Surgical Aortic Valve Replacement for Aortic Stenosis in Dialysis Patients
— Analysis of Japan Cardiovascular Surgery Database —

Takashi Yamauchi, MD, PhD; Hiroyuki Yamamoto, MD, PhD; Hiroaki Miyata, PhD; Junjiro Kobayashi, MD, PhD; Takafumi Masai, MD, PhD; Noboru Motomura, MD, PhD

Background: Perioperative risk during surgical aortic valve replacement (SAVR) is reportedly high in dialysis patients. We aimed to determine the postoperative mortality and morbidity and identify the perioperative risk factors of mortality during SAVR in dialysis-dependent patients.

Methods and Results: From the Japan Adult Cardiovascular Surgery Database, we compared 2,875 dialysis-dependent patients who all underwent SAVR between January 2013 and December 2016. The operative mortality was 8.7% vs. 2.0% in the dialysis and non-dialysis groups, respectively. Multivariate stepwise logistic regression analysis for operative mortality revealed 8 independent risk factors including age (odds ratio [OR]=1.2), concomitant coronary artery bypass grafting (OR=1.5), peripheral arterial disease (OR=1.9), atrial fibrillation (OR=2.5), New York Heart Association class IV (OR=2.5), liver dysfunction (OR=5.8), reduced left ventricular function (OR=1.4), and history of previous cardiac surgery (OR=2.1). In addition, 8 postoperative predictors of operative mortality were identified including bleeding deep sternal infection (OR=3.4), prolonged ventilation (OR=5.4) and gastrointestinal complications (OR=10.3).

Conclusions: Compared with non-dialysis patients, SAVR in dialysis patients was associated with high rates of mortality and morbidity. An appropriate surgical strategy and careful perioperative assessment and management for prevention of infection, and respiratory and gastrointestinal complications might contribute to improved clinical outcomes after SAVR in these patients.

Key Words: Aortic stenosis; Aortic valve replacement; Dialysis
with dialysis-dependent CRF in Japan. We hope the data in the present study will contribute to the establishment of an algorithm for SAVR or TAVR in dialysis-dependent patients.

**Methods**

**Study Population**

The JCVSD was initiated in 2000 to collate the outcomes after cardiovascular procedures in many centers throughout Japan. The JCVSD adult cardiovascular division currently captures clinical information from nearly half of all Japanese hospitals performing cardiovascular surgery. The data collection form has approximately 300 variables (definitions are available online at http://www.jacvsd.umin.jp), and these are almost identical to those in the Society of Thoracic Surgeons (STS) National Database (definitions are available online at http://sts.org). The JCVSD has developed software for a web-based data collection system through which the data manager of each participating hospital electronically submits the data to the central office. The JCVSD Review Board approved the present study.

We examined 21,714 cases of elective SAVR for AS with or without CABG registered in this database between January 1, 2013 and December 31, 2016. Exclusion criteria were as follows: urgent/emergency/salvage surgery, concomitant cardiac surgery other than CABG, aortic regurgitation dominant (grade 3 or 4), rheumatic heart disease, active infective endocarditis, annular abscess, graft infection, Marfan syndrome, aortitis, Behcet’s disease, and previous AVR (mechanical or bioprosthesis). Records with missing data or out of range data for age, sex, or 30-day status (see Endpoints section below) were also excluded. After data cleaning, the population for investigating risk factors in the mortality analysis consisted of 21,714 patients.

**Statistical Analysis**

Descriptive statistics are presented as frequencies with percentage for categorical variables or as median value with

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**Table 1. Dialysis and Non-Dialysis Patients’ Characteristics**

|                         | Non-HD AVR (n=18,839) | HD AVR (n=2,875) | P value |
|-------------------------|-----------------------|------------------|---------|
| Age, years              |                       |                  |         |
| ≥80 (%)                 | 35.4                  | 16.1             | <0.0001 |
| 75–79 (%)               | 28.0                  | 24.2             |         |
| 70–74 (%)               | 18.1                  | 23.1             |         |
| 65–69 (%)               | 10.1                  | 19.4             |         |
| 60–64 (%)               | 4.4                   | 10.2             |         |
| <60 (%)                 | 4.0                   | 7.0              |         |
| Median age, years       | 77 (72–81)            | 72 (67–78)       | <0.0001 |
| Male (%)                | 42.8                  | 64.3             | <0.0001 |
| BMI ≥30 (%)             | 5.3                   | 2.3              | <0.0001 |
| DM (%)                  | 30.8                  | 42.7             | <0.0001 |
| DM insulin use (%)      | 5.9                   | 14.3             | <0.0001 |
| Hyperlipidemia (%)      | 49.7                  | 31.4             | <0.001  |
| Hypertension (%)        | 75.8                  | 77.4             | 0.056   |
| Chronic lung disease ≥ moderate (%) | 3.1 | 3.3 | 0.473 |
| History of stroke/TIA (%) | 8.2 | 12.9 | <0.0001 |
| History of psychoneurotic disorder (%) | 1.7 | 1.5 | 0.502 |
| Liver cirrhosis (Child-Pugh B/C) (%) | 0.2 | 0.3 | 0.033 |
| Carotid stenosis (%)    | 4.9                   | 5.9              | 0.019   |
| Extracardiac vascular lesion (%) | 9 | 21.7 | <0.0001 |
| PAD (%)                 | 7.4                   | 20.1             | <0.0001 |
| Concomitant malignant neoplasm (%) | 2.6 | 2.6 | 0.776 |
| Congestive heart failure (%) | 35.5 | 40.9 | <0.0001 |
| AF (%)                  | 4.9                   | 7.2              | <0.0001 |
| Previous cardiac surgery (%) | 2.5 | 5.2 | <0.0001 |
| History of coronary intervention (%) | 9.8 | 18.7 | <0.0001 |
| Coronary lesion ≥2 vessels (%) | 18.6 | 29.3 | <0.0001 |
| LMT lesion (%)          | 5.4                   | 7.6              | <0.0001 |
| LV function medium (EF 0.3–0.6) (%) | 24.3 | 42.1 | <0.0001 |
| LV function bad (EF <0.3) (%) | 1.7 | 5.4 | <0.0001 |
| Concomitant mitral stenosis (%) | 2.9 | 5.6 | <0.0001 |
| Concomitant mitral regurgitation ≥2 (%) | 21.1 | 30 | <0.0001 |
| NYHA class 4 (%)        | 2.6                   | 4.7              | <0.0001 |
| Preoperative shock (%)  | 0.3                   | 0.5              | 0.064   |

AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus; EF, ejection fraction; HD, hemodialysis; LMT, left main trunk; LV, left ventricle; NYHA, New York Heart Association; PAD, peripheral arterial disease; TIA, transient ischemic attack.
SAVR in Dialysis Patients

surgery, history of coronary intervention, left main trunk (LMT) lesion, left ventricular (LV) function medium (ejection fraction [EF], 0.3–0.6), LV function bad (EF <0.3), concomitant mitral stenosis, concomitant mitral regurgitation ≥2, New York Heart Association (NYHA) class 4, preoperative shock, concomitant CABG, preoperative administration of inotropic agents and digitalis, and current smoker. Stability of the model was checked each time a variable was eliminated. To investigate the relationship between operative death and postoperative complications in dialysis patients, we conducted a multivariate stepwise logistic regression model (P>0.25 for removal, and P<0.2 for entry) for operative mortality including 11 factors. In the JCVSD, the presence or absence of 31 postoperative complications should be registered for each patient. In view of incidence, clinical causation and association

interquartile range. We examined differences between 2 groups (SAVR with and without dialysis) using bivariate tests: Fisher’s exact test and the Pearson’s chi-square test for categorical covariates, and the unpaired t-test or Wilcoxon rank sum test for continuous covariates. To investigate the risk factors of SAVR with dialysis, we conducted a multivariate stepwise logistic regression model (P>0.25 for removal, and P<0.2 for entry) for operative mortality including the following factors: age category, sex male, body mass index (BMI) ≥30, diabetes mellitus (DM), DM insulin use, chronic lung disease ≥ moderate, history of stroke/transient ischemic attack, history of psychoneurotic disorder, liver cirrhosis (Child-Pugh B/C), carotid stenosis, extracardiac vascular lesion, peripheral arterial disease (PAD), concomitant malignant neoplasm, congestive heart failure, atrial fibrillation (AF), previous cardiac

Table 2. Intraoperative Characteristics

|                      | Non-HD AVR (n=18,839) | HD AVR (n=2,875) | P value |
|----------------------|-----------------------|------------------|---------|
| Transfusion (%)      | 81.7                  | 95.9             | <0.001  |
| Operation time (min) | 273 (223–343)         | 308 (245–395)    | <0.001  |
| ECC time (min)       | 138 (111–174)         | 150 (119–193)    | <0.001  |
| Cardiac arrest time (min) | 95 (76–120)       | 99 (79–128)      | <0.001  |
| Valve type           |                       |                  |         |
| Bioprosthesis (%)    | 85.5                  | 68.5             | <0.001  |
| Mechanical valve (%) | 11.9                  | 30.1             |         |
| Unknown (%)          | 2.6                   | 1.5              |         |
| Concomitant CABG (%) | 26.7                  | 39.0             | <0.001  |

AVR, aortic valve replacement; CABG, coronary artery bypass grafting; ECC, extracorporeal circulation; HD, hemodialysis.

Table 3. Mortality and Morbidity

|                      | Non-HD AVR (n=18,839) | HD AVR (n=2,875) | P value |
|----------------------|-----------------------|------------------|---------|
| 30-day mortality (%) | 1.2                   | 5.1              | <0.001  |
| Operative mortality (%) | 2.0                | 8.7              | <0.001  |
| Reoperation (any reason) (%) | 4.4         | 7.7              | <0.001  |
| Reoperation for bleeding (%) | 2.8           | 4.2              | <0.001  |
| Deep sternal infection (%) | 1.0               | 3.1              | <0.001  |
| Septicemia (%)        | 1.3                   | 3.8              | <0.001  |
| Prolonged ventilation (%) | 3.2                | 8.1              | <0.001  |
| Pneumonia (%)         | 2.1                   | 6.3              | <0.001  |
| Stroke (%)            | 1.9                   | 4.2              | <0.001  |
| TIA (%)               | 1.7                   | 3.1              | <0.001  |
| Coma (%)              | 0.7                   | 2.0              | <0.001  |
| AF (%)                | 19.0                  | 18.1             | 0.29    |
| Heart block (%)       | 1.2                   | 1.3              | 0.69    |
| Cardiac arrest (%)    | 1.1                   | 3.4              | <0.001  |
| Perioperative MI (%)  | 0.6                   | 0.7              | 0.34    |
| Anticoagulant comp (%)| 0.5                   | 1.5              | <0.001  |
| Tamponade requiring drainage (%) | 1.7         | 2.9              | <0.001  |
| Gastrointestinal comp (%) | 1.1               | 4.6              | <0.001  |
| New dialysis (%)      | 2.0                   | –                | <0.001  |
| Renal failure (%)     | 3.0                   | –                | <0.001  |
| Readmission (%)       | 1.6                   | 1.7              | 0.48    |
| ICU stay >8 days (%)  | 5.5                   | 13.0             | <0.001  |

ICU, intensive care unit; MI, myocardial infarction. Other abbreviations as in Tables 1, 2.
between complications, 11 complications (reoperation for bleeding, stroke, periperaoperative myocardium infarction, cardiac block, cardiac arrest, anticoagulation-related complications (bleeding and thromboembolism), tamponade, gastrointestinal complication, AF, deep sternal infection) were used in the current analysis. Among the complications observed relatively often (incidence >3%), the following 7 factors (reoperation for bleeding (OR=2.9), stroke (OR=6.6), deep sternal infection (OR=3.4), cardiac arrest (OR=44.8), AF (OR=1.6), prolonged ventilation (OR=5.4), and gastrointestinal complications (OR=10.3)) were identified as independent risk factors for operative death.

### Results

#### Patients’ Demographics

Baseline characteristics of the study population are summarized in Table 1. Patients in the dialysis group were significantly younger and had lower BMI than the non-dialysis patients. As expected, the dialysis-dependent patients had a significantly greater number of baseline comorbidities than did the non-dialysis patients. Patients in the dialysis group were more likely to have a history of diabetes (42.7% vs. 30.8%; P<0.0001), PAD (20.1% vs. 7.4%; P<0.0001). A higher rate of current congestive heart failure (40.9% vs. 35.5%; P<0.0001) with a lower EF and lower NYHA status was observed in the dialysis group. For coronary artery disease (CAD), coronary stenosis (≥2 vessels: 29.3% vs. 18.6%; P<0.0001) and LMT disease (7.6% vs. 5.4%; P<0.0001) were more common in dialysis patients.

#### Postoperative Outcomes

Transfusion and concomitant CABG were required more often in the dialysis group. Operation time, extracorporeal time and cardiac arrest time were also significantly longer in the dialysis group. In the dialysis group, a mechanical valve was significantly applied compared with the non-dialysis group (30.1% vs. 11.9%; P<0.0001) (Table 2). In-hospital outcomes are summarized in Table 3. The 30-day mortality rate was 5.1% vs. 1.2% (P<0.0001) and the operative mortality rate was 8.7% vs. 2.0% (P<0.0001) in the dialysis and non-dialysis groups, respectively. Both the 30-day and operative deaths in dialysis patients were approximately 4-fold higher than in the non-dialysis patients. Major complications such as reoperation for any reason (7.7% vs. 4.4%; P<0.0001), prolonged ventilation (8.1% vs. 3.2%; P<0.0001), deep sternal infection (3.1% vs. 1.9%; P<0.0001) and stroke (4.2% vs. 1.9%; P<0.0001) were more frequent in the dialysis group.

#### Multivariate Pre- and Intraoperative Predictors of In-Hospital Death

Multivariate predictors of operative death are summarized in Table 4. Predictors included age (odds ratio OR=1.2, 95% CI=1.1–1.3, P<0.0001), history of cardiac surgery (OR=2.1, P=0.003), concomitant CABG (OR=1.5, P=0.005), NYHA class IV (OR=2.0, P=0.004), liver dysfunction (OR=5.8, P=0.011), EF 30–60% (OR=1.4, P=0.039), PAD (OR=1.9, P<0.0001), AF (OR=2.5, P<0.0001) and history of cardiac surgery (OR=2.1, P=0.003).

### Relationship Between Operative Mortality and Postoperative Complications

Results are summarized in Table 5. Among the complications observed relatively often (incidence >3%), the following 7 factors (reoperation for bleeding (OR=2.9), stroke (OR=6.6), deep sternal infection (OR=3.4), cardiac arrest (OR=44.8), AF (OR=1.6), prolonged ventilation (OR=5.4), and gastrointestinal complications (OR=10.3)) were identified as independent risk factors for operative death.

#### Discussion

Clinical Background and Outcome of SAVR in Dialysis Patients

The clinical outcomes of SAVR, including hemodialysis and/or peritoneal dialysis-dependent patients, have been reported.6,8 In the present study, the exact number of hemodialysis patients was unclear because the JCVS does not distinguish between hemodialysis- and peritoneal dialysis-dependent patients among those requiring dialysis. The annual dialysis data report from Japan has revealed that peritoneal dialysis-dependent patients comprised 2.7% of chronic dialysis patients in 2016.10 The operative mortality rate of dialysis patients after SAVR in this study was 8.7%, which was similar to previous studies reporting an operative mortality of approximately 10%.1,2,6–8,11 The postoperative mortality rate of the dialysis group was 3–4-fold higher than that in the non-dialysis group. Interestingly, the mortality rate of TAVR has been reported to be also around 10%.1,12 As previously reported, dialysis patients have more preoperative comorbidities.1,13 Com-
pared with the clinical outcomes of 2,264 dialysis-dependent patients undergoing SAVR from the National Inpatient Sample from 2005 to 2014, the present study the rates of hypertension, chronic lung disease, liver disease and AF tended to be low. Sex, DM, PAD, and history of cardiac surgery were comparable. Major postoperative morbidity (stroke, tamponade) was also comparable. Besides the major complications, the prevalence of transient ischemic attack, coma, cardiac arrest, anticoagulant complication, gastrointestinal complications and intensive care unit stay in dialysis patients were also significantly higher than in non-dialysis patients.

**Risk Factors of Mortality of SAVR in Dialysis-Dependent Patients**

Aljohani et al analyzed 2,264 dialysis patients who underwent SAVR that included valve surgery. They demonstrated male sex, age >75 years, cardiogenic shock, PAD, liver disease, concomitant surgery, intra-aortic balloon pumping/LV assist device as risk factors for perioperative mortality in dialysis-dependent patients, which is almost consistent with our findings.

Among the relatively frequent preoperative comorbidities in the dialysis patients, we also showed that PAD (OR=1.9) and AF (OR=2.5) were strong independent risk factors for mortality. We have previously shown that PAD was an independent risk factor for death among 13,961 patients (including 1,542 (11%) dialysis-dependent patients) undergoing SAVR for AS (OR=2.15). Kim et al also demonstrated that PAD was associated with a higher incidence of major postoperative vascular complications with higher 30-day mortality and PAD was identified as an independent predictor of 1-year mortality after TAVR. PAD might represent the systemic severity of atherosclerotic changes associated with a higher incidence of postoperative major complications and mortality. PAD might be a “troublesome” comorbidity for both SAVR and TAVR.

Regarding AF, it has been reported as a common morbidity in dialysis-dependent patients. The prevalence of AF in the present study was higher among the dialysis-dependent patients than the non-dialysis patients. Interestingly, our abovementioned previous report also demonstrated that AF was an independent risk factor of death (OR=2.08). The STS risk calculator uses the prevalence of AF for risk analysis of isolated AVR. The mechanism by which AF shows an adverse effect on mortality after SAVR remains unclear. AF in patients with reduced LV function has been reported to show an adverse effect on the survival rate. AF might be also associated with perioperative stroke, which increases the postoperative morbidity and mortality.

We also demonstrated that concomitant CAGB was an independent risk factor for operative mortality after SAVR in dialysis patients (OR=1.5). The question arises whether CAGB should be performed simultaneously with SAVR when coronary disease is complicated. Horst et al report that the risk for perioperative death associated with CAGB combined with valve operation is approximately 10-fold that for isolated CAGB. Nicolini et al report that valve surgery combined with CAGB increases the late mortality rate. The worse operative morbidity in dialysis patients compared with non-dialysis patients might be partially attributed to coronary disease being more severe and concomitant CAGB therefore being performed more frequently in dialysis patients (39.0% vs. 26.7%, P<0.0001). Percutaneous coronary intervention might contribute to improving the clinical outcome of SAVR in dialysis patients complicated with CAD. Concomitant CAGB should be performed with consideration of the “risks and benefits” and further study will be necessary to elucidate this important issue.

Aljohani et al also show that in-hospital mortality after SAVR in dialysis patients remained 2-fold higher than in non-dialysis patients in propensity-matched cohorts, suggesting the presence of unrevealed risk factors that affect the mortality rate of SAVR in dialysis patients. Further study is necessary to investigate such risk factors (e.g., porcelain aorta or duration of dialysis) in order to establish benchmarks for selecting the operative procedure (SAVR or TAVR) for these patients.

**Effect of Postoperative Complications on Mortality Rate of SAVR in Dialysis-Dependent Patients**

Relatively few large-series reports have documented the detailed incidence of postoperative morbidity after SAVR in dialysis-dependent patients. Compared with non-dialysis patients, the incidence of major postoperative complications was high in the dialysis-dependent patients in the present study, as previously reported. Postoperative complications could be considered to be closely associated with higher mortality rate. The higher incidence of these complications in dialysis-dependent patients might partly explain their poor clinical outcomes. However, the effect of each complication on mortality after SAVR in dialysis-dependent patients has never been demonstrated as far as we know. We have previously reported the effect of postoperative complications on mortality after CAGB in 1,300 dialysis-dependent patients, such as stroke (OR=9.85), infection (OR=6.72), prolonged ventilation (OR=3.82), pneumonia (OR=13.15), gastrointestinal complication (OR=5.43) and heart block (OR=12.46). To improve the clinical outcome of SAVR in dialysis patients, it seems important to prevent the 7 complications demonstrated in the present study.

**Study Limitations**

Frailty and intraoperative values were not evaluated in our study. Some specific factors that may affect the operative results, such as porcelain aorta or small aortic annulus, were not included in the possible factors.

**Conclusions**

Compared with non-dialysis patients, SAVR in dialysis patients was associated with high rates of mortality and morbidity in the present study. An appropriate surgical strategy and careful perioperative assessment and management for infection, and prevention of respiratory and gastrointestinal complications might contribute to improvements in clinical outcomes after SAVR in dialysis-dependent patients.

**Acknowledgments**

The authors thank the data managers in each cardiovascular institute participating in the JCVSD for their great effort in registering clinical data, and Shinichi Takamoto who contributed to the establishment of JCVSD. Hiroyuki Yamamoto, and Hiroaki Miyata are affiliated with the Department of Healthcare Quality Assessment at the University of Tokyo. The department is a social collaboration department supported by grants from the National Clinical Database, Johnson & Johnson K.K., and Nipro Co.
IRB Information

This study was retrospective and approved by Sakurabashi Watanabe Hospital’s institutional review board (IRB ref. no. 19-31).

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