Pre- and Postoperative Predictors of Long-Term Prognosis After Aortic Valve Replacement for Severe Chronic Aortic Regurgitation

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Background: There are few data on the long-term prognosis and chronological changes in left ventricular (LV) function after aortic valve replacement (AVR) in patients with severe chronic aortic regurgitation (AR) among the Japanese population.

Methods and Results: We retrospectively investigated the long-term prognosis in 80 consecutive patients with severe chronic AR who underwent AVR. Additionally, 65 patients with follow-up echocardiography at 1 year after AVR were investigated to evaluate chronological changes in LV function. The mean follow-up period was 8.9±5.2 years. Freedom from all-cause death and cardiac death at 10 years after AVR was 76% and 91%, respectively. The preoperative ejection fraction (EF) and estimated glomerular filtration rate were independent predictors of all-cause death. Preoperative EF, LV end-systolic diameter, and diabetes might be useful predictors of cardiac death. Among the 65 patients with follow-up echocardiographic data, LV function had normalized at 1 year after AVR in all patients, except for 2 who died of cardiac causes in the long-term after AVR. LV end-diastolic diameter, LV end-systolic diameter, and EF at 1 year after AVR might be useful predictors of long-term cardiac death.

Conclusions: In patients with severe chronic AR, preoperative LV dysfunction is remarkably improved at 1 year after AVR. Pre- and postoperative echocardiographic data are important for predicting long-term outcome after AVR. (Circ J 2016; 80: 2460–2467)

Key Words: Aortic regurgitation; Aortic valve replacement; Left ventricular dysfunction; Long-term follow-up; Prognostic predictors
Clinical Data
We investigated the preoperative clinical characteristics, including underlying disease, smoking habit, medications, and cardiac rhythm. The examined underlying diseases included hypertension, hyperlipidemia, diabetes mellitus (DM), and cerebral infarction. To evaluate the effects of medications, we investigated the use of antiplatelet drugs, anticoagulants, statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, diuretics, and digoxin. Preoperative laboratory data were investigated, including hemoglobin concentration, estimated glomerular filtration rate (eGFR), and blood levels of urea nitrogen, creatinine, total cholesterol, and B-type natriuretic peptide. Moreover, medications at 1 year after AVR were investigated. Patients were classified into the treatment group for a particular medication if they were taking it for more than 6 months. Postoperative atrial fibrillation was defined as detection on ECG at more than 6 months after discharge.

Echocardiographic Evaluation
Comprehensive transthoracic echocardiography was performed before AVR and at 1 year after AVR, using high-quality, commercially available ultrasound systems. LVDd, LVDs, EF, septal wall thickness, and posterior wall thickness were measured.
with the following variables: age, sex, background, laboratory data, medications, and LV function. To determine an adequate value of the prognostic predictors, LV function was dichotomized by the median value or the value described in the current Japanese Circulation Society guidelines, the American Heart Association/American Colleague of Cardiology guidelines, and the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines. Relative risk values were calculated with 95% confidence intervals (CIs). Statistical significance was set at a P<0.05.

**Results**

**Baseline Characteristics, and Perioperative and Long-Term Prognosis**

Baseline clinical characteristics and echocardiographic parameters are shown in Table 1. The mean follow-up period was 8.9±5.2 years. There were 19 deaths, including 7 cardiac deaths, and 25 MACCEs (7 cardiac deaths, 10 hospitalizations for heart failure, 1 hospitalization for ventricular arrhythmia, 3 hospitalizations for infective endocarditis, and 4 re-operations) during the follow-up period. The causes of death were as follows: heart failure in 4, sudden cardiac death in 2, and infective endocarditis in 1, with regard to cardiac death, and cancer in 5, intracerebral hemorrhage in 2, sepsis in 2, and other reasons in 2, with
Predicting Prognosis of AVR for Severe AR

had a poor prognosis, and these cut-off values were valuable for long-term prognostication after AVR (Figure 2). With regard to cardiac death, the univariable Cox proportional hazards model showed that preoperative EF, LVDs, and DM were predictors, but not eGFR.

Chronological Change in LV Function at 1 Year After AVR

In the 65 patients with follow-up echocardiographic data at 1 year after AVR, LV function had remarkably improved (Figure 3). Although 26 patients had a low preoperative EF (<50%), only 2 patients had an EF <50% at 1 year after AVR. Moreover, any patients with a preoperative EF ≥50% did not show an EF <50% at 1 year after AVR.

In one of the 2 patients with an EF <50% at 1 year after AVR, the Freedom from all-cause death at 5 and 10 years after AVR was 85% and 76%, respectively. Freedom from cardiac death and MACCE at 5 and 10 years after AVR was 96% and 91%, and 92% and 81%, respectively. The mean time of freedom from all-cause death, cardiac death, and the MACCE was 14.5 years with SE 0.7 (95% CI 13.0–16.0), 16.8 years with SE 0.6 (95% CI 15.7–17.9), and 13.9 years with SE 0.7 (95% CI 12.5–15.3), respectively (Figure 1).

Preoperative Predictors of Long-Term Prognosis

Table 2 and Table S1 show the results of univariable analysis for predictors of all-cause death and cardiac death. Table 3 shows the results of multivariable analysis for predictors of all-cause death including significant variables from the univariable analysis: DM, preoperative LVDs, preoperative EF, and eGFR. For cardiac death, only the univariable analysis was used because of the small number of events.

The multivariable Cox proportional hazards model showed that preoperative EF and eGFR were independent predictors of all-cause death. Preoperative LVDs was also a good predictor, but only in the univariable analysis. Regarding the cut-off values of EF and LVDs, the median value (EF, 56%; LVDs, 47 mm) as well as the cut-off value in the current guidelines (EF, 50%; LVDs, 50 or 55 mm) was useful for prognostic prediction. Freedom from all-cause death was compared between 2 groups subdivided by the median values of LVDd, LVDs, and EF. The patients with preoperative LVDs >47 mm or EF <56% had a poor prognosis, and these cut-off values were valuable for long-term prognostication after AVR (Figure 2). With regard to cardiac death, the univariable Cox proportional hazards model showed that preoperative EF, LVDs, and DM were predictors, but not eGFR.

### Table 2. Univariable Analysis of Predictors of Death in Patients Undergoing Aortic Valve Replacement for Severe Chronic Aortic Regurgitation

<table>
<thead>
<tr>
<th></th>
<th>All-cause death</th>
<th>Cardiac death</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Univariable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.03 (0.95–1.11)</td>
<td>0.45</td>
</tr>
<tr>
<td>Male</td>
<td>1.32 (0.47–3.66)</td>
<td>0.60</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.74 (0.27–2.07)</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.23 (1.20–14.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Preoperative AF</td>
<td>1.89 (0.62–5.70)</td>
<td>0.26</td>
</tr>
<tr>
<td>Preoperative LVDd (per mm)</td>
<td>1.05 (0.98–1.11)</td>
<td>0.15</td>
</tr>
<tr>
<td>Preoperative LVDd (&gt;75 mm: JCS)</td>
<td>1.36 (0.45–4.12)</td>
<td>0.58</td>
</tr>
<tr>
<td>Preoperative LVDd (&gt;70 mm: ESC)</td>
<td>1.89 (0.77–4.64)</td>
<td>0.17</td>
</tr>
<tr>
<td>Preoperative LVDd (&gt;69 mm: median)</td>
<td>2.12 (0.83–5.38)</td>
<td>0.12</td>
</tr>
<tr>
<td>Preoperative LVDd (&gt;65 mm: AHA)</td>
<td>1.51 (0.57–3.97)</td>
<td>0.41</td>
</tr>
<tr>
<td>Preoperative LVDs (per mm)</td>
<td>1.06 (1.02–1.10)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preoperative LVDs (&gt;55 mm: JCS)</td>
<td>2.91 (1.17–7.24)</td>
<td>0.02</td>
</tr>
<tr>
<td>Preoperative LVDs (&gt;50 mm: AHA &amp; ESC)</td>
<td>4.40 (1.67–11.58)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preoperative LVDs (&gt;47 mm: median)</td>
<td>3.27 (1.18–9.07)</td>
<td>0.02</td>
</tr>
<tr>
<td>Preoperative EF (per %)</td>
<td>0.94 (0.91–0.97)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preoperative EF (&lt;56%: median)</td>
<td>4.51 (1.49–13.59)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preoperative EF (&lt;50%: JCS, AHA &amp; ESC)</td>
<td>7.53 (2.49–22.75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preoperative LV mass index (g/m²)</td>
<td>1.01 (1.00–1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hb (per 0.1 g/L)</td>
<td>0.96 (0.73–1.27)</td>
<td>0.78</td>
</tr>
<tr>
<td>eGFR (per ml/min/1.73 m²)</td>
<td>0.96 (0.93–0.99)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>0.99 (0.38–2.60)</td>
<td>0.98</td>
</tr>
<tr>
<td>β-blockers</td>
<td>0.33 (0.04–2.49)</td>
<td>0.28</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1.31 (0.52–3.34)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

AHA, American Heart Association guidelines; CI, confidence interval; ESC, European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines; HR, hazard ratio; JCS, Japan Circulation Society guidelines. Other abbreviations as in Table 1.

### Table 3. Multivariable Analysis of Predictors of All-Cause Death in Patients Undergoing Aortic Valve Replacement for Severe Chronic Aortic Regurgitation

<table>
<thead>
<tr>
<th></th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.65 (0.42–6.55)</td>
</tr>
<tr>
<td>Preoperative LVDs (per mm)</td>
<td>0.98 (0.90–1.06)</td>
</tr>
<tr>
<td>Preoperative EF (per %)</td>
<td>0.94 (0.89–0.99)</td>
</tr>
<tr>
<td>eGFR (per ml/min/1.73 m²)</td>
<td>0.97 (0.94–1.00)</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1,2.
Figure 2. Kaplan-Meier curves of the cumulative survival of all-cause death for 2 groups of patients divided by preoperative median values of LVDd (A), LVDs (B), and EF (C). LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; EF, ejection fraction.

Figure 3. Chronological changes in echocardiographic data of 65 patients who were followed up with echocardiography for >1 year. Pre, preoperative; y, year; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; EF, ejection fraction.
AVR, the EF had normalized at 2 years after AVR. However, heart failure caused by diastolic dysfunction occurred 3 years later, and the patient died of uncontrollable heart failure with preserved EF 6 years later even though LV diameter and EF were normal. The other patient died suddenly 2 months after follow-up echocardiography at 1 year after AVR.

### Effect of LV Function at 1 Year After AVR on Long-Term Prognosis

Table 4 shows the early postoperative parameters as predictors of long-term prognosis in the 65 patients with follow-up echocardiography at 1 year after AVR. For all-cause death, neither postoperative echocardiographic parameters nor medications were predictors. However, LVDd, LVDs, and EF at 1 year after AVR were important predictors of long-term cardiac death. Figure 4 shows the relationship between EF before and at 1 year after AVR and long-term prognosis for individual patients. Two patients who did not show normalization of EF at 1 year after AVR died of cardiac causes in the long-term after AVR.

The mean of peak aortic jet velocity in the 65 patients with follow-up echocardiography at 1 year after AVR was 2.2 ± 0.4 m/s. In only 2 patients, the peak aortic jet velocity was >3.0 m/s (3.3 m/s and 3.1 m/s, respectively). However, the effective orifice area was 1.25 cm² and 1.03 cm², respectively, thus there were no patients with prosthesis-patient mismatch.

### Discussion

Symptoms and LV systolic function are the main predictors of the early and late outcomes after AVR in patients with severe chronic AR. However, operative mortality rates have been decreasing. Additionally, LV function improves in the short-term after AVR in patients with preoperative LV dysfunction. Several studies have shown that the long-term prognosis after AVR is not affected by preoperative LV dysfunction. Therefore, long-term outcomes and chronological changes in LV function after AVR for patients with severe chronic AR should be re-investigated. In the present study, we reconfirmed that preoperative EF and renal function are important predictors of prognosis, and newly identified that LV function at 1 year after AVR is also an important prognostic factor in the long-term outcome.

#### Preoperative LV Function and Long-Term Prognosis After AVR

In our study, a low preoperative EF was an independent predictor of all-cause death and cardiac death. Moreover, a large preoperative LVDs was an important predictor of all-cause death and cardiac death, but a large preoperative LVDd was not. Other reports have shown that a low preoperative EF or a large preoperative LVDs was associated with a poor long-term prognosis after AVR, which is consistent with our data. However, some previous studies showed that the long-term prognosis of patients who underwent AVR was not affected by preoperative LV dysfunction.

In the current guidelines of the Japanese Circulation Society, the American Heart Association/American College of Cardiology, and the European Society of Cardiology/European Association for Cardio-Thoracic Surgery, surgical intervention is recommended if the preoperative EF is ≤50%. However, in the present study, an EF <56% was also a good cut-off value.
for long-term prognosis after AVR. These findings suggest that the prognosis of patients with an EF of 50–55% is equivocal. Moreover, with regard to LVDs, LVDs >50 mm and LVDs >47 mm are also useful cut-off values for long-term prognosis after AVR. Therefore, the cut-off values of preoperative EF <50% or LVDs >55 mm according to the Japanese Circulation Society guidelines may need to be reconsidered. Additionally, earlier surgical intervention may need to be taken into consideration.

**Relationship Between LV Function at 1 Year After AVR and Long-Term Prognosis**

In our study, the LVDD, LVDs, and EF had normalized (EF >50%) at 1 year after AVR in 24 (92%) of 26 patients with a low preoperative EF. Previous reports on improvement in LV function early after AVR have suggested that such improvement was related early reduction in volume overloading and late remodeling after AVR. Bonow et al reported that EF normalized in 41% of patients with a low preoperative EF and the remaining patients showed a low EF at 6–8 months after AVR. The discrepancy between those findings and ours might be related to differences in the timing of follow-up echocardiography. The LV function of patients who have a low preoperative EF might improve markedly during the first year after AVR.

We investigated the echocardiographic parameters at 1 year after AVR as predictors of long-term outcome. EF was <50% in only 2 patients at 1 year after AVR, and these 2 patients died of heart failure at 2 and 6 years, respectively, after AVR. In both patients, LVDd and LVDs also did not improve at 1 year after AVR. This suggests the preoperative cardiac damage in the 2 patients was severe, which may be related to the occurrence of postoperative heart failure and poor prognosis after AVR. Moreover, in the Cox proportional hazards model, the EF, LVDD, and LVDs at 1 year after AVR were important predictors of long-term cardiac death. Therefore, a lack of normalization of EF, LVDD, and LVDs at 1 year after AVR may be important for predicting long-term cardiac death. However, some patients who showed a remarkable improvement in LV function at 1 year after AVR, despite severe preoperative LV dysfunction, died of non-cardiac causes in the long-term after AVR. Detecting a relationship between preoperative LV dysfunction and non-cardiac death in the long-term after AVR is difficult. However, follow-up for a long period is necessary, even if LV function has improved remarkably at 1 year after AVR. In our study, the prognosis of patients with early normalization of postoperative LV function, despite severe preoperative LV dysfunction, was not equivalent to that of patients with normal preoperative LV function. Corti et al described the postoperative echocardiographic findings as having an important prognostic effect on long-term outcome after AVR. In their study, echocardiography was performed at 3–6 months after AVR. However, we chose to measure echocardiographic parameters at 1 year after AVR because of the potential for the LV function of patients who had a low preoperative EF to greatly improve during the first year after AVR. Therefore, additional investigations are required to determine the best timing of follow-up echocardiography for predicting long-term outcomes.

**Effect of Renal Function and DM on Prognosis**

In the present study, a low eGFR was a predictor of all-cause death, but no relationship was detected with cardiac death. However, DM was a predictor of all-cause and cardiac death, and had a more significant relationship with cardiac death. Associations of preoperative renal insufficiency with mortality and morbidity after AVR have already been reported. Renal insufficiency is also related to a low preoperative EF. Moreover, DM is a well-known risk factor for coronary artery disease and other macrovascular events, and the relationship between renal function and DM is strong. Therefore, these factors may affect early and long-term mortality rates after AVR. In patients with DM, especially, LV diastolic dysfunction or coronary artery disease may progress after AVR, and these may cause cardiac death in the long-term after AVR.

**Study Limitations**

The present study’s limitations owe mainly to its retrospective nature. First, not all patients could be followed up systematically. Second, the small number of patients is a major issue. This study only evaluated 80 patients, and LV function at 1 year after AVR could only be evaluated in 65 patients. The small number of subjects might have affected the statistical power of the variables, especially in the multivariable analysis. Moreover, the number of events, especially cardiac death, was small. Therefore, univariable analysis was used to evaluate the postoperative predictors of long-term outcomes after AVR.

**Conclusions**

Postoperative outcomes of patients with severe chronic AR are favorable, and preoperative LV dysfunction is remarkably improved at 1 year after AVR. However, one-quarter of all patients with AVR died within 10 years. Preoperative EF and renal function are important predictors of prognosis. Moreover, LV function at 1 year after AVR is an important prognostic factor for long-term outcome.

**Funding Sources / Disclosures / Grants**

None.

**References**


Supplementary Files

Table S1. Univariable analysis of predictors of mortality among other tested variables

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-16-0782