A Real-World Comparison of 1-Year Survival and Expenditures for Transcatheter Aortic Valve Replacements: SAPIEN 3 Versus CoreValve Versus Evolut R

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A B S T R A C T

Objectives: New versions of balloon-expandable and self-expandable valves for transcatheter aortic valve replacement (TAVR) have been developed, but few studies have examined the outcomes associated with these devices using national-level data. This study aimed to elucidate the clinical and economic outcomes of TAVR for aortic stenosis in Japan through an analysis of real-world data.

Methods: This retrospective cohort study was performed using data from patients with aortic stenosis who had undergone transfemoral TAVR with Edwards SAPIEN 3, Medtronic CoreValve, or Medtronic Evolut R valves throughout Japan from April 2016 to March 2018. Pacemaker implantation, mortality, and health expenditure were examined for each valve type during hospitalization and at 1 month, 3 months, 6 months, and 1 year. Generalized linear regression models and Cox proportional hazards models were used to examine the associations between the valve types and outcomes.

Results: We analyzed 7244 TAVR cases (SAPIEN 3: 5276, CoreValve: 418, and Evolut R: 1550) across 145 hospitals. The adjusted 1-year expenditures for SAPIEN 3, CoreValve, and Evolut R were $79 402, $76 125, and $75 527, respectively; SAPIEN 3 was significantly more expensive than the other valves ($P < .05$). The pacemaker implantation hazard ratios (95% confidence intervals) for CoreValve and Evolut R were significantly higher ($P < .001$) than SAPIEN 3 at 2.61 (2.07-3.27) and 1.80 (1.53-2.12), respectively. The mortality hazard ratios (95% confidence intervals) for CoreValve and Evolut R were not significant at 1.11 (0.84-1.46) and 1.22 (0.97-1.54), respectively.

Conclusions: SAPIEN 3 users had generally lower pacemaker implantation and mortality but higher expenditures than CoreValve and Evolut R users.

Keywords: balloon-expandable valve, newer generation devices, self-expanding valve, transcatheter aortic valve replacement.

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Introduction

Transcatheter aortic valve replacement (TAVR) is a minimally invasive catheter-based surgical procedure performed under fluoroscopic guidance to implant aortic valves in high-risk or inoperable patients with aortic stenosis. This procedure is generally used in individuals who, due to advanced age or comorbidities, are unable to undergo thoracotomy with cardiopulmonary bypass.

The clinical efficacy of TAVR has been documented in 2 large-scale randomized controlled trials—the PARTNER Trial and the CoreValve US Pivotal Trial—in which TAVR demonstrated similar or better outcomes than surgical aortic valve replacement procedures.[1,2] Both trials examined the use of first-generation SAPIEN (Edwards Lifesciences, Irvine, CA) balloon-expandable valves and CoreValve (Medtronic, Minneapolis, MN) self-expandable valves.

However, manufacturers have since introduced newer versions of these devices, including the SAPIEN XT (Edwards Lifesciences, Irvine, CA), SAPIEN 3 (Edwards Lifesciences, Irvine, CA), Evolut R (Medtronic, Minneapolis, MN), and Evolut R PRO (Medtronic, Minneapolis, Minnesota), which further improve TAVR performance.[3-6]

The CHOICE (Randomized Comparison of Transcatheter Heart Valves in High Risk Patients with Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN XT) study is, at present, the only randomized controlled trial to have compared the success rates between balloon-expandable valves (SAPIEN XT) and self-expandable valves (CoreValve).[7] In addition, the differences among next-generation valves have only been investigated using multicenter observational studies involving several selected hospitals.[8–10] Because observational studies of medical devices may incorporate variations in surgeons' technical proficiency and

learning curve effects,[11] it is difficult to draw conclusions on the benefits of the valves themselves. As a consequence, observational studies that use a sample of selected hospitals may not be able to accurately assess the comparative effectiveness of these valves.

To overcome this limitation, this retrospective cohort study was performed to compare the 1-year survival and healthcare expenditures among SAPIEN 3, CoreValve, and Evolut R users in all hospitals throughout Japan. The inclusion of all hospitals in Japan allowed us to eliminate the selection bias that can arise from using a selected sample of hospitals due to variations in surgeons' technical proficiency. This study also examined whether TAVR procedures are susceptible to learning curve effects through an analysis of Evolut R use with increasing case experience. As Evolut R was approved for use in Japan during the study period, we were able to obtain data starting from the first Evolut R case in each hospital that used this device. Based on these data, we analyzed outcomes according to hospital-level case volume to examine the learning curve effects for this new device.

Methods

Data Source

Data for analysis were obtained from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB). The NDB is a government-managed database that contains patient-level health insurance claims data for all medical services provided under the national insurance system for almost all Japanese citizens from 2009 onward. Because the data are not limited to specific insurers, the NDB enables the tracking of individuals who would otherwise be lost to follow-up due to changes in insurers (eg, after job changes or retirement). Furthermore, the data are not limited to specific healthcare providers, which facilitates the tracking of medical service utilization in patients at any provider after being discharged from acute care hospitals. However, NDB data lack information on recipients of noninsured publicly funded healthcare or public assistance. In addition, the NDB stipulates that statistical aggregates with fewer than 10 individuals cannot be published in order to ensure patient anonymity.

The study was approved by the Kyushu University Institutional Review Board for Clinical Research (Approval Number 30-149).

Patient Selection

This retrospective cohort study was performed using patients with aortic stenosis who had undergone transfemoral TAVR using either a balloon-expandable valve (SAPIEN 3) or a self-expandable valve (CoreValve or Evolut R) throughout Japan between April 2016 and March 2018.

Recorded diagnoses of aortic stenosis were identified in the claims data using the relevant International Classification of Diseases, 10th Revision code (I350). The use of balloon-expandable and self-expandable valves was identified through their corresponding Japanese medical device codes in the NDB.

The use of SAPIEN XT for aortic stenosis has been covered under insurance since the introduction of TAVR to Japan in June 2013. However, Japan's health insurance system did not distinguish between transfemoral and transapical TAVR until March 2016. Therefore, our study focused on patients from April 2016 onward to allow the identification of transfemoral TAVR. Moreover, although the medical device codes in the NDB specify if a valve is balloon-expandable or self-expandable, they do not provide information on the individual valve products used (ie, valve generation or specific device name). As SAPIEN 3 was approved for insurance

coverage in May 2016, our analysis designated all patients who used balloon-expandable valves during the study period as the SAPIEN 3 group. Similarly, the CoreValve and Evolut R valves were approved in January 2016 and December 2016, respectively. Therefore, patients who used self-expandable valves between April 2016 and November 2016 were designated the CoreValve group, whereas patients who used self-expandable valves from December 2016 onward were designated the Evolut R group.

The study also included patients who underwent other surgical treatments (such as valve replacements and aortic valve expansion) in addition to TAVR and patients who used more than one valve.

Outcomes

The primary outcomes were pacemaker implantation and all-cause mortality rates. The occurrence of these outcomes was analyzed during hospitalization and at 1 month, 3 months, 6 months, and 1 year. The patients were also tracked until March 2018 or death, whichever occurred earlier. Because the NDB only provides information for the month of death, the month of hospital discharge was set as the first month when calculating mortality.

The study's secondary outcome was health expenditure. As the NDB only allows the calculation of health expenditures according to hospitalization episode or month, our analysis measured the following expenditures: total expenditure during hospitalization for the TAVR procedure (in-hospital expenditure), in-hospital expenditure and expenditure for the month of discharge (1-month total health expenditure), in-hospital expenditure and expenditure for 3 months after discharge (3-month total health expenditure), in-hospital expenditure and expenditure for 6 months after discharge (6-month total health expenditure), and in-hospital expenditure and expenditure for 12 months after discharge (1-year total health expenditure). In each tracking interval, the total health expenditure included all expenditure items covered by insurance, such as hospitalization expenditure for the TAVR procedure, the subsequent expenditures after discharge, and expenditures for other hospitalization episodes. Here, expenditures included all charges covered by Japan's public insurance system, such as base hospitalization charges, examination charges, dispensing charges, surgery charges, medical treatment charges, meal charges, and rehabilitation charges. Expenditures were converted from Japanese yen to US dollars using the 2019 purchasing power parity rate ($1.00 = 103.4 yen).

Covariates

To account for variations in patient characteristics for each of the valve groups, we examined patient sex, age, the number of risk factors used in the Society of Thoracic Surgeons (STS) risk score, and the Charlson comorbidity index (CCI) score. The NDB provides patient age in 5-year intervals, and each patient's age was calculated as the median of their listed 5-year interval (eg, a patient with a listed age of 80-84 years was given an age of 82 years for this study).

The NDB is a claims database and does not include information on patients' physical measurements (eg, body weight and height) or laboratory test results (eg, hematocrit, platelet count, hypertension). As a consequence, we were unable to calculate the STS risk score, which is used in the risk profiling of patients with aortic stenosis. Instead, we calculated the number of STS risk factors based on the occurrence of the following components: (1) heart failure within 2 weeks, (2) dialysis, (3) angina during admission, (4) previous myocardial infarction, (5) cardiac arrhythmia, (6) chronic lung disease, (7) cerebrovascular disease, (8) peripheral arterial disease, (9) diabetes, (10) hypertension, (11) endocarditis,

Table 1. Patient characteristics and unadjusted in-hospital outcomes according to valve type.

	SAPIEN 3 (n = 5276)	CoreValve (n = 418)	Evolut R (n = 1550)	P
Age, mean [SD]*	84.6 [5.1]	84.8 [5.1]	85.1 [5.2]	.011
Women, n (%)	3622 (68.7)	269 (64.4)	1 141 (73.6)	<.001
CCI score, mean [SD]	2.1 [1.3]	2.0 [1.4]	2.1 [1.3]	.316
No. of STS risk factors, mean [SD]	6.8 [2.5]	7.4 [2.4]	6.8 [2.4]	<.001
Heart failure within 2 weeks	2669 (50.6)	231 (55.3)	789 (50.9)	.184
Dialysis	117 (2.2)	13 (3.1)	40 (2.6)	.403
Angina during admission	3889 (73.7)	304 (72.7)	1136 (73.3)	.874
Previous myocardial infarction	768 (14.6)	63 (15.1)	226 (14.6)	.959
Cardiac arrhythmia	1743 (33.0)	147 (35.2)	468 (30.2)	.055
Chronic lung disease	1549 (29.4)	144 (34.5)	434 (28.0)	.037
Cerebrovascular disease	2683 (50.9)	244 (58.4)	830 (53.6)	.004
Peripheral arterial disease	1908 (36.2)	178 (42.6)	604 (39.0)	.008
Diabetes	1830 (34.7)	144 (34.5)	528 (34.1)	.902
Hypertension	5016 (95.1)	407 (97.4)	1486 (95.9)	.057
Endocarditis	527 (10.0)	58 (13.9)	165 (10.7)	.039
Coronary anatomy/disease known	1327 (25.2)	107 (25.6)	384 (24.8)	.928
Cardiogenic shock	157 (3.0)	13 (3.1)	50 (3.2)	.877
Intra-aortic balloon pump use	121 (2.3)	n.r.[†]	31 (2.0)	.785
Use of inotropes	2199 (41.7)	195 (46.7)	613 (39.6)	.029
Previous cardiac intervention	2807 (53.2)	301 (72.0)	819 (52.8)	<.001
LOS, mean [SD]	21.1 [17.9]	22.6 [15.7]	22.1 [20.8]	.063
In-hospital expenditure, mean [SD]	61 549 [11 737]	57 983 [11 807]	57 448 [14 557]	<.001
Pacemaker implantation, n (%)	357 (6.8)	78 (18.7)	196 (12.7)	<.001
In-hospital mortality, n (%)	67 (1.3)	n.r.[†]	35 (2.3)	.016

CCI indicates Charlson comorbidity index; LOS, length of stay; SD, standard deviation; STS, Society of Thoracic Surgeons.
*Mean ages were calculated using the median value of each patient's listed 5-year age interval.
[†]n.r. refers to nonreportable values as the use of the NDB does not allow the publication of aggregates with fewer than 10 patients.

(12) coronary anatomy/disease known (other acute ischemic heart disease), (13) cardiogenic shock, (14) intra-aortic balloon pump use, (15) use of inotropes (intravenous dopamine), (16) previous cardiac intervention, (17) rheumatic mitral valve disease, (18) rheumatic aortic valve disease, and (19) rheumatic tricuspid valve disease.

Statistical Analysis

First, the characteristics of patients who had been hospitalized (admitted and discharged) and had undergone TAVR between April 2016 and March 2018 were described according to valve type. We also examined the following unadjusted in-hospital outcomes: pacemaker implantation rate, in-hospital mortality rate, length of stay (LOS) duration, and in-hospital expenditure. The analysis was conducted using patient-level data provided by the NDB. However, NDB regulations stipulate that aggregate data with fewer than 10 patients cannot be disclosed in publicly available documents. In accordance with these regulations, such aggregates were designated "not reportable" but were still included in the statistical analysis. Next, the crude clinical outcomes and expenditures for the various tracking intervals (1 month, 3 months, 6 months, and 1 year, where possible) were calculated. The clinical outcomes included all-cause readmission rate, pacemaker implantation rate, and mortality rate.

Generalized linear regression models were used to produce estimates of in-hospital expenditures and 1-year total health expenditures for the different valve groups after accounting for variations in patient characteristics. As health expenditures are known to exhibit a gamma distribution[12,13], both in-hospital expenditures and 1-year total health expenditures were analyzed as dependent variables in generalized linear regression models. In each model, the exposure variables were the valve types (dummy variables for SAPIEN 3, CoreValve, and Evolut R), and the covariates were patient sex, age, number of STS risk factors, and CCI score. A gamma distribution and log link function were used for the probability distribution. Marginal means were estimated to calculate the in-hospital expenditures and 1-year total health expenditures for the different valve types that accounted for patient characteristics in the generalized linear regression models; these are mean values of each parameter in which the covariates are substituted with their mean values based on the estimates from the regression analysis. The estimation of 1-year total health expenditure was conducted using only patients who were surviving at 12 months after the TAVR procedure.

The examination of clinical outcomes (pacemaker implantation and mortality rates) among the valve types was performed using Cox proportional hazards models. The hazard ratios after adjusting for patient sex, age, number of STS risk factors, and CCI score were calculated.

Table 2. Expenditures and clinical outcomes for various tracking intervals according to valve type.

	SAPIEN 3	CoreValve	Evolut R
1-month outcomes			
N	4943	418	1432
Expenditure, mean [SD]	66 916 [17 663]	62 579 [15 581]	62 853 [19 281]
All-cause readmission, n (%)	902 (18.3)	86 (20.6)	324 (22.6)
Pacemaker implantation, n (%)	353 (7.1)	79 (18.9)	186 (13.0)
Mortality, n (%)	61 (1.2)	n.r.*	32 (2.2)
3-month outcomes			
N	4423	418	1235
Expenditure, mean [SD]	69 956 [19 544]	65 801 [17 342]	65 740 [19 861]
All-cause readmission, n (%)	1231 (27.8)	127 (30.4)	386 (31.3)
Pacemaker implantation, n (%)	335 (7.6)	79 (18.9)	167 (13.5)
Mortality, n (%)	97 (2.2)	13 (3.1)	45 (3.6)
6-month outcomes			
N	3452	418	901
Expenditure, mean [SD]	73 359 [21 636]	69 199 [19 372]	68 882 [20 877]
All-cause readmission, n (%)	1265 (36.7)	167 (40.0)	368 (40.8)
Pacemaker implantation, n (%)	287 (8.3)	83 (19.9)	132 (14.7)
Mortality, n (%)	128 (3.7)	21 (5.0)	46 (5.1)
1-year outcomes			
N	1809	418	263
Expenditure, mean [SD]	78 920 [28 596]	75 473 [23 539]	74 342 [25 724]
All-cause readmission, n (%)	900 (49.8)	232 (55.5)	143 (54.4)
Pacemaker implantation, n (%)	165 (9.1)	88 (21.1)	38 (14.5)
Mortality, n (%)	137 (7.6)	38 (9.1)	22 (8.4)

SD indicates standard deviation.
*n.r. refers to nonreportable values as the use of the NDB does not allow the publication of aggregates with fewer than 10 patients.

To examine if there were learning curve effects in TAVR, we conducted a secondary analysis of patients who had used Evolut R. These patients were first sorted within each hospital according to their date of surgery (earliest to latest) and then categorized into patients 1 through 20, patients 21 through 50, and patient 51 or later. These categories were used as exposure variables. The dependent variables were the following in-hospital outcomes: LOS duration, in-hospital expenditure, in-hospital pacemaker implantation, and in-hospital mortality. The covariates included patient sex, age, number of STS risk factors, and CCI score. Gamma models were employed to calculate cost ratios of the patient categories for LOS duration and in-hospital expenditure, and logit models were used to calculate the odds ratios for in-hospital pacemaker implantation and mortality.

P values below .05 were considered statistically significant. All statistical analyses were conducted using Stata version 15.1 (Stata Corp, College Station, TX).

Sensitivity Analysis

The effectiveness of an implantable medical device encompasses both the effectiveness of the device itself and the technical proficiency of the surgeons who implant the device. In order to account for the possible variations in surgeons' technical proficiency, we conducted a sensitivity analysis with propensity score matching. Here, we evaluated the in-hospital expenditure, 1-year total health expenditure, and clinical outcomes in SAPIEN 3 and

Evolut R users. Three models were constructed (in-hospital expenditure model, 1-year total health expenditure model, and clinical outcome model) using SAPIEN 3 and Evolut R users from the same hospital who were matched through propensity scores. These propensity scores were calculated using a logistic regression model that included patient sex, age, number of STS risk factors, and CCI score as covariates. The patients were then matched with a caliper of 0.25 standard deviations of the logit propensity score.

Results

The characteristics of the patients are summarized in Table 1. During the study period, we identified 7244 TAVR cases across 145 hospitals. Among these, there were 5276 patients in the SAPIEN 3 group, 418 patients in the CoreValve group, and 1550 patients in the Evolut R group. The patients had a mean age of approximately 85 years, with patients in the Evolut R group slightly older (85.1 years). The proportion of women was highest in the Evolut R group (73.6%) and lowest in the CoreValve group (64.4%). CCI scores were similar across the groups, but the CoreValve group had a slightly higher number of STS risk factors than the other groups. The LOS duration was 21.1 days in the SAPIEN 3 group, 22.6 days in the CoreValve group, and 22.1 days in the Evolut R group; hospitalizations for self-expandable valve procedures were approximately 1 day longer than for balloon-expandable valve

Table 3. Associations of valve type with in-hospital expenditure and 1-year expenditure: results from the generalized linear regression analysis.

	In-hospital expenditure*		1-year expenditur†	
	Cost ratio (95% CI)	*P*	Cost ratio (95% CI)	*P*
Valve				
SAPIEN 3	REF		REF	
CoreValve	–0.062 (–0.081 to –0.044)	<.001	–0.042 (–0.077 to –0.007)	.019
Evolut R	–0.071 (–0.082 to –0.061)	<.001	–0.050 (–0.093 to –0.007)	.022
Patient characteristics				
Age	0.002 (0.001, 0.003)	<.001	–0.008 (–0.011 to –0.006)	<.001
Women	0.019 (0.010, 0.028)	<.001	0.033 (0.005, 0.061)	.022
CCI score	0.026 (0.023, 0.029)	<.001	0.033 (0.023, 0.043)	<.001
No. of STS risk factors	0.010 (0.008, 0.012)	<.001	0.036 (0.030, 0.041)	<.001

CCI indicates Charlson comorbidity index; CI, confidence interval; STS, Society of Thoracic Surgeons.
*Estimates using the margins command in Stata: SAPIEN 3 = $61 169, CoreValve = $57 467, Evolut R = $56 962.
†Estimates using the margins command in Stata: SAPIEN 3 = $79 402, CoreValve = $76 125, Evolut R = $75 527.

procedures. The SAPIEN 3 group had higher in-hospital expenditures ($61 549) than the CoreValve group ($57 983) and the Evolut R group ($57 448). Pacemaker implantation was more frequent for the self-expandable valves (CoreValve: 18.7%; Evolut R: 12.7%) than the balloon-expandable valve (SAPIEN 3: 6.8%). The in-hospital mortality rates were 1.3% in the SAPIEN 3 group and 2.3% in the Evolut R group (mortality in the CoreValve group was not reportable due to the low number of patients).

The unadjusted outcomes according to tracking interval after discharge are presented in Table 2. The SAPIEN 3 group generally showed higher expenditures but lower all-cause readmission, pacemaker implantation, and mortality rates than the other groups throughout all tracking intervals. The differences in expenditures between the SAPIEN 3 and Evolut R groups were generally stable for the year following admission, and the differences in in-hospital expenditures were indicative of the differences in subsequent expenditures. The unadjusted 1-year pacemaker implantation rate was 9.1% in the SAPIEN 3 group, 21.1% in the CoreValve group, and 14.5% in the Evolut R group. The unadjusted 1-year mortality rate was 7.6% in the SAPIEN 3 group, 9.1% in the CoreValve group, and 8.4% in the Evolut R group.

Table 3 shows the associations of valve types with in-hospital expenditures and 1-year total health expenditures after adjusting for patient characteristics. In both generalized linear regression models, the self-expandable valves (CoreValve and Evolut R) were associated with significantly lower expenditures than the balloon-expandable valve (SAPIEN 3). In particular, Evolut R use was associated with a 7.1% reduction in in-hospital expenditures (*P* < .001) and 5.0% reduction in 1-year total health expenditures (*P* = .022) when compared with SAPIEN 3 use. In the estimates of marginal means, the in-hospital expenditures for the SAPIEN 3 group, CoreValve group, and Evolut R group were $61 169, $57 467, and $56 962, respectively; the 1-year total health expenditures for the SAPIEN 3 group, CoreValve group, and Evolut R group were $79 402, $76 125, and $75 527, respectively. The characteristics of patients before and after propensity score matching are summarized in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.10.022, and the expenditure estimates after propensity score matching are presented in Appendix Table 2. Evolut R use was associated with a 7.2% reduction in in-hospital expenditures (*P* < .001) and 6.7% reduction in 1-year total health expenditures (*P* = .093) when compared with SAPIEN 3 use.

The hazard ratios for the clinical outcomes of pacemaker implantation and mortality throughout the study period among the valve groups are presented in Table 4. The hazard ratios (95% confidence intervals) for pacemaker implantation associated with CoreValve and Evolut R use were 2.61 (2.07–3.27) and 1.80 (1.53–2.12), respectively; these were significantly higher (*P* < .001) when compared with SAPIEN 3 use. The hazard ratios (95% confidence intervals) for mortality associated with CoreValve and Evolut R use were 1.11 (0.84–1.46) and 1.22 (0.97–1.54), respectively; however, no significant differences with SAPIEN 3 use were detected. The majority of pacemaker implantations were performed during the index TAVR hospitalization, with a gradual increase after discharge. All valve types demonstrated increased mortality rates with longer tracking intervals. The hazard ratios for pacemaker implantation and mortality after propensity score matching are presented in Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.10.022. The hazard ratios (95% confidence intervals) for pacemaker implantation and mortality associated with Evolut R use were 1.64 (1.30–2.07) and 1.16 (0.86–1.58), respectively, when compared to SAPIEN 3 use.

The in-hospital outcomes in patients who received an Evolut R valve according to the number of treated patients (representing cumulative case experience) in each hospital are shown in Table 5. When compared to patients 1 through 20, the treatment of patients 21 through 50 and patient 51 or later showed general trends toward reductions in LOS duration, in-hospital expenditure, pacemaker implantation, and in-hospital mortality. The treatment of patients 21 through 50 was significantly associated with lower LOS duration and in-hospital expenditure.

Discussion

This study provides real-world evidence for the clinical and economic outcomes of TAVR use at the national level among patients with aortic stenosis in Japan. Our investigation is characterized by the following: (1) almost all patients with TAVR in Japan were included in analysis, (2) all institutions that performed TAVR procedures were included in analysis, and (3) each patient was tracked for 1 year after treatment where possible. Through this retrospective cohort study, we were able to determine the outcomes of each valve type during the study period. SAPIEN 3 use

Table 4. Associations of valve type with clinical outcomes during the study period: results from the Cox proportional hazards analysis.

	Pacemaker implantation		Mortality	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Valve				
SAPIEN 3	REF		REF	
CoreValve	2.61 (2.07-3.27)	<.001	1.11 (0.84-1.46)	.453
Evolut R	1.80 (1.53-2.12)	<.001	1.22 (0.97-1.54)	.085
Patient characteristics				
Age	1.02 (1.01-1.04)	.001	1.02 (1.00-1.04)	.024
Women	1.07 (0.91-1.26)	.405	0.74 (0.62-0.89)	.001
CCI score	1.16 (1.10-1.21)	<.001	1.25 (1.18-1.32)	<.001
No. of STS risk factors	1.02 (0.99-1.05)	.294	1.23 (1.19-1.27)	<.001

CCI indicates Charlson comorbidity index; CI, confidence interval; STS, Society of Thoracic Surgeons.

was associated with a significantly lower rate of pacemaker implantation than Evolut R use. Although SAPIEN 3 use also had a lower mortality rate, the association was not significant. However, CoreValve and Evolut R use were significantly cheaper than SAPIEN 3 use. The results of the sensitivity analysis suggest that these findings are robust to surgeon-level variations. Our analysis of Evolut R also indicated that there were learning curve effects for this TAVR procedure.

The finding that pacemaker implantation rates were higher for self-expanding valves corroborates the results compiled in a recent systematic review.[14] The majority of these pacemaker implantations occurred during the TAVR hospitalization, and the 1-month pacemaker implantation rates for the SAPIEN 3 and Evolut R groups were 7.1% and 13.0%, respectively; the hazard ratio for Evolut R use was 1.80 (P < .001) relative to SAPIEN 3 use. An observational study conducted in Israel estimated the 30-day pacemaker implantation rates in SAPIEN 3 and Evolut R users to be 14.4% and 17.5%, respectively.[8] Numerous studies have also reported the pacemaker implantation rates for SAPIEN 3 users to be higher than 10%,[15–29] whereas the rates for Evolut R users are generally reported to exceed 15%.[5,6,29–33] Therefore, the pacemaker implantation rates in Japan for both valve types are lower than those previously reported.

Studies from the United States and Israel have noted similar mortality rates between SAPIEN 3 and Evolut R.[8,10] In contrast, our study found that the 1-month mortality rates were higher for Evolut R (2.2%) than for SAPIEN 3 (1.2%); however, the hazard ratio for Evolut R was not significant at 1.22 (P = .085). The mortality rates associated with SAPIEN 3 use have been reported to be 2.2% in the European SOURCE 3 Registry,[26] 2.2% in the US PARTNER II Trial,[28] and 2.8% in the Swiss TAVI Registry.[24] Similarly, the mortality rates associated with Evolut R use have been reported to be 2.7 % in the US STS/ACC TVT Registry,[6] 3.2% in the Swiss TAVI Registry,[5] 2.3% in the UK & Ireland Evolut R Implanters' Registry,[33] 2.5% in the Evolut R US Study,[32] and 1.9% in the US FORWARD Study.[15,31] When compared with these studies conducted in other countries, our analysis showed lower mortality rates for SAPIEN 3 and Evolut R use in Japan.

The difference in mortality rates between SAPIEN 3 and Evolut R use in our study may be attributable to 2 possible reasons. First, the Evolut R valve incorporates technical improvements over the previous generation CoreValve, which may have necessitated changes in its operability by surgeons. In particular, the design of the Evolut R valve allows it to be recaptured and repositioned to facilitate its optimal placement during implantation. This valve is

also devised to be implanted through a new proprietary system. In this way, there was unlikely to be a continuous learning curve effect in the transition from CoreValve to Evolut R. Instead, this change would have required some technical training to allow surgeons to become familiar with the newer device. Our analysis indicated that the accumulation of case experience at the hospital level may have reduced pacemaker implantation and in-hospital mortality rates in later patients, but these associations were not statistically significant. However, the analysis detected significantly lower LOS durations in later patients. An analysis of the STS/ACC TVT registry also reported the presence of initial learning curve effects after the introduction of balloon-expandable valves.[11] The second reason for the differing mortality rates between SAPIEN 3 and Evolut R is the high possibility that self-expandable valves are selectively used in patients who cannot be treated using balloon-expandable valves due to advanced calcification of their aortic valves. Although our study was unable to ascertain the extent of aortic valve calcification, severe calcification is known to increase the risk of annular rupture.[34] Furthermore, self-expandable valves are used more frequently than balloon-expandable valves in patients with severely calcified aortic valves.[10,35] As severe calcification of aortic valves is a high-risk factor for pacemaker implantation and mortality,[22,36] the Evolut R group in our study may have included a greater proportion of high-risk patients that could not be accounted for using the number of STS risk factors.

SAPIEN 3 was significantly more expensive than the self-expandable valves, with the main difference in expenditures occurring during TAVR hospitalization. Because there was only a difference of 1 day in LOS between the balloon-expandable valves and self-expandable valves, the difference in expenditure is likely primarily due to the price differences in valve types. In Japan, the price of the SAPIEN 3 balloon-expandable valve is approximately $43 220, which is $7415 more expensive than the self-expandable valves ($35 805). However, patients who used the self-expandable valves had a higher pacemaker implantation rate during hospitalization, which would reduce the difference in in-hospital expenditures. Nevertheless, SAPIEN 3 use was still approximately $4000 more expensive than the self-expandable valves even after accounting for these additional expenditures. A German study reported that although SAPIEN 3 is approximately €4390 more expensive than Evolut R, there was no significant difference in total in-hospital expenditures between the 2 valve types.[37] This suggests that there is an excessive price difference between balloon-expandable valves and self-expandable valves in Japan.

Table 5. In-hospital outcomes for patients who received an Evolut R valve according to the hospital-level number of treated patients.

Hospital-level number of treated patients	LOS		In-hospital expenditure		Pacemaker implantation		In-hospital mortality	
	Cost ratio	P	Cost ratio	P	Odds ratio	P	Odds ratio	P
Patients 1-20	REF		REF		REF		REF	
Patients 21-50	−0.114 (−0.208 to −0.020)	.017	−0.031 (−0.060 to −0.002)	.034	0.826 (0.355, 1.922)	.657	0.810 (0.556, 1.180)	.273
Patients 51 or later	−0.161 (−0.348 to −0.026)	.091	−0.054 (−0.111 to −0.003)	.065	0.589 (0.078, 4.423)	.607	0.676 (0.302, 1.512)	.341

LOS indicates length of stay.

This study is the first to examine 1-year expenditure differences among medical devices using the NDB. It is particularly notable that a nationally representative data source such as the NDB was used to examine aspects of medical devices, which tend to be highly dependent on surgeons' skills and techniques. The large scale of the database therefore allowed us to account for these surgeon-level variations. Moreover, the NDB allows the comprehensive coverage of medical services provided at other healthcare institutions after patients are discharged from hospital. This is useful for assessments of medical technologies where postsurgical adverse events can occur with some degree of frequency. This enabled comprehensive estimates of total health expenditures that incorporated all insured healthcare utilization after discharge.

The findings of this study should be interpreted with consideration to the following limitations. First, this study was conducted with the assumption that each valve would be uniformly adopted throughout Japan after the month in which sales were approved, but the actual transition from older-generation devices to the latest versions would not be immediate. Therefore, it is possible that the SAPIEN XT balloon-expandable valve was still in use in some hospitals after May 2016, as was the CoreValve self-expandable valve after December 2016. Nevertheless, it is unlikely that surgeons would persist in using older-generation devices after newer versions are approved, especially if studies demonstrate the superiority of the newer models.[3–6] Second, the number of STS risk factors, which was used to account for variations in patient severity, did not include all components used in the STS risk score. This aspect of patient characteristics may therefore have been inadequately adjusted. In particular, self-expandable valves may be selectively used for cases with severely calcified aortic valves,[10,35] and the CoreValve and Evolut R groups could have included a larger proportion of patients who require more difficult surgeries than the SAPIEN 3 group. Third, the study was conducted using a claims database, which lacked the data needed to allow the assessment of outcomes such as MACCE and readmissions due to heart failure. Treatment episodes in Japanese claims data often include recorded diagnoses of pre-existing conditions, and it is difficult to determine if such conditions (eg, MACCE) first occurred before or after the TAVR procedure. Also, the data do not support the identification of patients who are only eligible for a specific procedure. In contrast, outcomes such as death and pacemaker implantation are easier to accurately identify using these data. In an analysis of Japan's OCEAN registry, which focuses on SAPIEN XT cases in high-volume centers, the 30-day mortality rate between October 2013 and June 2016 was reported to be 1.74%.[38] The corresponding mortality rate using the NDB was higher at 2.06% (data not shown). However, our study did not focus only on high-volume centers but included data from almost all cases in Japan, which provided a more accurate representation of the situation. Fourth, there were only 263 Evolut R users who could be tracked for 1 year after discharge. As our study period ended in March 2018, we were only able to examine 1-year outcomes in patients who received an Evolut R valve from December 2016 (when it was approved) until March 2017. The presence of learning curve effects for this device (Table 5) suggests that the expenditures in Table 3 may be overestimated. A longer study period is therefore required to obtain more accurate estimates for Evolut R use.

Conclusions

In this analysis of clinical and economic outcomes in almost all TAVR cases in Japan, the SAPIEN 3 balloon-expandable valve showed generally lower pacemaker implantation and mortality rates, but had higher expenditures when compared with the CoreValve and Evolut R self-expandable valves. As the newer Evolut R device may still be susceptible to learning curve effects, the disparities in clinical outcomes may gradually diminish as surgeon proficiency and experience increase.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.10.022.

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