in this study

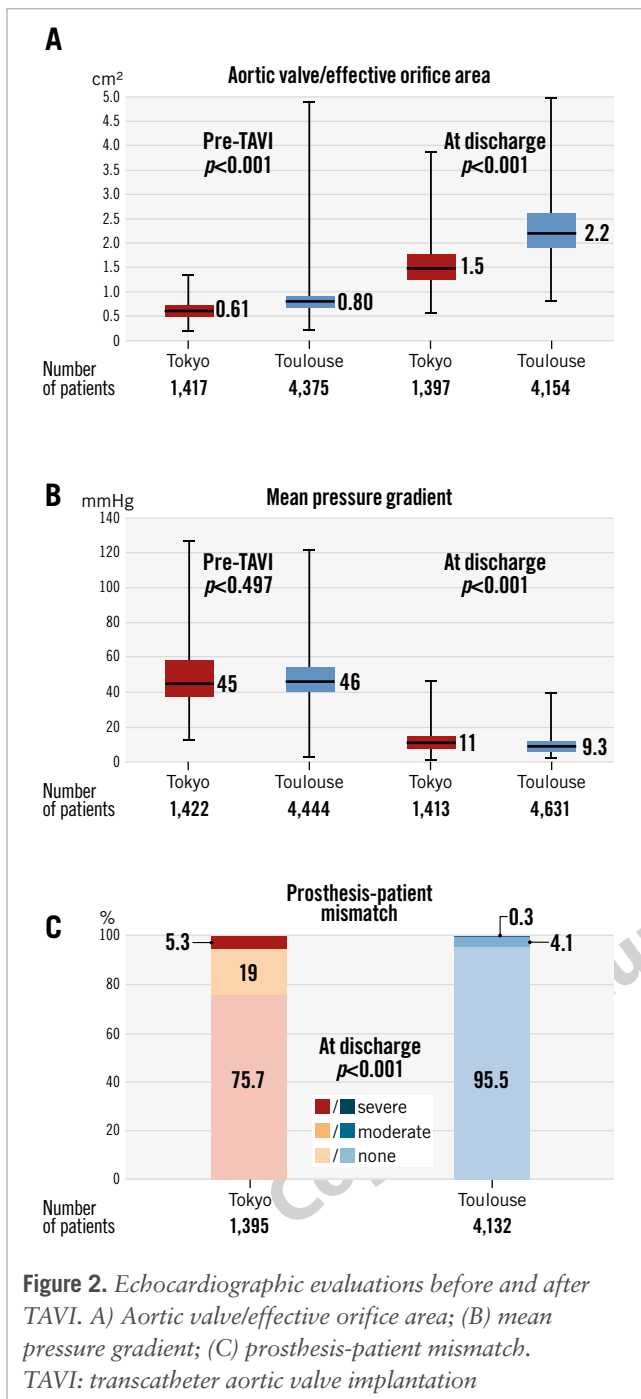


Figure 2. Echocardiographic evaluations before and after TAVI. A) Aortic valve/effective orifice area; (B) mean pressure gradient; (C) prosthesis-patient mismatch. TAVI: transcatheter aortic valve implantation

(severe PPM: 5.3% vs 0.3%), the incidence of severe PPM was very low in both Japan and France. As previous studies have primarily identified severe PPM – rather than moderate PPM – as having an impact on long-term prognosis,¹⁷⁻¹⁹ we believe this may explain why no difference in prognosis was observed in this study. Furthermore, because the follow-up period was limited to 3 years and the patients were of advanced age, longer-term studies are required to evaluate outcomes further. Not only was the native aortic valve complex inherently small but the higher utilisation of balloon-expandable valves compared with self-expanding valves was also considered a reason for the higher rate of PPM in Japan. Recent reports indicate that self-expanding

valves performed superiorly with respect to bioprosthetic valve dysfunction up to 12 months compared with balloon-expandable valves for aortic annuli ≤ 430 mm².⁹ Therefore, determining the optimal treatment strategy for patients with smaller anatomy, such as Asian patients, is crucial. However, this study included patients from 2016. The latest valve, the SAPIEN 3 Ultra RESILIA, can provide a larger EOA compared with previous models. Consequently, studies using the latest valves are also essential.^{11,20} Given the small native size of the aortic complex in the Asian population, they are treated with smaller valve sizes, resulting in a smaller EOA. Future studies, including long-term patient and valve function follow-up, are crucial.

The pacemaker implantation rate was higher in France, which may be partly attributed to the greater use of self-expanding valves. However, given that the pacemaker rate following balloon-expandable valve implantation was also higher in France than in Japan, it is important to consider technical factors such as the membrane septum, the depth of valve placement, and the angle of placement. However, since these factors were not included in this registry, conducting a detailed study remains a challenge for the future. Additionally, pacemaker implantation was performed approximately 2 days postoperatively in France. It is known that atrioventricular block after TAVI recovers spontaneously in a certain proportion of cases, suggesting that prompt pacemaker implantation after TAVI may represent overtreatment.

In subgroup analyses, the TAVI outcomes at both hospitals were consistently excellent; as the number of events – specifically deaths and strokes – was very low, a composite endpoint was used rather than a hard endpoint. This suggests that TAVI is a safe and reliable treatment regardless of the region. Factors such as female sex, low body mass index, and low haemoglobin level – which may pose a significant risk for composite in-hospital outcomes in French patients – are patient background factors frequently observed in Japan. However, in-hospital mortality was comparable between Japan and France, and there were no major differences in safety outcomes, including stroke or bleeding events. These results therefore indicate the importance of individually tailored management of comorbidities, including procedural management and medication, based on each patient's background. As TAVI indications expand, an increasing number of patients with diverse backgrounds will be treated, making an increasingly personalised, tailor-made approach for each patient essential.

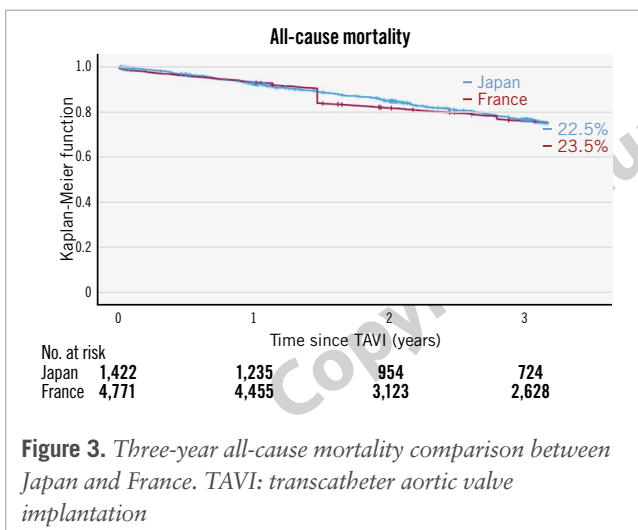
Limitations

This study has several limitations inherent to its design. It was based on observational, unblinded, and non-randomised registry data, such that unmeasured variables may have influenced the results. Moreover, one of the limitations of a retrospective registry is that there were significant differences between Japan and France in the types of valves used for TAVI. It cannot be denied that this could be interpreted as a comparison of the valves themselves; therefore, the results of this study should not be overinterpreted as regional differences only. Echocardiographic data were collected according to VARC-3 criteria but were not adjudicated by an independent

Table 3. Postprocedural clinical outcomes.

	Japan N=1,422	France N=4,771	p-value
Hospital stay, days	8 (6-13)	6 (5-7)	<0.001
ICU stay, days	1 (1-1)	1 (1-2)	<0.001
Haemoglobin, g/dL	10.3±1.6	11.4±1.7	<0.001
In-hospital death	9 (0.6)	60 (1.3)	0.068
Cardiovascular death	3 (0.2)	49 (1.0)	0.003
Conversion to open surgery	2 (0.1)	5 (0.1)	0.724
Coronary obstruction	7 (0.5)	10 (0.2)	0.074
Disabling stroke	15 (1.1)	32 (0.7)	0.147
Transient ischaemic attack	2 (0.1)	9 (0.2)	0.702
Acute kidney dysfunction	44 (3.1)	184 (3.9)	0.171
Major bleeding	18 (1.3)	153 (3.2)	<0.001
Minor bleeding	47 (3.3)	104 (2.2)	0.017
Major vascular complication	34 (2.4)	116 (2.4)	0.916
Minor vascular complication	79 (5.6)	320 (6.7)	0.112
New pacemaker implantation	112 (7.9)	724 (15.3)	<0.001
New onset of atrial fibrillation	21 (1.5)	145 (3.1)	0.002

Values are mean±standard deviation, median (interquartile range), or n (%). P-values are from Fisher's exact test (2x2 comparison), the chi-square test (nx2 comparisons), or t-tests (continuous parameters). ICU: intensive care unit



core laboratory. Regarding paravalvular leakage, while we suspect this may be due to issues with the echocardiographers' records, 94.8% of cases in the French database were classified as "non-trivial". Given that 52.3% of cases in Japan were classified as "non-trivial", it would be a misinterpretation to assume there were significantly worse outcomes in Japan. As this is a significant discrepancy that does not reflect real-world clinical practice, and it suggests that there are issues with the methods used to collect data on paravalvular leakage, we deliberately chose not to make such a comparison. Regarding statistics, we tried to perform propensity score matching, adjusting for baseline characteristics; however, due to the many differences between Japan and France, there remained too few matched cohorts to analyse appropriately. We concluded that this difficulty in matching means the patient

profiles differed greatly between groups. Post-TAVI computed tomography data were unavailable, precluding detailed assessment of calcium scores. The types of valves used for TAVI differed between the two regions (for example, SAPIEN 3 Ultra was used in France but not in Japan), so post-TAVI paravalvular leakage assessment could not be performed by echocardiography. In the 3-year mortality comparison, missing survival status and date of death data were imputed using multiple imputation methods; however, this statistical approach is not perfect. It cannot be ruled out that selection bias in the patients whose survival status was confirmed and the low reproducibility of analyses using multiple imputation methods may have influenced the results. However, this study represents a comparison of TAVI procedures performed at the largest and most advanced facilities in Japan and France, and it is considered to retain its novelty and uniqueness.

Conclusions

Although there were many differences in patient characteristics between Japan and France, the clinical outcomes of TAVI, including in-hospital and 3-year outcomes, were similar and excellent. These results suggest that the current TAVI safety profile was established regardless of the patients' background risks. Future studies clarifying the long-term prognosis or valve durability after TAVI, considering the regional differences, are warranted.

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Table 4. Logistic regression models for in-hospital composite outcomes (death, stroke, and bleeding).

Variables	Japan			France		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.020	0.974-1.069	0.406	1.018	0.997-1.040	0.087
Female sex	0.937	0.573-1.531	0.794	1.310	1.028-1.669	0.029
Body mass index	1.026	0.965-1.090	0.417	0.970	0.947-0.994	0.015
Haemoglobin	1.005	0.865-1.168	0.944	0.826	0.770-0.887	<0.001
NYHA III or IV	1.493	0.908-2.455	0.114	1.100	0.858-1.411	0.451
STS-PROM score	0.960	0.901-1.023	0.207	1.022	0.992-1.053	0.155
Atrial fibrillation	0.735	0.407-1.328	0.308	1.005	0.764-1.323	0.970
Chronic pulmonary disease	1.181	0.574-2.427	0.651	0.951	0.689-1.312	0.758
Chronic kidney disease	1.145	0.672-1.952	0.619	0.912	0.725-1.149	0.435
Peripheral artery disease	1.641	0.835-3.225	0.151	1.076	0.768-1.509	0.669
Previous CABG	2.222	0.783-6.302	0.133	1.868	1.182-2.954	0.007
Previous cerebral vascular disease	1.885	0.948-3.751	0.071	1.717	1.245-2.367	<0.001
Left ventricular ejection fraction	0.999	0.976-1.022	0.925	1.003	0.993-1.014	0.498
Bicuspid annulus	0.590	0.077-4.495	0.610	1.825	1.228-2.711	0.003
Transfemoral	1.081	0.179-6.519	0.932	1.390	0.598-3.230	0.445
Local anaesthesia	0.251	0.057-1.104	0.067	0.443	0.246-0.797	0.007
Self-expanding valves	1.570	0.953-2.588	0.077	1.225	0.952-1.576	0.115

P-values, ORs, and 95% CIs from the logistic regression model. CABG: coronary artery bypass grafting; CI: confidence interval; NYHA: New York Heart Association; OR: odds ratio; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

Conflict of interest statement

K. Hayashida is a clinical proctor for Edwards Lifesciences, Abbott, and Medtronic. H. Shimizu is a clinical proctor at Edwards Lifesciences. N. Dumonteil and D. Tchéché are proctors for Edwards Lifesciences, Abbott, Medtronic, and Boston Scientific. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Comparison of balloon-expandable valve procedures between Japan and France.

Supplementary Table 2. Comparison of self-expanding valve procedures between Japan and France.

Data availability statement.

Ethics approval statement.

Patient consent statement.

The supplementary data are published online at:

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Supplementary data

Supplementary Table 1. Comparison of balloon-expandable valve procedures between Japan and France.

	Japan	France	
	N=1123	N=1579	p
Pre-echocardiographic data			
Aortic valve area, cm ²	0.64±0.18	0.81±0.24	<0.001
Index aortic valve area, cm ² /m ²	0.43±0.12	0.45±0.14	<0.001
Peak flow velocity, m/s	4.6±0.69	4.2±0.64	<0.001
Aortic valve mean gradient, mmHg	47.8±16.3	45.6±13.4	0.126
Left ventricular ejection fraction, %	62.2±10.5	57.0±12.9	<0.001
Left ventricular ejection fraction <40%	56 (5.0)	199 (12.6)	<0.001
Systolic pulmonary artery pressure, mmHg	32.6±10.8	42.1±11.4	<0.001
Computed Tomography			
Annulus area, mm ²	405±70	505±97	<0.001
Annulus area ≤430 mm ²	753 (67.1)	358 (22.7)	<0.001
Annulus perimeter, mm	23.1±2.0	25.7±2.5	<0.001
Bicuspid	29 (2.6)	137 (8.7)	<0.001
Minimum lumen diameter (right), mm	6.4±1.2	8.5±1.8	<0.001
Minimum lumen diameter (left), mm	6.2±1.2	8.5±1.8	<0.001
Procedure			
Transfemoral	1110 (98.8)	1511 (95.7)	<0.001
Contrast volume, mL	42±16	75±37	<0.001
Local anesthesia	1101 (98.0)	1488 (94.7)	<0.001
Pre-dilatation	143 (12.7)	149 (9.4)	<0.001
Post-echocardiographic data			
Effective orifice area, cm ²	1.49±0.40	2.11±0.53	<0.001
Index effective orifice area, cm ² /m ²	1.01±0.26	1.16±0.31	<0.001
Peak flow velocity, m/s	2.4±0.50	2.3±0.41	<0.001
Mean pressure gradient, mmHg	12.6±5.3	11.8±4.3	0.009
Prosthesis-patient mismatch			
none	797 (71.0)	1268 (80.3)	<0.001
moderate	242 (21.5)	117 (7.4)	
severe	65 (5.8)	7 (0.4)	

Post-procedure outcomes

Hospital stays, day	8 [5-12]	5 [5-7]	<0.001
ICU stay, day	1 [1-1]	1 [1-2]	<0.001
Hemoglobin, g/dL	10.5±1.7	11.4±1.7	<0.001
In-hospital death	5 (0.4)	18 (1.1)	0.053
Cardiovascular death	4 (0.4)	17 (1.1)	0.060
Conversion to open surgery	2 (0.2)	4 (0.3)	0.682
Coronary obstruction	5 (0.4)	4 (0.3)	0.394
Disabling stroke	9 (0.8)	9 (0.6)	0.045
Transient ischemic attack	2 (0.2)	2 (0.1)	0.054
Acute kidney injury	26 (2.3)	70 (4.5)	0.004
Major bleeding	14 (1.2)	50 (3.2)	<0.001
Minor bleeding	36 (3.2)	22 (1.4)	0.001
Major vascular complication	24 (2.1)	31 (2.0)	0.171
Minor vascular complication	65 (5.8)	93 (5.9)	0.040
New pacemaker implantation	60 (5.3)	209 (13.3)	<0.001
New onset of atrial fibrillation	14 (1.3)	51 (3.3)	0.002

Depicted are means with standard deviations ($\pm$ SD), medians with interquartile range, or counts with percentages (%). ICU, intensive care unit. P-values from Fisher's test (2 x 2 comparison), chi-square test (n x 2 comparisons), or t-tests (continuous parameters).

Supplementary Table 2. Comparison of self-expanding valve procedures between Japan and France.

	Japan	France	
	N=299	N=3192	p
Pre-echocardiographic data			
Aortic valve area, cm ²	0.58±0.18	0.79±0.23	<0.001
Index aortic valve area, cm ² /m ²	0.41±0.12	0.46±0.14	<0.001
Peak flow velocity, m/s	4.8±0.78	4.2±0.61	<0.001
Aortic valve mean gradient, mmHg	52.4±18.8	47.8±13.7	0.002
Left ventricular ejection fraction, %	63.1±10.2	60.2±11.2	<0.001
Left ventricular ejection fraction <40%	12 (4.0)	241 (7.6)	<0.001
Systolic pulmonary artery pressure, mmHg	34.5±10.5	42.1±10.8	<0.001
Computed Tomography			
Annulus area, mm ²	377±71	435±83	<0.001
Annulus area ≤430 mm ²	232 (77.6)	1556 (48.7)	<0.001
Annulus perimeter, mm	22.3±2.1	23.9±2.2	<0.001
Bicuspid	5 (1.7)	159 (5.0)	0.013
Minimum lumen diameter (right), mm	5.9±1.2	8.1±1.6	<0.001
Minimum lumen diameter (left), mm	5.7±1.2	8.1±1.5	<0.001
Procedure			
Transfemoral	293 (98.0)	3153 (98.8)	0.235
Contrast volume, mL	45±24	86±34	<0.001
Local anesthesia	290 (97.0)	3118 (97.8)	0.345
Pre-dilatation	286 (95.7)	489 (15.3)	<0.001
Post-echocardiographic data			
Effective orifice area, cm ²	1.69±0.45	2.40±0.60	<0.001
Index effective orifice area, cm ² /m ²	1.19±0.31	1.39±0.38	<0.001
Peak flow velocity, m/s	2.1±0.50	1.9±0.40	<0.001
Mean pressure gradient, mmHg	9.1±4.6	8.2±3.6	0.003
Prosthesis-patient mismatch			
none	259 (86.6)	2680 (84.0)	<0.001
moderate	23 (7.7)	54 (1.7)	
severe	9 (3.0)	6 (0.2)	
Post-procedure outcomes			
Hospital stays, day	10 [8-17]	6 [5-7]	<0.001

ICU stay, day	1 [1-1]	1 [1-2]	<0.001
Hemoglobin, g/dL	10.1±1.6	11.3±1.7	<0.001
In-hospital death	4 (1.3)	42 (1.3)	0.975
Cardiovascular death	3 (1.0)	32 (1.0)	0.999
Conversion to open surgery	0 (0)	1 (0)	0.760
Coronary obstruction	2 (0.7)	6 (0.2)	0.096
Disabling stroke	6 (2.0)	23 (0.7)	0.034
Transient ischemic attack	0 (0)	7 (0.2)	0.390
Acute kidney injury	18 (6.0)	114 (3.6)	0.051
Major bleeding	4 (1.3)	103 (3.2)	0.108
Minor bleeding	11 (3.7)	82 (2.6)	0.262
Major vascular complication	10 (3.3)	85 (2.7)	0.451
Minor vascular complication	14 (4.7)	227 (7.1)	0.150
New pacemaker implantation	52 (17.4)	515 (15.3)	<0.001
New onset of atrial fibrillation	7 (2.3)	94 (3.0)	0.544

Depicted are means with standard deviations ($\pm$ SD), medians with interquartile range, or counts with percentages (%). ICU, intensive care unit. P-values from Fisher's test (2 x 2 comparison), chi-square test (n x 2 comparisons), or t-tests (continuous parameters).

Data availability statement.

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics approval statement.

The Keio University School of Medicine Ethics Committee and the Clinique Pasteur Ethics Committee approved the study protocol (Institutional Review Board information, reference numbers: 20130270, UMIN000020423).

Patient consent statement.

All study participants provided written informed consent.