Learning Curve for Transcatheter Aortic Valve Implantation Under a Controlled Introduction System  
— Initial Analysis of a Japanese Nationwide Registry —

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Background: The introduction of transcatheter aortic valve implantation (TAVI) into Japan was strictly controlled to optimize patient outcomes. The goal of this study was to assess if increasing experience during the introduction of this procedure was associated with outcomes.

Methods and Results: The initial 1,752 patients registered in the Japanese national TAVI registry were included in the study. The association between operator procedure number and incidence of the early safety endpoint at 30 days (ESE30) as defined in the Valve Academic Research Consortium-2 consensus document was evaluated. Patients were divided into 4 groups by quartiles of procedure count (Groups I–IV in order of increasing number of procedures). Median patient age was 85 years, and 30.5% were male. The 30-day mortality rate was 1.4% (n=24), and 78 patients (7.9%) experienced 95 ESE30. Among the variables included in the model, ESE30 was associated with non-transfemoral approach (P=0.004), renal dysfunction (Cr >2.0 mg/dL) (P=0.01) and NYHA class III/IV (P=0.04). ESE30 incidence was not significantly different between Groups I–III and Group IV. Spline plots demonstrated that experience of 15–20 cases in total was needed to achieve a consistent low risk of ESE30.

Conclusions: Increasing experience was associated with better outcomes, but to a lesser degree than in previous reports. Our findings suggested that the risks associated with the learning curve process were appropriately mitigated.

Key Words: Learning curve assessment; National registry; Transcatheter aortic valve replacement
The purpose of this study was to assess the learning curve for the TAVI procedure when it was introduced into real-world clinical practice in Japan. The study was designed to (1) evaluate the association between the number of TAVI procedures performed by the individual operator and procedure-related early mortality and morbidity, and (2) define the number of cases required to achieve a steady state of success and safety. The qualified institutions were obligated to register all TAVI cases with the Ministry of Health, Labour and Welfare (MHLW).

Methods

Data Source and Study Population

In collaboration with the PMDA and product manufacturers, the J-TVT registry was established by 4 academic societies (Japanese Circulation Society, The Society of Japanese Cardiovascular Surgery, Japanese Association for Thoracic Surgery and Japanese Association of Cardiovascular Intervention and Therapeutics) to develop a database containing information about TAVI procedures in Japan. Consecutive case registration was required for certification of the institutions and operators, and complete case registration is confirmed every 3 years for renewal of institutional certification (http://j-tavr.com/guideline.html). Data quality
A total of 1752 consecutive TAVI procedures performed by 94 operators at the 55 institutions from 1 August 2013 to 16 July 2015 were included in the study. Valve-in-valve procedures, utilizing previously replaced bioprosthetics that had failed, were not included in the present study because the treatment had not been approved for this indication. Rescue valve-in-valve procedures, conducted within 30 days after a failed TAVI procedure, were counted as adverse events. In this study period, only the Edwards Sapien XT bioprosthesis was approved and used. Modification of the device, which could potentially affect its safety profile, was not performed during the study period.

With respect to risk calculation, STS PROM Scores (Society of Thoracic Surgeons Predicted Risk of Mortality Score) and EURO score II (European System for Cardiac Risk in COPD) were assured via automatic system validation, reporting of data completeness, and training of site data managers. When the 5-year of follow-up period is completed, compliance inspection is scheduled for future re-assessment/re-evaluation.

The institutional review board at each participating site approved the registration of patient information into the database with an opt-out process according to the ethical guidelines for medical and health research involving human subjects, published by the Ministry of Education, Culture, Sports, Science and Technology and the MHLW of Japan (2005). The current study protocol was approved by the steering committee of the TAVI registry. As of July 2015, a total of 55 institutions had been certified by the consortium of academic societies. Healthcare professionals enter information into a web-based data entry system residing in the National Clinical Database. A total of 290 data elements were selected, corresponding to data reported based on the updated standardized endpoint definitions for TAVI in the Valve Academic Research Consortium-2 consensus document (VARC-2). Data elements include institutional information and a unique operator identifier of medical license number. This enabled a procedure count for each operator. Registry data of the initial 600 consecutive cases, and the corresponding results of effectiveness and safety analyses by the manufacturers, were legally mandated to be reported to the PMDA under the provision of the Japanese ministerial ordinance of Good Post-Marketing Study Practice. A total of 1,752 consecutive TAVI procedures performed by 94 operators at the 55 institutions from 1 August 2013 to 16 July 2015 were included in the study. Valve-in-valve procedures, utilizing previously replaced bioprosthetics that had failed, were not included in the present study because the treatment had not been approved for this indication. Rescue valve-in-valve procedures, conducted within 30 days after a failed TAVI procedure, were counted as adverse events. In this study period, only the Edwards Sapien XT bioprosthesis was approved and used. Modification of the device, which could potentially affect its safety profile, was not performed during the study period.

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With respect to risk calculation, STS PROM Scores (Society of Thoracic Surgeons Predicted Risk of Mortality Score) and EURO score II (European System for Cardiac
Operative Risk Evaluation Score) were entered into the system, and Japan Scores (Surgical risk calculation for Japanese patients) were calculated using baseline variables.

Outcome Measures and Statistical Analysis
The primary endpoint was an early safety endpoint at 30 days (ESE30), which is a composite endpoint detailed in VARC-2. The definition of ESE30 was all-cause death, all severe adverse events, including stroke, life-threatening bleeding, acute kidney injury, coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure, such as repeat TAVI, balloon aortic valvuloplasty and surgical aortic valve replacement (SAVR) according to the VARC-2 criteria. Secondary outcome measures included procedure time, radiation exposure time, and the use of cardiopulmonary bypass during the procedure. All severe adverse events reported within 30 days (AAE30) was another secondary endpoint, which comprised ESE30 and other cardiovascular complications, such as conduction disturbances requiring permanent pacemaker placement.

To examine the relationship between operator procedure number and ESE30, and the relationship between operator procedure number and AAE30, restricted cubic splines were plotted to explore potential nonlinear relationships because we anticipated the association of 3 phases, namely, an initial phase of rapid improvement, a second phase of gradual decline, and a final plateau phase. We plotted the predicted incidences of events from the cubic spline model against increasing operator procedure number. To characterize patient and procedural features for descriptive purposes, cases were categorized into 4 groups based on the number of procedures performed by the operator: Group I, 1–8 (564 patients treated by 94 operators); Group II, 9–19 (431 by 64); Group III, 20–39 (378 by 35); and Group IV, ≥40 procedures (379 by 15). These cutoff values were determined by visual inspection of the cubic spline analysis results and based on the fact that experienced proctors supported individual operators in preprocedural assessment and procedure skill for 8 initial cases. Categorical variables are expressed as frequencies and percentages, and continuous variables are expressed as medians with the interquartile range (IQR). Comparisons among categorical and continuous variables were performed using Pearson’s chi-squared test and the Kruskal-Wallis test, respectively. We report observed incidences of the primary and secondary outcomes based on procedure count.

We then conducted multiple logistic regression analysis with occurrences of primary or secondary events as dependent variables, and potential confounding baseline factors (e.g., age, STS PROM score, chronic dialysis, chronic obstructive pulmonary disease, and approach site (femoral or non-femoral) as independent variables. Confidence intervals (CIs) were estimated using sandwich variance estimators in order to account for the within-physician clustering. A case sequence approach was used to assess the association between the operator’s procedure count and the incidence of ESE30 and AAE30. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results
Cumulative TAVI Experience by Individual Operator
All 1,752 consecutive patients, from the very first case in August 2013 to the final case on 16 July 2015, were treated by 94 operators. The distribution of the number of TAVI procedures among these operators is shown in Figure S1. Ultimately, 32% of the procedures were performed by physicians with procedure counts <9, and they were supported by the proctors. Only 15 operators had more than 40 total TAVI procedures.
Patients’ Characteristics

Characteristics of all patients, as well as in the 4 groups, are presented in Table 1. Median patient age in our cohort was 85 (IQR, 81–88) years, and 30.5% were male. Several patient characteristics showed significant differences across the procedure count groups, including peripheral vascular disease (P<0.001), coronary artery disease (P=0.002), previous coronary bypass surgery (P=0.001), previous percutaneous coronary intervention (P=0.006), porcelain aorta (P<0.001), left ventricular ejection fraction by cardiac echocardiography (P=0.003) and concomitant mitral valve disease (P<0.001). Age, sex, history of a cerebrovascular event and New York Heart Association (NYHA) functional class III/IV were not significantly different across the groups. Median STS PROM score, EURO Score II and Japan score were 6.5 (IQR, 4.5–9.3), 4.1 (2.7–6.3) and 3.2 (2.0–5.2), respectively. Most patients (47.6%) were intermediate risk (STS PROM score 4–8) and the remaining were high-risk patients (STS PROM score >8; 34.2%) and low-risk patients (STS PROM score <4; 18.2%). There was no significant difference in STS PROM score, EURO Score II or Japan Score across the groups.

![Figure](https://example.com/figure.png)

**Figure.** (A) Restricted cubic spline plot of the incidence of the early safety endpoint at 30 days (ESE30). The curve shows an initial rapid decrease with a subsequent gradual decrease. The inflection point appears to be around 10–15 cases. (B) Restricted cubic spline plot of incidence of all adverse events within 30 days (AAE30). The curve shows an initial rapid decrease with a subsequent gradual decrease. The inflection point appears to be around 8–12 cases.
Procedural Characteristics and Outcomes

Procedural characteristics and early outcomes among the 4 groups are presented in Table 2. Procedure time and radiation exposure time decreased over time from Group I to Group IV (P<0.001 and P<0.001, respectively). Use of cardiopulmonary bypass, either scheduled or emergency during the procedure, was significantly less in Group IV (P=0.02). Access site to insert the delivery system data showed that the transfemoral approach increased from 10–15 cases. The inflection point of the curves gradually decreased (Figure 4). The 30-day mortality and stroke rates of patients with intermediate risk were reported in several randomized trials or observational studies have ranged from 2.7% to 7.1%, and from 2.0% to 6.4%, respectively. The present study had intermediate risk (STS PROM score of 6.6). The STS PROM score is widely used for estimating the risks of SAVR. The majority of the patients (47.6%) in the study utilized a Japanese national registry revealed 2 important findings in terms of medical device safety. First, following the introduction of TAVI across Japanese institutions, the overall 30-day mortality and stroke rates during the study period remained low (1.4% and 0.9%, respectively). Secondly, the incidence of the safety endpoint (ESE30) was not significant, although increased technical proficiency was reflected in decreases in procedure time and radiation exposure time from Group I to Group IV. A spline plot showed a rapid decline of ESE30 incidence and quickly plateaued with 15–20 cases.

The STS PROM score was widely used for estimating the risks of SAVR. The majority of the patients (47.6%) in the present study had intermediate risk (STS PROM score 4–8). The 30-day mortality and stroke rates of patients with intermediate risk were reported in several randomized trials or observational studies have ranged from 2.7% to 7.1%, and from 2.0% to 6.4%, respectively. A study comparing TAVI (PARTNER SAPIEN 3 cohort) with SAVR by propensity score matching demonstrated that 30-day mortality in the TAVI cohort was 1.1% for the median STS PROM score of 5.2. A US nationwide registry showed 30-day mortality of 4.0% in patients with a median STS PROM score of 6.6. The present study involving real-world Japanese patients showed a lower early mortality rate. In Japan, TAVI was introduced after saturation of the device in other parts of the world. Universal safety measures were shared through scientific sessions, and the proctors were widely available. In particular, proctoring by experienced foreign physicians is thought to have reduced the early mortality and morbidity.

Table 4. Multiple Logistic Regression Analysis for ESE at 30 Days According to VARC-2 Definition as Well as AAE at 30 Days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ESE30</th>
<th>AAE30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Procedure count (1–8, &lt;9)</td>
<td>1.48</td>
<td>0.88</td>
</tr>
<tr>
<td>Procedure count (9–19, 9–19)</td>
<td>0.94</td>
<td>0.53</td>
</tr>
<tr>
<td>Procedure count (20–39, 20–39)</td>
<td>1.21</td>
<td>0.66</td>
</tr>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.96</td>
</tr>
<tr>
<td>STS PROM score</td>
<td>1.02</td>
<td>1.0</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.39</td>
<td>0.08</td>
</tr>
<tr>
<td>COPD</td>
<td>1.26</td>
<td>0.69</td>
</tr>
<tr>
<td>Hostile chest</td>
<td>0.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>1.61</td>
<td>0.73</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>1.55</td>
<td>1.03</td>
</tr>
<tr>
<td>CAD</td>
<td>0.67</td>
<td>0.37</td>
</tr>
<tr>
<td>Porcelain aorta</td>
<td>1.12</td>
<td>0.56</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>2.74</td>
<td>1.35</td>
</tr>
<tr>
<td>Non-transfemoral approach, Other</td>
<td>1.96</td>
<td>1.24</td>
</tr>
</tbody>
</table>

CI, confidence interval; Hostile chest, chest wall deformity or previous surgery on mediastinum or chest wall; OR, odds ratio; Porcelain aorta, extensive calcification of the ascending aorta or aortic arch; Renal dysfunction, creatine >2.0 mg/dL; STS PROM score, Society of Thoracic Surgeons Predicted Risk of Mortality score. Other abbreviations as in Tables 1,3.

Multiple Logistic Regression Analysis

Among the variables included in the model, non-transfemoral approach (odds ratio [OR], 1.96; 95% CI, 1.24–3.12; P=0.004), renal dysfunction defined as elevated creatinine level (Cr >2.0 mg/dL) (OR, 2.74; 95% CI, 1.35–5.56; P=0.005) and NYHA class III/IV (OR, 1.55; 95% CI, 1.03–2.34; P=0.04) had statistically significant associations with ESE30. The OR of ESE30 among patients in Group I relative to Group IV was 1.48 (95% CI, 0.88–2.51). The point estimates for ESE30 were lower in Group II vs. VI (OR, 0.94; 95% CI, 0.53–1.64) and Group III vs. IV (OR, 1.21; 95% CI, 0.66–2.23) (Table 4). On the other hand, significant predictors for AAE30 incidence included STS PROM score (OR, 1.03; 95% CI, 1.01–1.05; P=0.003), and renal dysfunction (OR, 1.98; 95% CI, 1.00–3.91; P=0.049). Non-transfemoral approach was again identified as a significant predictor of increased odds for the event (OR, 1.58; 95% CI, 1.07–2.35; P=0.02).

Discussion

This study utilizing a Japanese national registry revealed 2 important findings in terms of medical device safety. First, following the introduction of TAVI across Japanese institutions, the overall 30-day mortality and stroke rates during the study period remained low (1.4% and 0.9%, respectively). Secondly, the incidence of the safety endpoint (ESE30) was not significant, although increased technical proficiency was reflected in decreases in procedure time and radiation exposure time from Group I to Group IV. A spline plot showed a rapid decline of ESE30 incidence and quickly plateaued with 15–20 cases.

The STS PROM score was widely used for estimating the risks of SAVR. The majority of the patients (47.6%) in the present study had intermediate risk (STS PROM score 4–8). The 30-day mortality and stroke rates of patients with intermediate risk were reported in several randomized trials or observational studies have ranged from 2.7% to 7.1%, and from 2.0% to 6.4%, respectively. A study comparing TAVI (PARTNER SAPIEN 3 cohort) with SAVR by propensity score matching demonstrated that 30-day mortality in the TAVI cohort was 1.1% for the median STS PROM score of 5.2. A US nationwide registry showed 30-day mortality of 4.0% in patients with a median STS PROM score of 6.6. The present study involving real-world Japanese patients showed a lower early mortality rate. In Japan, TAVI was introduced after saturation of the device in other parts of the world. Universal safety measures were shared through scientific sessions, and the proctors were widely available. In particular, proctoring by experienced foreign physicians is thought to have reduced the early mortality and morbidity. Yamawaki et al compared outcomes of TAVI between procedures performed
during the early proctoring period and those performed independently after proctoring. Although there was no difference in terms of early mortality, ESE30 (VARC-2 definition) was significantly reduced after the proctoring phase finished.24 We speculate that several safety measures had beneficial effects on the outcomes.

The concept of a learning curve associated with TAVI is not new. In our study, contrary to reports from previous studies, we did not observe a uniform decrease in the odds of adverse events when the procedures were categorized into 4 groups based on numbers performed, although cardiopulmonary bypass use to prevent or treat hemodynamic collapse was reduced in the group with the highest procedure count. Spline plots suggested that an average of 15–20 cases was needed to achieve a consistent low risk of ESE30. These results are lower than typical numbers reported in previous studies.22–24 Carroll et al, utilizing more than 40,000 TAVI procedures registered in the US TVT registry,16 reported an inverse relationship between increasing institutional case volume and in-hospital death, particularly for the first 100 cases. In a similar analysis of 1,521 patients who had transfemoral TAVI in the PARTNER I trial, a consistent low risk of adverse events was achieved after 26 cases.24

Safety protocols devised for the introduction of TAVI into the Japanese market appeared to be successful. The results of the present study suggested that controlled site selection of qualified institutions and physicians and the training/proctoring provided by manufacturers facilitated the achievement of good clinical outcomes from the very beginning. The PMDA and the MHLW strongly support this type of controlled release of the new innovative technology into clinical practice in good collaboration with academic societies and device manufacturers. The Japanese Pharmaceuticals and Medical Devices Act (Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics) amended in 2015, strengthened the safety measures for medical products, including specially controlled medical devices that are permanently implanted. This legal initiative provides the infrastructure for registry development with highly reliable data. The provision of registry data to device manufacturer for a re-assessment/re-evaluation program under the Act was also agreed upon within this legal framework.

Study Limitations
First, data elements in the registry were decided when the device and the procedure were approved in 2013, and data elements related to patient frailty and other potential confounders were not included. Unmeasured confounding factors may affect the results of the analysis. Only one TAVI device, Edward Sapien XT, was available in Japan during the study period and was used without any modification. The presence of multiple devices in the market and any potential modification may lead to possible bias for this type of analysis.

Secondly, we chose to evaluate operator experience rather than institutional experience. This is because the whole procedure poses several risks, including wire manipulation, delivery system insertion, device placement, and device expansion. Risks can be mitigated by detailed assessment of aortic valve morphology and route of device insertion. For example, if a calcified lesion is identified in the aortic valve annulus, the operator often decides during the procedure to expand the balloon with a reduced volume as a post-dilatation measure. Catheter-based interventions require detailed preprocedural assessment and sophisticated procedural techniques that are highly dependent on the operator. Therefore, we surmised that the role of the main operator is extremely important, and thus opted to analyze operator experience.

Finally, there is possibility of underreporting. In this study, events that occurred within 30 days were used for the analyses. Based on algorithmic system settings, web-based data entry was not completed unless all data elements within 30 days were inputted. Registration of all cases is a requirement for the qualification of institutions and physicians, so we expect that underreporting is minimal in the registry.

Conclusions
Although there was a distinct learning curve in the introduction of TAVI into Japanese clinical practice, overall early mortality and morbidity were extremely low in the real world. There was a decline in the risk for major adverse outcomes for patients treated in Japan, but to a lesser degree than in previous reports. Our data suggested that the risks associated with the learning curve process were appropriately mitigated. The results also suggested that the safety management process to release the TAVI device into clinical practice was well-controlled in terms of the learning curve of the procedure and optimizing the early outcomes. The PMDA strongly supports this type of controlled release for new medical device technologies.

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Author Conflicts of Interest
H.K., S.K. and H.M. are affiliated with the Department of Healthcare Quality Assessment at the University of Tokyo, which is a social collaboration department supported by National Clinical Database, Johnson & Johnson K.K., and Nipro Corporation. K.T. and Y.S. are affiliated with the Department of Cardiovascular Surgery, Osaka University Hospital. The Department was supported by an unlimited grant from Edwards Lifescience Co. Ltd. The rest of the authors have no conflicts of interest.

References

Appendix. Author Contributions

- Nobuhiro Handa: Study concept, study design, data interpretation, medical writing
- Hiraku Kumamaru: Study concept, data analysis, data interpretation, medical writing
- Kei Torikai: Study concept, study design, management of registry, critical revision
- Shun Koshaka: Data collection, management of registry, data interpretation, medical writing
- Morimasa Takayama: Data collection, management of registry, critical revision
- Junjiro Kobayashi: Data collection, management of registry, critical revision
- Hisao Ogawa: Data collection, management of registry, critical revision
- Haruhisa Shirato: Study design, data interpretation, critical revision
- Kensuke Ishii: Study design, data interpretation, critical revision
- Kazuhiro Koike: Study design, data interpretation, critical revision
- Yoshimasa Yokoyama: Study design, data interpretation, critical revision
- Hiroaki Miyata: Data analysis, data interpretation, critical revision
- Noboru Motomura: Data collection, management of registry, data interpretation, critical revision
- Yoshiki Sawa: Data collection, management of registry, data interpretation, critical revision, final approval

Supplementary Files

Supplementary File 1

Figure S1. Proportion of procedures for each count of TAVI procedures.

Please find supplementary file(s):