Early Outcomes in Japanese Dialysis Patients Treated With Transcatheter Aortic Valve Implantation

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Background: Although transcatheter aortic valve implantation (TAVI) is a new alternative treatment with acceptable midterm results for high surgical risk patients, at present performing the procedure in dialysis patients is not reimbursed in Japan.

Methods and Results: The study group of 17 dialysis patients (mean age, 76.7±5.0 years) underwent TAVI with the SAPIEN/SAPIEN XT. EuroSCORE and STS score were 25.0±19.0% and 15.4±12.3%, respectively. Transfemoral and transapical approaches were performed in 7 (41.2%) and 10 patients (58.8%), respectively. ICU and hospital stays after TAVI were 1.8±1.6 and 12.9±12.7 days, respectively. Mean transvalvular gradients at discharge significantly decreased from 45.9±13.3 mmHg to 10.7±4.3 mmHg (P<0.0001) and effective orifice area significantly increased from 0.78±0.17 to 1.69±0.37 cm² (P<0.0001). Device success was 87.5%. One patient required a valve-in-valve procedure on 187-postoperative-day for an acute increase in paravalvular leakage caused by initial lower implantation of the device. The overall mortality at 1 year was 0% and clinical efficacies at 30 days, 6 months, and 1 year were 93.8%, 83.3%, and 69.2%, respectively.

Conclusions: Satisfactory early results were achieved with TAVI in Japanese dialysis patients with a high surgical risk, indicating it is a safe and effective alternative for the treatment of aortic valve stenosis in such patients. (Circ J 2015; 79: 2713–2719)

Key Words: Aortic valve stenosis; Dialysis; Transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) is an important, new, alternative treatment for aortic valve stenosis (AS) in patients considered inoperable or at high surgical risk for conventional aortic valve replacement (AVR). Although AVR in dialysis patients is generally high risk, considering their comorbidities, TAVI has not been recommended in this patient group, because of a lack of evidence regarding durability, early and midterm outcomes, and life expectancy. Early and midterm outcomes of AVR in Japanese dialysis patients have been reported to be significantly improved when compared with those in European or American countries, which may be attributable to the superior clinical and social management of dialysis patients in Japan. However, results are not yet adequate when compared with those of non-dialysis patients. It is therefore necessary to prove the efficacy and safety of TAVI in Japanese dialysis patients. In the present study, we evaluated the clinical outcomes of 17 dialysis patients who underwent TAVI supported by advanced medical treatment.

Editorial p2557

Methods

AS patients with endstage renal disease (ESRD) necessitating dialysis and who were considered to be inoperable or at high surgical risk for conventional AVR were enrolled in this study. Severe AS was defined as an aortic valve area <0.8 cm² or an effective orifice area (EOA) index <0.5 cm²/m², a mean pressure gradient ≥40 mmHg, or a peak aortic jet velocity ≥4.0 m/s. Patients were required to be New York Heart Association (NYHA) class ≥II with an STS score ≥10% (if not, at least 1 surgeon and 1 cardiologist considered that the patient was not suitable for surgery because of comorbidities). Pert-
Patients with adequate iliofemoral access underwent TAVI using a SAPIEN/ SAPIEN XT with Retroflex 3/Novaflex+ delivery system via a transfemoral approach (TF) with standard surgical cut-down of the common femoral or common iliac artery, while remaining patients underwent TAVI with the Ascendra/Ascendra+ delivery system via a TA with a mini left anterior thoracotomy. All procedures were performed by a team of cardiac surgeons, cardiologists, and anesthesiologists in a hybrid operating room. Under general anesthesia, balloon aortic valvuloplasty and rapid ventricular pacing were routinely used. Transesophageal echocardiography (TEE) was utilized during the procedure in all cases. Patients began treatment postoperatively with a daily 100-mg dose of aspirin for life.

Follow-up
Patients underwent follow-up examinations, including TTE and NYHA functional class status classification, at 3 different time points: at the time of the procedure, at discharge from hospital, and at the 30-day follow-up examination. Additional follow-up visits were scheduled for 6 and 12 months postprocedure. In order to generate accurate baseline and follow-up data comparisons, all echocardiographic data relate to TTE. Adverse events data classified according to VARC 2 criteria and major cardiovascular and cerebral events (MACCE, including (non-disabling or disabling stroke and rehospitalization because of heart failure or any vascular event) were collected throughout the study.

During the follow-up period, the data for 1 patient was not collected at 30 days and 6 months for personal reasons, and 4 other patients did not pass the 6-month time point after undergoing TAVI.

Statistical Analysis
Continuous variables are presented as the mean±standard deviation and groups were compared using a 2-sample t-test. Survival analysis was performed by Kaplan-Meier method, with patients censored as of the last date known alive. A 2-sided P-value <0.05 was considered statistically significant. Freedom from MACCE analysis was performed by Kaplan-Meier method. Statistical analyses were performed using statistical analysis software (SPSS, Version 22.0. Armonk, NY, USA). All authors had full access to the complete data set and take responsibility for its integrity. In addition, the authors have read and agreed to the manuscript as written.

Results
Patients
Patients included 10 men (58.8%) and 7 women (41.2%) with a mean age of 76.7±5.0 years (range, 66–85 years). NYHA functional class was III in 8 patients (47.1%) and II in 9 patients (52.9%). Mean LVEF was 60.1±10.9% (mean, 35–73%). Mean logistic EuroSCORE and STS score were 25.0±19.0 and 15.4±12.3, respectively. Previous CABG was identified in 5 patients (29.4%) and peripheral vessel disease was found in 6 patients (35.3%). Patients on peritoneal

### Table 1. Baseline Characteristics of 17 Japanese Dialysis Patients Treated With TAVI

<table>
<thead>
<tr>
<th>Demographics/assessments</th>
<th>Patients Treated With TAVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>76.7±5.0</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>10 (58.8)</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.48±0.16</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
</tr>
<tr>
<td>Class II, n (%)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Class III, n (%)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>STS score, %</td>
<td>15.4±12.3</td>
</tr>
<tr>
<td>&lt;5, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5–10, n (%)</td>
<td>7 (41.2)</td>
</tr>
<tr>
<td>&gt;10, n (%)</td>
<td>10 (58.8)</td>
</tr>
<tr>
<td>Logistic EuroSCORE, %</td>
<td>25.0±19.0</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>COPD ≥moderate, n (%)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>12 (70.6)</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Immunosuppressant agents, n (%)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>7 (41.2)</td>
</tr>
<tr>
<td>Prior coronary artery bypass surgery, n (%)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Prior percutaneous coronary artery intervention, n (%)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Prior balloon valvuloplasty, n (%)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Pre-existing pacemaker, n (%)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Prior (paroxysmal) atrial fibrillation, n (%)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>DM-related nephropathy, n (%)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Duration of dialysis, years</td>
<td>9.2±8.3</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
</tr>
<tr>
<td>Mean pressure gradient, mmHg</td>
<td>45.9±13.3</td>
</tr>
<tr>
<td>Mean EOA, cm²</td>
<td>0.78±0.17</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>60.1±10.9</td>
</tr>
<tr>
<td>Grade of aortic insufficiency, grade</td>
<td>2.0±0.5</td>
</tr>
</tbody>
</table>

Data presented as number of patients (%) or mean±SD. COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EOA, effective orifice area; MI, myocardial infarction; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

Table 1. Baseline Characteristics of 17 Japanese Dialysis Patients Treated With TAVI

Patients gave written informed consent.

Study Device and Procedure
SAPIEN (THV 9000) and SAPIEN XT (THV 9300) (Edwards Lifesciences, Irvine, CA, USA) were used before and after a reimbursement of SAPIEN XT in Japan (October 2013), respectively.

Data presented as number of patients (%) or mean±SD. COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EOA, effective orifice area; MI, myocardial infarction; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
**Figure 1.** Prosthetic valve function, showing no deterioration during the follow-up period. *P<0.0001 compared with preoperative data. EOA, effective orifice area; mPG, mean pressure gradient.

**Figure 2.** Paravalvular leakage (PVL) during the follow-up period. With the exception of 1 patient who required a valve-in-valve procedure for an acute increase in PVL, no significant difference in PVL was observed during the follow-up period.
dialysis were not found in this cohort. Diabetes (DM)-related and non-DM-related nephropathies were found in 4 (23.5%) and 13 (76.5%) patients, respectively. The mean duration of dialysis was 9.2±8.3 years (range, 1–28 years). Demographic and baseline characteristics inclusive of comorbidities are presented in Table 1.

Procedural Results and 1 Week/Discharge Outcomes (n=17)
The TF and TA approaches were performed in 7 (41.2%); femoral: 6, iliac: 1) and 10 patients (58.8%), respectively. The SAPIEN XT (THV 9300) and the SAPIEN (THV 9000) were implanted in 10 (58.8%) and 7 patients (41.2%), respectively. The TF and TA approaches were performed in 7 (41.2%; femoral: 6, iliac: 1) and 10 patients (58.8%), respectively. The mean duration of dialysis was 9.2±8.3 years (range, 1–28 years). Demographic and baseline characteristics inclusive of comorbidities are presented in Table 1.

Table 1. Demographic and Clinical Data of Dialysis Patients From the Japanese Society for Dialysis Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>Mean ± SD 57.4 ± 11.3</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 15 (93.8%)</td>
</tr>
<tr>
<td>Race</td>
<td>Japanese 16 (100%)</td>
</tr>
<tr>
<td>BMI</td>
<td>Mean ± SD 22.4 ± 2.9</td>
</tr>
<tr>
<td>eGFR</td>
<td>Mean ± SD 45.9 ± 13.2</td>
</tr>
<tr>
<td>Diabetes (DM)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Non-DM-related nephropathies</td>
<td>13 (81.2%)</td>
</tr>
<tr>
<td>Dialysis duration</td>
<td>Mean ± SD 9.2 ± 8.3 years (range, 1–28 years)</td>
</tr>
</tbody>
</table>

Procedural Outcomes (n=17)

- **Operating time**: 109±33 min
- **Approach**:
  - Transfemoral, n (%) 6 (35.3)
  - Transiliac, n (%) 1 (5.9)
  - Transapical, n (%) 10 (58.8)
- **Bleeding**: 500±436 ml
- **Amount of contrast agents**: 100±35 ml
- **Implanted valve**:
  - SAPIEN (THV9000), n (%) 7 (41.2)
  - SAPIEN XT, n (%) 10 (58.8)
- **Implanted valve size**:
  - 23-mm, n (%) 6 (35.3)
  - 26-mm, n (%) 11 (64.7)
- **Percutaneous cardiopulmonary bypass (emergency)**, n (%) 1 (5.9)
- **Conversion to open surgery**, n (%) 0 (0)
- **Valve-in-valve**, n (%) 0 (0)
- **Coronary obstruction**, n (%) 0 (0)
- **Exstusation on operating room**, n (%) 16 (94.1)

1-week outcomes (n=17)

- **ICU stay**: 1.8±1.6 days
- **Re-initiation of dialysis (not CHDF)**, n (%) 1 (6.3)
  - 1, n (%) 14 (82.4)
  - 2, n (%) 3 (17.6)
  - Hospital-to-home discharge, n (%) 17 (100)
  - Hospital stay after the procedure, days 12.9±12.7

30-day outcomes (n=16)

- **All-cause mortality**, n (%) 0 (0)
- **Stroke**, n (%) 1 (6.3)
- **Disabling**, n (%) 0 (0)
- **Non-disabling**, n (%) 1 (6.3)
- **Life-threatening bleeding**, n (%) 1 (6.3)
- **Periprocedural MI**, n (%) 0 (0)
- **Access-related complications**, n (%) 1 (6.3)
- **Device success**, n (%) 14 (87.5)
- **Valve dysfunction**, n (%) 1 (6.3)
- **Incorrect positioning of a single prosthetic valve**, n (%) 1 (6.3)
- **Early safety**, n (%) 14 (87.5)
- **Clinical efficacy**, n (%) 15 (93.8)

Data presented as number of patients (%) or mean±SD. CHDF, continuous hemodialfiltration; ICU, intensive care unit. Other abbreviations as in Table 1.

All bioprostheses were successfully implanted and there was no conversion to surgical AVR. Emergency percutaneous cardiopulmonary bypass was required in 1 patient (5.9%) as a result of a cryptogenic hemodynamic collapse immediately after valve implantation (successfully recovered immediately after mechanical support). Transvalvular pressure gradients at discharge significantly decreased from a mean of 45.9±13.3 mmHg (preprocedural) to 10.7±4.3 mmHg (P<0.0001). The EOA increased from a mean of 0.78±0.17 to 1.69±0.37 cm² (P<0.0001) (Figure 1). Post-procedure (1 week/at discharge), 6 patients showed either no or trace paravalvular leakage (PVL) (35.3%); PVL of either moderate or greater severity was not observed (Figure 2). Mean ICU stay was 1.8±1.6 days and conventional hemodialysis (non-continuous hemodiafiltration) was reinitiated at postoperative day 1 in 14 patients (82.4%) and at postoperative day 2 in 3 patients (17.6%). All patients were ultimately discharged and mean hospital stay after TAVI was 12.9±12.7 days (range, 4–56 days). Procedural and 1 week/discharge outcomes are presented in Table 2, and echocardiographic outcomes are presented in Figure 1.

Follow-up at 30 Days (n=16) and 6 Months (n=12)
The analysis revealed that overall mortality at 6 months was 0%. The VARC 2 defined 30-day early safety rate was 87.5% (2 patients: major vascular complication in the first patient and non-disabling stroke in the second patient). Overall device success at 30 days was 87.5% (2 patients: mean PG 20 mmHg in the first patient, lower implantation in the second patient). During the follow-up period, a single patient (6.7%) required permanent pacemaker implantation because of AV block. NYHA functional class improved significantly at both 30 days and 6 months (Figure 3). Furthermore, clinical efficacies at 30 days and 6 months were 93.8% and 83.3%, respectively.

One Year Follow-up (n=13)
The analysis revealed that the overall mortality at 1 year was 0% (follow-up period: 431±270 days; range, 30–1,049 days). Freedom from MACCE at 1 year was 65.5% (Figure 4). Additional adverse events from 30 days to 1 year after the procedure included disabling stroke (1 patient) and heart failure requiring rehospitalization (2 patients). Of these, 1 patient required a valve-in-valve procedure for acute severe PVL caused by valve migration. NYHA functional class did not differ significantly from classifications at 30 days up to 1 year (Figure 3), and clinical efficacy was 69.2%. The 6- and 12-month outcomes are presented in Table 3.

Valve Function at 1 Year (n=11)
With the exception of 2 patients (the valve-in-valve and disabling stroke cases), 11 patients underwent echocardiographic follow-up. No deterioration of the bioprosthetic valve was observed in any case (Figures 1, 2).

Discussion

Clinical Data of Dialysis Patients From the Japanese Society for Dialysis Therapy

The prognosis in dialysis patients appears to be dependent on clinical and social patient support. In Japan, the numbers of dialysis patients, elderly patients, and patients with a long history of dialysis have been increasing, which seems to provide evidentiary support for the satisfactory clinical and social management available in this country. However, as the prognosis of dialysis patients improves, the number of patients with major comorbidities typified by calcified vascular and
Early Outcomes of TAVI in Japanese Dialysis Patients

Although surgical AVR is generally the first choice for treatment of AS, ESRD necessitating dialysis has been reported to increase the risk of early and midterm mortality when compared with non-ESRD patients. However, this is attributable to specific challenges regarding procedural techniques and perioperative management. Thourani et al highlighted that valvular disease is expected to inevitably increase. ESRD requiring dialysis is associated with an increased risk of calcified vascular and valvular disease, a well-known prognostic factor. In patients with calcified valvular disease, AS is common with long-term dialysis. Henceforth, a safe and effective treatment intervention for AS in Japanese dialysis patients should be mandatory.

AVR in Dialysis Patients

Figure 3. New York Heart Association (NYHA) functional class during the follow-up period improved significantly at 30 days and 6 months, and did not differ significantly from those at 30 days to 1 year.

Figure 4. Freedom from major cardiovascular and cerebral events (MACCE), including (non-disabling or disabling) stroke and rehospitalization for heart failure or any vascular event.
preoperative renal disease, especially that leading to dialysis, is significantly associated with worsened outcomes after AVR (5-year survival after AVR in dialysis patients: 28.5%).

Furthermore, Boning et al reported that AVR with a bioprosthetic valve is not contraindicated of poor prognosis in dialysis patients (5-year survival after AVR: 29.5%).

**TAVI in Dialysis Patients**

TAVI is reported to be an alternative, less invasive therapy with satisfactory early results for patients with severe AS who are considered inoperable or high surgical risk. However, in general, dialysis patients have been excluded from previous clinical trials, because of poor evidence, and so data regarding outcomes after TAVI in these patients are limited.

Indeed, in that TAVI series, ESRD requiring dialysis was significantly associated with an increased risk of both early and midterm mortality. Allende et al previously reported that of the patients in their study, who were grouped into 5 stages according to estimated glomerular filtration rate (eGFR), advanced chronic kidney disease (CKD) (stages 4 and 5) including dialysis was significantly associated with higher rates of early and late mortality. They mentioned that freedom from all-cause mortality at 1 year in CKD stage 1–2 (eGFR ≥60 ml/min/1.73 m²) was significantly higher than that of patients in CKD stage 5 (eGFR <15 ml/min/1.73 m² or dialysis) (84.4% vs. 64.5%).

However, in our study, which to the best of our knowledge is the first report of TAVI in Japanese dialysis patients, observed outcomes (especially early outcomes i.e, 1-year mortality of 0%) were satisfactory, despite our high surgical risk cohort when compared with previous reports.

Furthermore, minimizing ICU stay (1.8±1.6 days) and preservation of patients’ activities of daily living (hospital-to-home discharge: 100%) proved to be successful, even in dialysis patients. However, MACCE occurred during the follow-up period. Major bleeding at the access site (femoral artery) caused by site infection occurred in a single patient and was eventually treated with femoro-femoral bypass. An acute increase in PVL occurred in 1 patient with previous CABG, which required rehospitalization for worsening congestive heart failure and was finally treated by performing a valve-in-valve technique. Retrospective investigation using ECG-gated multi-slice CT found that this was caused by an initial lower site of implantation. Furthermore, disabling stroke occurred in 1 patient (post-operative day 343) with a history of paroxysmal atrial fibrillation. Even in a high surgical risk cohort, freedom from cardiovascular and cerebral events in the present study (65.5% at 1 year) was similar to previous reports of AVR in dialysis patients (60.5% at 1 year).

**Durability of the Transcatheter Valve in Dialysis Patients**

Regarding surgical bioprostheses, structural valve deterioration is estimated to occur more rapidly in dialysis patients. Okada et al noted that rates of freedom from structural valve deterioration at 5 years was 82% in dialysis patients and 100% in non-dialysis patients. On the other hand, during the 1-year follow-up period of the present study, no valve deterioration was observed for either the SAPIEN (THV9000) or the SAPIEN XT (THV9300). However, a mean PG 20 mmHg was observed in 1 patient (who happened to be the first patient enrolled in this study) at discharge. The gradient gradually decreased to 20 mmHg at 30 days, 17 mmHg at 6 months, and 16 mmHg at 1 year.

**Study Limitations**

This study had several limitations, including its single-center and non-randomized design, as well as the small number of enrolled patients and the short follow-up period. Furthermore, our cohort included a small number of DM-related dialysis patients (4: 23.5%), a condition that is significantly associated with late death in dialysis patients.

**Conclusions**

In 17 dialysis patients with severe AS, satisfactory outcomes after TAVI were achieved in this study. TAVI should be considered as an alternative treatment option in Japanese dialysis patients with AS. Further investigations regarding durability of transcatheter valve implants and medical statistics for mid- and long-term outcomes are recommended.

**Disclosures**

The study was supported by Edwards Lifesciences (device donation) and the Health and Labor Sciences Research Grant.

**Conflict of Interest**

The authors have no additional conflicts of interest to declare.

**References**


**Supplementary Files**

**Supplementary File 1**

**Appendix S1.** Exclusion criteria

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-15-0829