Severe Aortic Stenosis in Dialysis Patients

Yuichi Kawase, MD; Tomohiko Taniguchi, MD; Takeshi Morimoto, MD, MPH; Kazushige Kadota, MD; Keiichiro Iwasaki, MD; Akimune Kuwayama, MD; Masanobu Ohya, MD; Takenobu Shimada, MD; Hidewo Amano, MD; Takeshi Maruo, MD; Yasushi Fuku, MD; Chisato Izumi, MD; Takeshi Kitai, MD; Naritatsu Saito, MD; Eri Minamino-Muta, MD; Takao Kato, MD; Tsukasa Inada, MD; Moriaki Inoko, MD; Katsuhisa Ishii, MD; Tatsuhiko Komiya, MD; Michiya Hanyu, MD; Kenji Minatoya, MD; Takeshi Kimura, MD; on behalf of the CURRENT AS Registry Investigators*

Background—Characteristics and prognosis of hemodialysis patients with severe aortic stenosis have not yet been well defined.

Methods and Results—The CURRENT AS (contemporary outcomes after surgery and medical treatment in patients with severe aortic stenosis) registry, a Japanese multicenter registry, enrolled 3815 consecutive patients with severe aortic stenosis. There were 405 hemodialysis patients (initial aortic valve replacement [AVR] group: N=135 [33.3%], and conservative group: N=270) and 3410 nonhemodialysis patients (initial AVR group: N=1062 [31.1%], and conservative group: N=2348). The median follow-up duration after the index echocardiography was 1361 days, with 90% follow-up rate at 2 years. The cumulative 5-year incidence of all-cause death was significantly higher in hemodialysis patients than in nonhemodialysis patients in both the entire cohort (71% versus 40%, P<0.001) and in the initial AVR group (63.2% versus 17.9%, P<0.001). Among hemodialysis patients, the initial AVR group as compared with the conservative group was associated with significantly lower cumulative 5-year incidences of all-cause death (60.6% versus 75.5%, P<0.001) and sudden death (10.2% versus 31.7%, P<0.001). Nevertheless, the rate of aortic valve procedure–related death, which predominantly occurred within 6 months of the AVR procedure, was markedly higher in the hemodialysis patients than in the nonhemodialysis patients (21.2% and 2.3%, P<0.001).

Conclusions—Among hemodialysis patients with severe aortic stenosis, the initial AVR strategy as compared with the conservative strategy was associated with significantly lower long-term mortality risk, particularly the risk for sudden death, although the effect size for the survival benefit of the initial AVR strategy was smaller than that in the nonhemodialysis patients. (J Am Heart Assoc. 2017;6:e004961. DOI: 10.1161/JAHA.116.004961.)

Key Words: aortic stenosis • hemodialysis • prognosis

The number of patients with end-stage renal disease requiring hemodialysis has been gradually increasing. In 2012, more than 400 000 American patients with end-stage renal disease were on hemodialysis, including over 98 000 new patients.1 In Japan, more than 300 000 patients with end-stage renal disease are on hemodialysis, and the candidate pool increases by over 30 000 patients per year.2 Dialysis patients are associated with a higher risk for the development of cardiovascular diseases with calcified degeneration of cardiac valves and/or heavy calcification of coronary arteries.3–6 Calcified aortic stenosis (AS) is particularly common in hemodialysis patients, and has been found...
to be an independent risk factor for death in hemodialysis patients.\textsuperscript{6,7} Regarding the clinical outcomes of hemodialysis patients with severe AS, there are only a few small studies suggesting the higher mortality and morbidity rates following surgical aortic valve replacement (AVR).\textsuperscript{8–10} However, the characteristics and prognosis of hemodialysis patients with severe AS have not yet been well defined in comparison with those in nonhemodialysis patients with severe AS. Also, it is not clear whether the effect size of the initial AVR strategy relative to the conservative strategy differs between hemodialysis patients and nonhemodialysis patients, although we previously reported that the initial AVR strategy was associated with markedly lower mortality risk than the conservative strategy in the asymptomatic patients with severe AS.\textsuperscript{11} Therefore, we sought to investigate the long-term outcomes of hemodialysis patients with severe AS and to evaluate the effect of the initial AVR strategy relative to the conservative strategy in clinical outcomes compared between hemodialysis and nonhemodialysis patients in a large Japanese observational database of consecutive patients with severe AS.

**Methods**

**Study Design and Patient Population**

The study design of the CURRENT AS (contemporary outcomes after surgery and medical treatment in patients with severe aortic stenosis) registry was previously described in detail.\textsuperscript{11} In brief, the CURRENT AS registry is a retrospective, multicenter registry that enrolled 3815 consecutive patients with severe AS from 27 centers (Appendix S1, on-site surgical facility in 20 centers) in Japan between January 2003 and December 2011. We examined the hospital database of transthoracic echocardiography and enrolled consecutive patients meeting the definition of severe AS (peak aortic jet velocity $>4.0$ m/s, mean aortic pressure gradient $>40$ mm Hg, or aortic valve area $<1.0$ cm$^2$) for the first time during the study period. We excluded patients with a history of aortic valve repair/replacement/plasty or percutaneous aortic balloon valvuloplasty. The institutional review boards in all 27 participating centers approved the protocol. Written informed consent from each patient was waived because clinical information was obtained from the routine practice, and no patient refused to participate in the study when contacted for follow-up.

Among the 3815 study patients, there were 405 hemodialysis patients (initial AVR group: N=135 [33.3%], and conservative group: N=270) and 3410 nonhemodialysis patients (initial AVR group: N=1062 [31.1%], and conservative group: N=2348) at the time of the index echocardiography (Figure 1). The conservative group consisted of all the patients other than those in whom AVR was planned based on the index echocardiographic findings. The conservative

**Clinical Perspective**

**What Is New?**

- Although the initial aortic valve replacement strategy improves prognosis of hemodialysis patients with severe aortic stenosis, the magnitude of its benefit is smaller in hemodialysis patients than in nonhemodialysis patients, which could at least in part be explained by the extremely high rate of aortic valve procedure–related death in hemodialysis patients.

**What Are the Clinical Implications?**

- The initial aortic valve replacement is an effective procedure to treat hemodialysis patients with severe aortic stenosis, but there is an urgent unmet need to improve the procedural outcomes of aortic valve replacement in hemodialysis patients.

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**Figure 1.** Study flow chart. AS indicates aortic stenosis; AVR, aortic valve replacement.
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management included watchful waiting for symptoms in asymptomatic patients, and medical management of angina and/or heart failure in symptomatic patients. There were 3 main reasons why AVR was not performed in the conservative group. First, patients were considered to have no formal AVR indications by their attending physician (1388 patients, 53.0%) either because of absence of symptoms (1067 patients) or improvement of symptoms by medication (237 patients). Second, patients had unacceptably high surgical risk (798 patients, 30.5%). Third, patients refused to undergo AVR (403 patients, 15.4%).

The effect of the initial AVR strategy relative to the conservative strategy was assessed based on the initial strategies regardless of the actual performance of AVR. The follow-up was commenced on the day of the index echocardiography except for the analysis comparing the clinical outcomes after AVR between hemodialysis and nonhemodialysis patients, in which the follow-up was commenced on the day of AVR.

Echocardiography

All patients underwent a comprehensive 2-dimensional and Doppler echocardiographic evaluation in each participating center. Peak aortic jet velocity and mean pressure gradient were obtained with the use of the simplified Bernoulli equation. Aortic valve area was calculated with the use of the standard continuity equation and was indexed by body surface area.12

Data Collections and Definitions

Baseline clinical information was collected by reviewing the hospital charts or database. Follow-up information was collected mainly by reviewing the hospital charts, and additional information was collected through contact with patients, their families, and/or referring physicians by sending mails regarding survival status, symptoms, and subsequent hospitalizations.

The primary outcome measure in the present analysis was all-cause death. The secondary outcome measures included cardiovascular death, aortic valve–related death, aortic valve procedure–related death, sudden death, noncardiovascular death, hospitalization for heart failure (HF), and a composite of aortic valve–related death and hospitalization for HF. The causes of death were classified according to the Valve Academic Research Consortium definitions and were adjudicated by a clinical event committee (Data S1).13,14 Aortic valve–related death included aortic valve procedure–related death, sudden death, and death attributable to HF possibly related to the aortic valve. Hospitalization for HF was defined as hospitalization because of worsening HF requiring intravenous drug therapy.

Statistical Analysis

Categorical variables are presented as numbers and percentages and were compared with the χ² test or Fisher exact test. Continuous variables are presented as the mean and SD or median and interquartile range. Continuous variables were compared using Student t test or Wilcoxon rank sum test based on their distributions. The Kaplan–Meier method was used to calculate the cumulative incidence of events, and the differences were assessed with the log-rank test.

The Cox proportional hazard models were used to estimate the adjusted risk of hemodialysis patients relative to nonhemodialysis patients or the adjusted risk of initial AVR strategy relative to conservative strategy for all-cause death, cardiovascular death, aortic valve–related death, aortic valve procedure–related death, sudden death, noncardiovascular death, hospitalization for HF, and a composite of aortic valve–related death and hospitalization for HF. We selected 20 clinically relevant factors listed in Table 1 and Tables S1 and S2 as the risk-adjusting variables consistent with the previous report. We constructed parsimonious models with a limited number of variables for aortic valve procedure–related death, because the number of patients with this event was too small for the nonparsimonious model. We selected 6 clinically relevant variables as the risk-adjusted variables as listed in Table 1 and Tables S1 and S2 in the parsimonious models. The centers were incorporated into all the models as the stratification variable. With the exception of age, the continuous variables were dichotomized by the median values or clinically meaningful reference values. Because the differences in the age distributions between the hemodialysis and nonhemodialysis groups and between the initial AVR and conservative strategies were too large to allow the dichotomous approach, we treated age as a continuous variable in the Cox proportional hazard models. The risks for the clinical end points were expressed as hazard ratios and their 95% CI. We also evaluated the interaction between hemodialysis/nonhemodialysis subgroups and the effect of the initial AVR strategy relative to the conservative strategy for the primary and secondary outcome measures.

All statistical analyses were conducted by 2 physicians (Y.K. and T.T.) and a statistician (T.M.) with the use of JMP 10.0.2 or SAS 9.4. All reported P values were 2-tailed, and P<0.05 was considered statistically significant.

Results

Baseline Characteristics and Clinical Outcomes: Hemodialysis Versus Nonhemodialysis Patients

Baseline characteristics were significantly different between hemodialysis patients and nonhemodialysis patients (Table 1).
Table 1. Baseline Characteristics: Dialysis VS Nondialysis Patients

| Variables                                      | Dialysis Patients (N=405) | Nondialysis Patients (N=3410) | P Value |
|------------------------------------------------|---------------------------|-------------------------------|---------|
| Age, y                                          | 73.2±8.6                  | 78.3±9.7                      | <0.001  |
| Age ≥80 y†                                      | 93 (23)                   | 1636 (48)                     | <0.001  |
| Men*                                            | 242 (60)                  | 1201 (35)                     | <0.001  |
| Body mass index‡                                 | 20.5±3.6                  | 21.9±3.8                      | <0.001  |
| Body mass index ≤22*                            | 298 (74)                  | 2028 (59)                     | <0.001  |
| Body surface area, m²                            | 1.46±0.18                 | 1.46±0.19                     | 0.47    |
| Initial treatment strategies                    |                           |                               | 0.37    |
| Initial AVR strategy*                           | 135 (33)                  | 1062 (31)                     |         |
| Conservative strategy*                          | 270 (67)                  | 2348 (69)                     |         |
| Any symptoms possibly related to aortic stenosis| 198 (49)                  | 1807 (53)                     | 0.12    |
| Angina                                          | 60 (15)                   | 438 (13)                      |         |
| Syncope                                         | 25 (6)                    | 173 (5)                       | 0.34    |
| Heart failure                                   | 143 (35)                  | 1460 (43)                     | 0.004   |
| Admission for heart failure at index echocardiography†| 60 (15)                  | 730 (21)                      | 0.002   |
| Hypertension*                                   | 287 (71)                  | 2380 (70)                     | 0.66    |
| Current smoking*                                 | 22 (5)                    | 174 (5)                       | 0.78    |
| History of smoking                              | 120 (30)                  | 710 (21)                      | <0.001  |
| Dyslipidemia                                     | 78 (19)                   | 1249 (37)                     | <0.001  |
| On statin therapy                               | 45 (11)                   | 925 (27)                      | <0.001  |
| Diabetes mellitus                               | 127 (31)                  | 770 (23)                      | <0.001  |
| On insulin therapy*                             | 36 (9)                    | 152 (4)                       | <0.001  |
| Prior myocardial infarction*                    | 48 (12)                   | 275 (8)                       | 0.01    |
| Prior percutaneous coronary intervention         | 97 (24)                   | 405 (12)                      | <0.001  |
| Prior coronary artery bypass grafting           | 45 (11)                   | 154 (5)                       | <0.001  |
| Prior open heart surgery                        | 51 (13)                   | 265 (8)                       | <0.001  |
| Prior symptomatic stroke*                       | 70 (17)                   | 433 (13)                      | 0.01    |
| Atrial fibrillation or flutter†                  | 100 (25)                  | 728 (21)                      | 0.12    |
| Aortic/peripheral vascular disease*             | 82 (20)                   | 200 (6)                       | <0.001  |
| Serum creatinine, mg/dL                         |                           | 0.83 (0.68–1.1)               |         |

Years from dialysis introduction

| Years from dialysis introduction | Dialysis Patients | Nondialysis Patients | P Value |
|----------------------------------|-------------------|----------------------|---------|
| <1 y                              | 33 (8)            |                      |         |
| ≥1 y, <5 y                       | 116 (29)          |                      |         |
| ≥5 y, <10 y                      | 87 (21)           |                      |         |
| ≥10 y                            | 169 (42)          |                      |         |
| Anemia‡                          | 335 (83)          | 1782 (52)            | <0.001  |
| Liver cirrhosis (Child-Pugh B or C)*| 6 (1)            | 32 (1)               | 0.29    |
| Malignancy                       | 59 (15)           | 458 (13)             | 0.53    |
| Malignancy currently under treatment†| 13 (3)           | 136 (4)              | 0.44    |
| Chest wall irradiation           | 2 (0.5)           | 23 (1)               | 1.0     |
| Immunosuppressive therapy        | 17 (4)            | 114 (3)              | 0.37    |

Continued
Table 1. Continued

| Variables                                              | Dialysis Patients (N=405) | Nondialysis Patients (N=3410) | P Value |
|--------------------------------------------------------|---------------------------|-------------------------------|---------|
| Chronic lung disease                                   | 40 (10)                   | 360 (11)                      | 0.67    |
| Chronic lung disease (moderate or severe)*             | 11 (3)                    | 101 (3)                       | 0.78    |
| Coronary artery disease*                               | 195 (48)                  | 949 (28)                      | <0.001  |
| Logistic EuroSCORE, %                                  | 13.4 (7.9–23.0)           | 9.4 (5.5–16.1)                | <0.001  |
| EuroSCORE II, %                                        | 2.7 (1.9–4.6)             | 2.9 (1.6–4.9)                 | 0.10    |
| STS-PROM score, %                                      | 8.5 (5.6–12.3)            | 3.5 (2.1–5.7)                 | <0.001  |
| Etiology of aortic stenosis                            |                           |                               |         |
| Degenerative                                           | 394 (97)                  | 2985 (88)                     |         |
| Congenital (unicuspid, bicuspid, quadricuspid)         | 4 (1)                     | 254 (7)                       |         |
| Rheumatic                                              | 5 (1)                     | 145 (4)                       |         |
| Infective endocarditis                                 | 1 (0.3)                   | 6 (0.2)                       |         |
| Others                                                 | 1 (0.3)                   | 20 (0.6)                      |         |
| Echocardiographic variables                            |                           |                               |         |
| Left ventricular end-diastolic diameter, mm            | 48.9±7.2                  | 45.6±6.9                      | <0.001  |
| Left ventricular end-systolic diameter, mm             | 34.2±8.8                  | 29.8±7.7                      | <0.001  |
| Left ventricular ejection fraction, %                  | 56.9±14.0                 | 63.5±13.3                     | <0.001  |
| Left ventricular ejection fraction <40%                | 57 (14)                   | 236 (7)                       | <0.001  |
| Left ventricular ejection fraction <50%                | 105 (26)                  | 488 (14)                      | <0.001  |
| Interventricular septum thickness in diastole, mm      | 11.7±2.3                  | 11.3±2.3                      | <0.001  |
| Posterior wall thickness in diastole, mm               | 11.4±2.0                  | 10.9±2.0                      | <0.001  |
| Peak aortic jet velocity, m/s                          | 3.96±0.87                 | 4.16±0.92                     | <0.001  |
| Peak aortic jet velocity ≥5 m/s                        | 52 (13)                   | 646 (19)                      | 0.003   |
| Peak aortic jet velocity ≥4 m/s*                       | 211 (52)                  | 1974 (58)                     | 0.03    |
| Peak aortic pressure gradient, mm Hg                   | 66±28                     | 72±32                         | <0.001  |
| Mean aortic pressure gradient, mm Hg                   | 37±17                     | 41±20                         | <0.001  |
| Aortic valve area (equation of continuity), cm²        | 0.74±0.17                 | 0.72±0.19                     | 0.03    |
| Aortic valve area index, cm²/m²                        | 0.51±0.12                 | 0.50±0.13                     | 0.18    |
| Any combined valvular disease (moderate or severe)*    | 166 (41)                  | 1392 (41)                     | 0.95    |
| Moderate or severe aortic regurgitation                | 77 (19)                   | 714 (21)                      | 0.37    |
| Moderate or severe mitral stenosis                     | 14 (3)                    | 119 (3)                       | 0.97    |
| Moderate or severe mitral regurgitation                | 102 (25)                  | 661 (19)                      | 0.006   |
| Moderate or severe tricuspid regurgitation             | 64 (16)                   | 564 (17)                      | 0.71    |
| Tricuspid regurgitation pressure gradient ≥40 mm Hg*   | 80 (20)                   | 526 (15)                      | 0.02    |

Values are number (%), mean±SD, or median (interquartile range) unless otherwise stated. AVR indicates aortic valve replacement; PROM, predicted risk of mortality; STS, Society of Thoracic Surgeons.

*Potential independent variables selected in the Cox proportional hazard models for all-cause death, cardiovascular death, aortic valve-related death, sudden death, noncardiovascular death, hospitalization for heart failure, and a composite of aortic valve-related death or hospitalization for heart failure.

†Potential independent variables selected in the Cox proportional hazard models for aortic valve procedure-related death.

‡Body mass index was calculated as weight in kilograms divided by height in meters squared.

§Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men).
The median follow-up period after the index echocardiography was 1361 (interquartile range: 1055–1697) days, with a 90% follow-up rate at 2 years. Cumulative 5-year incidence of the first surgical AVR or transcatheter aortic valve implantation (TAVI) was significantly higher in hemodialysis patients than in nonhemodialysis patients in the entire study population as well as in the conservatively managed population (Figure 2 and Figure S1). TAVI was performed in 40 patients including 1 hemodialysis patient during the follow-up period.

Cumulative 5-year incidence of the primary outcome measure (all-cause death) was significantly higher in hemodialysis patients than in nonhemodialysis patients (71% versus 40%, P<0.001) with a notably higher rate in the first year (35.9% versus 13.4%) after the index echocardiography (Table 2 and Figure 3). The risk for sudden death was markedly higher in hemodialysis patients than in nonhemodialysis patients (Table 2 and Figure 3). Cumulative 5-year incidence of hospitalization for HF was not significantly different between hemodialysis and nonhemodialysis patients (Table 3). The results from the adjusted analysis were fully consistent with those from the unadjusted analysis (Table 3).

### Baseline Characteristics and Clinical Outcomes in Hemodialysis and Nonhemodialysis Patients: Initial AVR Versus Conservative Strategies

The differences in baseline characteristics between the initial AVR and conservative groups were basically consistent in both hemodialysis and nonhemodialysis patients. Surgical risk scores were significantly lower in the initial AVR group than in the conservative group. Patients in the initial AVR group had greater echocardiographic AS severity and left ventricular wall thickness than those in the conservative group (Table 3, Table S1).

In both hemodialysis and nonhemodialysis patients, cumulative 5-year incidence of all-cause death was significantly lower in the initial AVR group than in the conservative group (Table 4 and Figure 4). However, the effect size of the initial
AVR strategy relative to the conservative strategy on mortality was smaller in hemodialysis patients than in nonhemodialysis patients (adjusted hazard ratio 0.62, 95% CI 0.43–0.90, P=0.01, and adjusted hazard ratio 0.40, 95% CI 0.33–0.48, P<0.001, P interaction=0.001) (Table 4). In both hemodialysis and nonhemodialysis patients, the lower risks of the initial AVR group relative to the conservative group were highly significant for sudden death and HF hospitalization (Table 4 and Figure 4). In addition, we have conducted a propensity-score matched analysis as a sensitivity analysis and analyzed the initial AVR versus conservative groups in hemodialysis and nonhemodialysis patients, respectively. The results of

### Table 2. Clinical Outcomes: Dialysis VS Nondialysis Patients

|                      | Dialysis Patients | N=405 | Number of Patients With at Least 1 Event (Cumulative 5-Y Incidence [%]) | Nondialysis Patients | N=3410 | Number of Patients With at Least 1 Event (Cumulative 5-Y Incidence [%]) | Unadjusted HR (95% CI) | P Value | Adjusted HR (95% CI) | P Value |
|----------------------|-------------------|-------|-------------------------------------------------|----------------------|-------|-------------------------------------------------|---------------------|---------|---------------------|---------|
| All-cause death      | 248 (71.0)        |       | 2.69 (2.34–3.08)                                 | 1201 (40.0)          | 6.28 (5.32–7.30) | 2.76 (2.35–3.25)                                 | <0.001              |         | 2.76 (2.35–3.25)   | <0.001  |
| Cardiovascular death | 183 (59.5)        |       | 3.07 (2.60–3.60)                                 | 769 (27.8)           | 4.61 (3.87–5.36) | 3.18 (2.62–3.86)                                 | <0.001              |         | 3.18 (2.62–3.86)   | <0.001  |
| Aortic valve–related death | 107 (36.1) |       | 2.69 (2.17–3.31)                                 | 502 (19.2)           | 3.57 (3.01–4.14) | 3.10 (2.41–3.98)                                 | <0.001              |         | 3.10 (2.41–3.98)   | <0.001  |
| Aortic valve procedure–related death | 32 (9.9) |       | 7.02 (4.44–10.93)                                | 49 (1.9)             | 10.05 (7.38–13.60) | 6.74 (4.17–10.91)                                | <0.001              |         | 6.74 (4.17–10.91)  | <0.001  |
| Sudden death         | 52 (24.7)         |       | 4.70 (3.38–6.43)                                 | 144 (5.7)            | 7.20 (5.03–10.10) | 4.80 (3.23–7.14)                                 | <0.001              |         | 4.80 (3.23–7.14)   | <0.001  |
| Noncardiovascular death | 65 (28.5) |       | 2.00 (1.52–2.57)                                 | 432 (16.9)           | 2.86 (2.29–3.60) | 2.05 (1.52–2.77)                                 | <0.001              |         | 2.05 (1.52–2.77)   | <0.001  |
| Hospitalization for heart failure | 57 (31.9) |       | 0.96 (0.72–1.24)                                 | 755 (29.2)           | 2.10 (1.72–2.54) | 0.84 (0.63–1.13)                                 | 0.035               |         | 0.84 (0.63–1.13)   | 0.035   |
| A composite of aortic valve–related death or hospitalization for heart failure | 136 (51.6) |       | 1.78 (1.48–2.12)                                 | 936 (34.1)           | 1.83 (1.55–2.16) | 1.63 (1.33–2.00)                                 | <0.001              |         | 1.63 (1.33–2.00)   | <0.001  |

Number of patients with at least 1 event was counted through the entire follow-up period, while the cumulative incidence was truncated at 5 years. Follow-up was commenced on the day of the index echocardiography. HR indicates hazard ratio.

AVR strategy relative to the conservative strategy on mortality was smaller in hemodialysis patients than in nonhemodialysis patients (adjusted hazard ratio 0.62, 95% CI 0.43–0.90, P=0.01, and adjusted hazard ratio 0.40, 95% CI 0.33–0.48, P<0.001, P interaction=0.001) (Table 4). In both hemodialysis and nonhemodialysis patients, the lower risks of the initial AVR group relative to the conservative group were highly significant for sudden death and HF hospitalization (Table 4 and Figure 4). In addition, we have conducted a propensity-score matched analysis as a sensitivity analysis and analyzed the initial AVR versus conservative groups in hemodialysis and nonhemodialysis patients, respectively. The results of

**Figure 3.** Cumulative incidence of all-cause death and sudden death: dialysis vs nondialysis patients. Follow-up was commenced on the day of the index echocardiography.
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Table 3. Baseline Characteristics in Dialysis and Nondialysis Patients: Initial AVR VS Conservative Groups

| Variables                                           | Dialysis Patients | Nondialysis Patients | P Value | Dialysis Patients | Nondialysis Patients | P Value |
|-----------------------------------------------------|-------------------|----------------------|---------|-------------------|----------------------|---------|
|                                                     | Initial AVR Group (N=135) | Conservative Group (N=270) |         | Initial AVR Group (N=1062) | Conservative Group (N=2348) |         |
| Age, y                                              | 70.3±8.2          | 74.7±8.4             | <0.001  | 73.7±8.9          | 80.3±9.4             | <0.001  |
| Age ≥80 y<sup>+</sup>                               | 17 (13)           | 76 (28)              | <0.001  | 282 (27)          | 1354 (58)           | <0.001  |
| Men*                                                | 87 (64)           | 155 (57)             | 0.17    | 420 (40)          | 781 (33)             | <0.001  |
| Body mass index<sup>+</sup>                         | 20.8±3.1          | 20.3±3.9             | 0.24    | 22.5±3.6          | 21.7±3.9             | <0.001  |
| Body mass index <22<sup>+</sup>                     | 95 (70)           | 203 (75)             | 0.30    | 527 (50)          | 1501 (64)            | <0.001  |
| Any symptoms possibly related to aortic stenosis   | 103 (76)          | 95 (35)              | <0.001  | 802 (76)          | 1005 (43)            | <0.001  |
| Angina                                              | 33 (24)           | 27 (10)              | <0.001  | 258 (24)          | 180 (8)              | <0.001  |
| Syncope                                             | 15 (11)           | 10 (4)               | 0.007   | 95 (9)            | 78 (3)               | <0.001  |
| Heart failure                                       | 72 (53)           | 71 (26)              | <0.001  | 587 (55)          | 873 (37)             | <0.001  |
| Admission for heart failure at index echocardiography<sup>+</sup> | 28 (21)           | 32 (12)              | 0.02    | 242 (23)          | 488 (21)             | 0.19    |
| Hypertension*                                       | 97 (72)           | 190 (70)             | 0.76    | 710 (67)          | 1670 (71)            | 0.01    |
| Current smoking*                                    | 12 (9)            | 10 (4)               | 0.03    | 71 (7)            | 103 (4)              | 0.005   |
| Diabetes mellitus on insulin therapy*               | 11 (8)            | 25 (9)               | 0.71    | 47 (4)            | 105 (4)              | 0.95    |
| Prior myocardial infarction*                        | 11 (8)            | 37 (14)              | 0.10    | 40 (4)            | 235 (10)             | <0.001  |
| Prior open heart surgery                            | 12 (9)            | 39 (14)              | 0.11    | 36 (3)            | 229 (10)             | <0.001  |
| Prior symptomatic stroke*                           | 19 (14)           | 51 (19)              | 0.23    | 88 (8)            | 345 (15)             | <0.001  |
| Atrial fibrillation or flutter<sup>+</sup>          | 29 (21)           | 71 (26)              | 0.29    | 178 (17)          | 550 (23)             | <0.001  |
| Aortic/peripheral vascular disease*                 | 12 (9)            | 70 (26)              | <0.001  | 58 (5)            | 142 (6)              | 0.50    |
| Years from dialysis introduction                    |                   |                      | 0.21    |                  |                      |         |
| <1 y                                                | 8 (6)             | 25 (9)               |         |                  |                      |         |
| ≥1 y, <5 y                                         | 33 (24)           | 83 (31)              |         |                  |                      |         |
| ≥5 y, <10 y                                        | 29 (21)           | 58 (21)              |         |                  |                      |         |
| ≥10 y                                               | 65 (48)           | 104 (39)             |         |                  |                      |         |
| Anemia<sup>+</sup>                                  | 121 (90)          | 214 (79)             | 0.009   | 508 (48)          | 1274 (54)            | <0.001  |
| Liver cirrhosis (Child-Pugh B or C)*                | 2 (1)             | 4 (1)                | 1.0     | 4 (0.4)           | 28 (1)               | 0.02    |
| Malignancy currently under treatment<sup>+</sup>    | 2 (1)             | 11 (4)               | 0.23    | 22 (2)            | 114 (5)              | <0.001  |
| Chronic lung disease (moderate or severe)*          | 5 (4)             | 6 (2)                | 0.52    | 14 (1)            | 87 (4)               | <0.001  |
| Coronary artery disease*                            | 76 (56)           | 119 (44)             | 0.02    | 322 (30)          | 627 (27)             | 0.03    |
| STS-PROM score, %                                   | 7.3 (4.8–11.4)    | 8.9 (5.9–13.0)       | 0.007   | 2.5 (1.6–4.1)     | 3.9 (2.4–6.7)        | <0.001  |
| Echocardiographic variables                         |                   |                      |         |                  |                      |         |
| Left ventricular ejection fraction, %*              | 58.1±13.2         | 56.4±14.4            | 0.25    | 63.4±14.0         | 63.5±12.9            | 0.72    |
| Left ventricular ejection fraction <50%             | 32 (24)           | 73 (27)              | 0.47    | 173 (16)          | 315 (13)             | 0.03    |
| Peak aortic jet velocity, m/s<sup>+</sup>           | 4.41±0.82         | 3.74±0.80            | <0.001  | 4.74±0.82         | 3.89±0.84            | <0.001  |
| Peak aortic jet velocity ≥4 m/s<sup>+</sup>         | 100 (74)          | 111 (41)             | <0.001  | 894 (84)          | 1080 (46)            | <0.001  |
| Mean aortic pressure gradient, mm Hg                | 49±18             | 32±15                | <0.001  | 54±20             | 36±17                | <0.001  |
| Aortic valve area (equation of continuity), cm<sup>+</sup> | 0.69±0.16         | 0.76±0.16            | <0.001  | 0.64±0.17         | 0.75±0.18            | <0.001  |
| Any combined valvular disease (moderate or severe)<sup>+</sup> | 65 (48)           | 101 (37)             | 0.04    | 414 (39)          | 978 (42)             | 0.14    |
| Tricuspid regurgitation pressure gradient ≥40 mm Hg*| 32 (24)           | 48 (18)              | 0.16    | 148 (14)          | 378 (16)             | 0.11    |

Values are number (%), mean±SD, or median (interquartile range) unless otherwise stated. AVR indicates aortic valve replacement; PROM, predicted risk of mortality; STS, Society of Thoracic Surgeons.

<sup>+</sup>Potential independent variables selected in the Cox proportional hazard models for all-cause death, cardiovascular death, and a composite of aortic valve–related death or hospitalization for heart failure.

<sup>+</sup>Potential independent variables selected in the Cox proportional hazard models for aortic valve–related death, aortic valve–procedure death, sudden death, noncardiovascular death, and hospitalization for heart failure.

<sup>+</sup>Body mass index was calculated as weight in kilograms divided by height in meters squared.

<sup>+</sup>Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men).

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sensitivity analysis were similar to those of the primary analysis (Tables S3 through S6 and Figures S2 and S3).

Baseline Characteristics and Clinical Outcomes After AVR: Hemodialysis Versus Nonhemodialysis Patients

Among the 135 hemodialysis and 1062 nonhemodialysis patients in the initial AVR group, surgical AVR or TAVI was actually performed in 131 patients (97%) and 1043 patients (98%), respectively. TAVI was performed only in 11 non-hemodialysis patients. The differences in baseline clinical and echocardiographic characteristics between hemodialysis and nonhemodialysis patients in the initial AVR group were consistent with those in the entire study population (Table S2). The procedural characteristics in 1174 patients who actually underwent AVR based on the initial treatment strategy are presented in Table S3. Hemodialysis patients

| Table 4. Clinical Outcomes in Dialysis and Nondialysis Patients: Initial AVR VS Conservative Groups |
|-------------------------------------------------------------|
|                  | Initial AVR Group | Conservative Group |
|                  | Number of Patients | Number of Patients |
|                  | With at Least 1 Event | (Cumulative 5-Y Incidence [%]) | (Cumulative 5-Y Incidence [%]) |
| Dialysis: N=135 | N=1062 |
| Nondialysis: N=2348 | Unadjusted HR (95% CI) | P Value | Adjusted HR (95% CI) | P Value | P Interaction |
| All-cause death | 0.001 |
| Dialysis patients | 66 (60.6) | 182 (75.5) | 0.61 (0.46–0.81) | <0.001 | 0.62 (0.43–0.90) | 0.01 |
| Nondialysis patients | 170 (18.7) | 1031 (49.3) | 0.30 (0.25–0.35) | <0.001 | 0.40 (0.33–0.48) | <0.001 |
| Cardiovascular death | 0.004 |
| Dialysis patients | 48 (48.6) | 135 (64.5) | 0.61 (0.43–0.84) | 0.002 | 0.64 (0.41–0.98) | 0.04 |
| Nondialysis patients | 103 (11.3) | 666 (35.6) | 0.28 (0.23–0.35) | <0.001 | 0.36 (0.28–0.45) | <0.001 |
| Aortic valve–related death | <0.001 |
| Dialysis patients | 27 (21.8) | 80 (44.6) | 0.60 (0.38–0.91) | 0.02 | 0.57 (0.34–0.94) | 0.03 |
| Nondialysis patients | 41 (4.2) | 461 (26.7) | 0.16 (0.12–0.23) | <0.001 | 0.18 (0.13–0.26) | <0.001 |
| Aortic valve procedure–related death | 0.005 |
| Dialysis patients | 26 (21.2) | 6 (3.4) | 8.19 (3.60–22.00) | <0.001 | 7.99 (2.91–21.93) | <0.001 |
| Nondialysis patients | 24 (2.3) | 25 (1.8) | 1.87 (1.07–3.28) | 0.03 | 1.43 (0.75–2.73) | 0.28 |
| Sudden death | 0.06 |
| Dialysis patients | 4 (10.2) | 48 (31.7) | 0.14 (0.04–0.35) | <0.001 | 0.15 (0.05–0.44) | <0.001 |
| Nondialysis patients | 23 (3.0) | 121 (7.2) | 0.35 (0.22–0.54) | <0.001 | 0.38 (0.23–0.62) | <0.001 |
| Noncardiovascular death | 0.11 |
| Dialysis patients | 18 (23.4) | 47 (30.9) | 0.64 (0.36–1.09) | 0.10 | 0.73 (0.37–1.45) | 0.37 |
| Nondialysis patients | 67 (8.3) | 365 (21.3) | 0.33 (0.26–0.43) | <0.001 | 0.50 (0.37–0.67) | <0.001 |
| Hospitalization for heart failure | 0.66 |
| Dialysis patients | 10 (26.9) | 47 (31.7) | 0.32 (0.15–0.61) | <0.001 | 0.16 (0.06–0.42) | <0.001 |
| Nondialysis patients | 92 (10.5) | 663 (38.7) | 0.23 (0.19–0.29) | <0.001 | 0.24 (0.19–0.31) | <0.001 |
| A composite of aortic valve–related death or hospitalization because of heart failure | 0.01 |
| Dialysis patients | 36 (42.2) | 100 (56.1) | 0.59 (0.40–0.85) | 0.005 | 0.62 (0.38–1.02) | 0.06 |
| Nondialysis patients | 129 (13.9) | 807 (44.0) | 0.27 (0.23–0.33) | <0.001 | 0.27 (0.22–0.33) | <0.001 |

Number of patients with at least 1 event was counted through the entire follow-up period, while the cumulative incidence was truncated at 5 years. Follow-up was commenced on the day of the index echocardiography. AVR indicates aortic valve replacement; HR, hazard ratio.
**Figure 4.** Cumulative incidence of all-cause death (A) and sudden death (B) in dialysis patients and nondialysis patients: initial AVR vs conservative strategies. Follow-up was commenced on the day of the index echocardiography. AVR indicates aortic valve replacement.
Table 5. Clinical Outcomes After AVR: Dialysis VS Nondialysis Patients

| Event                                      | Dialysis Patients | Nondialysis Patients | Unadjusted HR (95% CI) | P Value | Adjusted HR (95% CI) | P Value |
|--------------------------------------------|-------------------|----------------------|------------------------|---------|----------------------|---------|
| Number of Patients With at Least 1 Event (Cumulative 5-Y Incidence [%]) | N=131         | N=1043                |                        |         |                      |         |
| All-cause death                            | 64 (63.2)        | 156 (17.9)            | 5.19 (3.84–6.93)       | <0.001  | 4.00 (2.75–5.81)     | <0.001  |
| Cardiovascular death                       | 47 (52.6)        | 92 (10.7)             | 6.24 (4.34–8.86)       | <0.001  | 5.30 (3.32–8.48)     | <0.001  |
| Aortic valve–related death                 | 26 (21.2)        | 30 (3.0)              | 8.22 (4.82–13.94)      | <0.001  | 9.31 (5.20–16.68)    | <0.001  |
| Aortic valve procedure–related death       | 26 (21.2)        | 24 (2.3)              | 10.12 (5.78–17.78)     | <0.001  | 10.86 (5.87–20.07)   | <0.001  |
| Noncardiovascular death                    | 17 (22.4)        | 64 (8.0)              | 3.57 (2.02–5.99)       | <0.001  | 4.87 (2.69–8.82)     | <0.001  |
| Hospitalization for heart failure          | 9 (25.6)         | 84 (9.8)              | 1.43 (0.67–2.70)       | 0.33    | 1.65 (0.80–3.40)     | 0.18    |
| A composite of aortic valve–related death or hospitalization for heart failure | 34 (40.8)        | 112 (12.3)            | 3.63 (2.43–5.28)       | <0.001  | 2.90 (1.80–4.66)     | <0.001  |

Number of patients with at least 1 event was counted through the entire follow-up period, while the cumulative incidence was truncated at 5 years. Follow-up was commenced on the day of surgical AVR or TAVI. AVR indicates aortic valve replacement; HR, hazard ratio; TAVI, transcatheter aortic valve implantation.

more often underwent AVR combined with coronary artery bypass grafting and less often AVR combined with replacement of ascending aorta than nonhemodialysis patients. A bioprosthetic valve was less often used in hemodialysis patients than in nonhemodialysis patients (Table S7). Hemodialysis patients were associated with markedly higher risk for all-cause death and aortic valve procedure–related death after AVR than nonhemodialysis patients (Table 5, Figure 5). The 30-day mortality rate after AVR was 7.6% in hemodialysis patients, which was markedly higher than 1.3% in nonhemodialysis patients (Figure 5). The rate of aortic valve procedure–related death, which predominantly occurred within 6 months of the AVR procedure, was markedly higher in the hemodialysis patients than in the nonhemodialysis patients (21.2% and 2.3%, P<0.001) (Table 5 and Figure 5). In hemodialysis patients, the cumulative 5-year incidences of all-cause death and hospitalization for HF were not significantly different between the bioprosthetic and mechanical valves (Figure S4). Only 2 patients underwent redo AVR in the 80 hemodialysis patients who received the bioprosthetic valve.

Discussion

The main findings of the present study are as follows: (1) Hemodialysis patients with severe AS have a significantly poorer prognosis than nonhemodialysis patients with severe AS; (2) The initial AVR strategy as compared with the conservative strategy in hemodialysis patients was associated with significantly lower long-term mortality risk, particularly the risk for sudden death; (3) However, the AVR procedure–related mortality was much higher in hemodialysis patients than that in nonhemodialysis patients.

Previous small studies have suggested the poor prognosis after AVR in hemodialysis patients with severe AS.6–10 The present study including a large number of hemodialysis patients with severe AS clearly demonstrated that hemodialysis patients had a significantly higher 5-year cumulative mortality rate than nonhemodialysis patients (71% versus 40%) with a notably higher rate in the first year (35.9% versus 13.4%), although AVR was more often performed in hemodialysis patients than in nonhemodialysis patients. Compared with the survival rates of 89.7% at 1 year and 60.5% at 5 years after hemodialysis introduction reported from the Society for Dialysis Therapy, the mortality rate of our study is considerably higher, suggesting the grimmer prognosis of hemodialysis patients with severe AS, although the durations after the hemodialysis introduction were variable in the present study.2 Furthermore, the rate of sudden death in hemodialysis patients was remarkably high (9.3% at 1 year and 24.7% at 5 years) in the present study. The 5-year rate of sudden death was much higher than 10.5% at 4 years after percutaneous coronary intervention reported in Japanese hemodialysis patients.15

AVR is the only definitive treatment in patients with severe AS. In the present study, the initial AVR strategy as compared with the conservative strategy was associated with a significantly lower long-term mortality rate in hemodialysis patients as well as in nonhemodialysis patients. A dramatically lower risk for sudden death in the initial AVR group would have been one of the major contributors for the lower long-term mortality in hemodialysis patients with severe AS. Furthermore, markedly lower risk for HF hospitalization in the initial
AVR strategy might also have contributed to the lower long-term mortality in hemodialysis patients with severe AS. On the other hand, it should be noted that the long-term mortality rate of hemodialysis patients with severe AS is very high even after AVR as compared with that in nonhemodialysis patients. Thourani et al reported the 5-year mortality rate of 71.5% after AVR in 114 hemodialysis patients, which was comparable to 63.2% in 131 hemodialysis patients in the present study.8 The effect size of the initial AVR strategy relative to the conservative strategy for all-cause death was smaller in hemodialysis patients than in nonhemodialysis patients, which could be explained by the extremely high rate of aortic valve procedure–related death in hemodialysis patients, predominantly occurring within 6 months of the AVR procedure. The major causes of aortic valve procedure–related death were infection and hemorrhage. When undergoing surgical AVR, hemodialysis patients are more likely to have an increased risk of perioperative infection and hemorrhage because of having higher preoperative morbidity, more concomitant diseases, and more severe atherosclerosis than nonhemodialysis patients, which may have increased postoperative mortality rates in hemodialysis patients. Therefore, reduction in the procedural mortality of AVR is essential to improve the overall mortality outcome of hemodialysis patients with severe AS. In this context, less invasive TAVI might be an attractive alternative to surgical AVR in hemodialysis patients with severe AS. Currently, there are only a few small studies reporting outcomes of TAVI in hemodialysis patients; reported 30-day mortality rates included 14.0% (6/43) (transfemoral: 6.5%, and nontransfemoral: 33.3%) by Szerlip et al, 15.2% (5/33) by Dumonteil et al, and 0% (0/17) by Maeda et al.16–18 Further investigation on the role of TAVI in hemodialysis patients with severe AS is urgently needed.

**Figure 5.** Cumulative incidence of all-cause death and aortic valve procedure–related death after surgical AVR/TAVI in the initial AVR group: dialysis vs nondialysis patients. In the initial AVR group, 1174 of 1197 patients actually underwent surgical AVR or TAVI. Follow-up was commenced on the day of surgical AVR or TAVI. AVR indicates aortic valve replacement; TAVI, transcatheter aortic valve implantation.

**Study Limitations**

The present study has several limitations. First, its observational study design was prone to inherent bias. Particularly, the comparison between the initial AVR and conservative strategies would have been influenced by selection bias toward choosing less morbid patients in the initial AVR strategy. Also, the conservative group is a heterogeneous population and includes those with indications for surgery who were thought to be too risky and those not meeting indications for AVR because they were without symptoms. This could be noted as the Society of Thoracic Surgeons predicted risk of mortality is higher in the conservative group, yet the mean aortic pressure gradient is lower in this group. Despite an extensive multivariable adjustment, we could not
deny the possibility of unmeasured confounders and selection bias. Also, we did not take the competing risk of death into account for the nonfatal outcomes and also the competing risks of various causes of death. Secondly, we did not evaluate the influence of the duration after introduction of hemodialysis on long-term outcomes. Thirdly, the threshold to choose the AVR strategy and procedural outcomes of AVR might be different across the participating centers in this multicenter registry. Finally, the number of patients undergoing TAVI in our study was too small to clarify prognosis of hemodialysis patients undergoing TAVI.

Conclusions

Among hemodialysis patients with severe AS, the initial AVR strategy as compared with the conservative strategy was significantly lower long-term mortality risk, particularly the risk for sudden death, although the effect size for the survival benefit of the initial AVR strategy was smaller than that in the nonhemodialysis patients.

Disclosures

None.

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Supplemental Material
CURRENT AS Registry Investigators:

Principal investigators
Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
Ryuzo Sakata, Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan

List of participating centers and investigators for the CURRENT AS registry

Cardiology
Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine: Takeshi Kimura, Tomohiko Taniguchi, Hiroki Shiomi, Naritatsu Saito, Masao Imai, Junichi Tazaki, Toshiaki Toyota, Hirooki Higami, Tetsuma Kawaji
Department of Cardiology, Kokura Memorial Hospital: Kenji Ando, Shinichi Shirai, Kengo Korai, Takeshi Arita, Shiro Miura, Kyohei Yamaji
Division of Cardiology, Shimada Municipal Hospital: Takeshi Aoyama, Norio Kanamori
Department of Cardiology, Shizuoka City Shizuoka Hospital: Tomoya Onodera, Koichiro Murata
Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital: Yutaka Furukawa, Takeshi Kitai, Kitae Kim
Department of Cardiology, Kurashiki Central Hospital: Kazushige Kadota, Yuichi Kawase, Keiichiro Iwasaki, Hiroshi Miyawaki, Ayumi Misao, Akimune Kuwayama, Masanobu Ohya, Takenobu Shimada, Hidewo Amano
Department of Cardiology, Tenri Hospital: Yoshihisa Nakagawa, Chisato Izumi, Makoto Miyake, Masashi Amano, Yusuke Takahashi, Yusuke Yoshikawa, Shunsuke Nishimura, Maiko Kuroda
Division of Cardiology, Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani, Hirokazu Mitsuoka
Department of Cardiology, Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi, Masashi Kato, Takafumi Yomomatsu, Akihiro Kushiyama, Hidenori Yaku, Toshimitsu Watanabe
Department of Cardiology, Kinki University Hospital: Shunichi Miyazaki, Yutaka Hirano
Department of Cardiology, Kishiwada City Hospital: Mitsuo Matsuda, Shintaro Matsuda, Sachiko Sugioka
Department of Cardiovascular Center, Osaka Red Cross Hospital: Tsukasa Inada, Kazuya Nagao, Naoki Takahashi, Kohei Fukuchi
Department of Cardiology, Koto Memorial Hospital: Tomoyuki Murakami, Hiroshi Mabuchi, Teruki Takeda, Tomoko Sakaguchi, Keiko Maeda, Masayuki Yamaji, Motoyoshi Maenaka, Yutaka Tadano
Department of Cardiology, Shizuoka General Hospital: Hiroki Sakamoto, Yasuyo Takeuchi, Makoto Motooka, Ryusuke Nishikawa
Department of Cardiology, Nishikobe Medical Center: Hiroshi Eizawa, Keiichiro Yamane, Mitsunori Kawato, Minako Kinoshita, Kenji Aida
Department of Cardiology, Japanese Red Cross Wakayama Medical Center: Takashi Tamura, Mamoru Toyofuku, Kousuke Takahashi, Euihong Ko
Department of Cardiology, National Hospital Organization Kyoto Medical Center: Masaharu Akao, Mitsuru Ishii, Nobutoyo Masunaga, Hisashi Ogawa, Moritake Iguchi, Takashi Unoki, Kensuke Takabayashi, Yasuhiro Hamatani, Yugo Yamashita
Cardiovascular Center, The Tazuke Kofukai Medical Research Institute, Kitano Hospital: Moriaki Inoko, Eri Minamino-Muta, Takao Kato
Department of Cardiology, Hikone Municipal Hospital: Yoshihiro Himura, Tomoyuki Ikeda
Department of Cardiology, Kansai Electric Power Hospital: Katsuhisa Ishii, Akihiro Komasa
Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center: Yukihito Sato, Kozo Hotta, Shuhei Tsuji
Department of Cardiology, Rakuwakai Otowa Hospital: Yuji Hiraoka, Nobuya Higashitani
Department of Cardiology, Saiseikai Noe Hospital: Ichiro Kouchi, Yoshihiro Kato
Department of Cardiology, Shiga Medical Center for Adults: Shigeru Ikekuchi, Yasutaka Inuzuka, Soji Nishio, Jyunya Seki
Department of Cardiology, Hamamatsu Rosai Hospital: Eiji Shinoda, Miho Yamada, Akira Kawamoto, Chiyo Maeda
Department of Cardiology, Japanese Red Cross Otsu Hospital: Takashi Konishi, Toshikazu Jinnai, Kouji Sogabe, Michiya Tachiiri, Yukiko Matsumura, Chihiro Ota
Department of Cardiology, Hirakata Kohsai Hospital: Shoji Kitaguchi, Yuko Morikami
Cardiovascular Surgery
Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine: Ryuzo Sakata, Kenji Minakata, Kenji Minatoya
Department of Cardiovascular Surgery, Kokura Memorial Hospital: Michiya Hanyu
Department of Cardiovascular Surgery, Shizuoka City Shizuoka Hospital: Fumio Yamazaki
Department of Cardiovascular Surgery, Kobe City Medical Center General Hospital: Tadaaki Koyama
Department of Cardiovascular Surgery, Kurashiki Central Hospital: Tatsuhiko Komiya
Department of Cardiovascular Surgery, Tenri Hospital: Kazuo Yamashita
Department of Cardiovascular Surgery, Nara Hospital, Kinki University Faculty of Medicine: Noboru Nishiwaki
Department of Cardiovascular Surgery, Mitsubishi Kyoto Hospital: Hiroyuki Nakajima, Motoaki Ohnaka, Hiroaki Osada, Katsuaki Meshii
Department of Cardiovascular Surgery, Kinki University Hospital: Toshihiko Saga
Department of Cardiovascular Surgery, Kishiwada City Hospital: Masahiko Onoe, Hitoshi Kitayama
Department of Cardiovascular Surgery, Osaka Red Cross Hospital: Shogo Nakayama
Department of Cardiovascular Surgery, Shizuoka General Hospital: Genichi Sakaguchi
Department of Cardiovascular Surgery, Japanese Red Cross Wakayama Medical Center: Atsushi Iwakura
Department of Cardiovascular Surgery, National Hospital Organization Kyoto Medical Center: Kotaro Shiraga
Department of Cardiovascular Surgery, Cardiovascular Center, The Tazuke Kofukai Medical Research Institute, Kitano Hospital: Koji Ueyama
Department of Cardiovascular Surgery, Hyogo Prefectural Amagasaki General Medical Center: Keiichi Fujiwara
Department of Cardiovascular Surgery, Rakuwakai Otowa Hospital: Atsushi Fukumoto
Department of Cardiovascular Surgery, Shiga Medical Center for Adults: Senri Miwa
Department of Cardiovascular Surgery, Hamamatsu Rosai Hospital: Junichiro Nishizawa
Department of Cardiovascular Surgery, Japanese Red Cross Otsu Hospital: Mitsuru Kitano

A clinical event committee
Hirotoshi Watanabe, MD (Kyoto University Graduate School of Medicine); Kenji Nakatsuma, MD (Kyoto University Graduate School of Medicine), Tomoki Sasa, MD (Kishiwada City Hospital)
**Data S1.**

**Definitions of the clinical events**
Death was regarded as having its origin in cardiovascular unless obvious non-cardiovascular causes were identified. Sudden death was defined as unexplained death of stable patients. Any death during hospitalization for aortic valve replacement or transcatheter aortic valve implantation was regarded as aortic valve procedure-related death. Aortic valve-related death included aortic valve procedure death, sudden death, and death due to heart failure related to aortic stenosis. Heart failure hospitalization was defined as hospitalization due to worsening heart failure requiring intravenous drug therapy. Myocardial infarction during the follow-up period was defined in accordance with the universal myocardial infarction guidelines.\(^1\) Stroke was defined as ischemic or hemorrhagic stroke either requiring or prolonging hospitalization with symptoms lasting >24 hours. Life-threatening/disabling or major bleeding was defined as Bleeding Academic Research Consortium (BARC) classifications type 5, 3c, 3b, or 3a.\(^2\)
| Variables                                                              | Dialysis patients                                                                 | Non-dialysis patients                                                                 |
|-----------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
|                                                                       | Initial AVR group N=135                                                          | Initial AVR group N=1062                                                             |
|                                                                       | Conservative group N=270                                                         | Conservative group N=2348                                                             |
|                                                                       | P value                                                                         | P value                                                                               |
| Age, years                                                            | 70.3±8.2                                                                         | 73.7±8.9                                                                             | 80.3±9.4                                                                             | <0.001 |
| Age ≥80 years*†                                                        | 17 (13)                                                                         | 282 (27)                                                                             | 1354 (58)                                                                            | <0.001 |
| Men*                                                                  | 87 (64)                                                                         | 420 (40)                                                                             | 781 (33)                                                                             | <0.001 |
| Body mass index‡                                                       | 20.8±3.1                                                                         | 22.5±3.6                                                                             | 21.7±3.9                                                                             | <0.001 |
| Body mass index <22*                                                   | 95 (70)                                                                         | 527 (50)                                                                             | 1501 (64)                                                                            | <0.001 |
| Body surface area, m²                                                  | 1.49±0.18                                                                        | 1.50±0.18                                                                            | 1.43±0.19                                                                            | <0.001 |
| Any symptoms possibly related to aortic stenosis                      | 103 (76)                                                                         | 802 (76)                                                                             | 1005 (43)                                                                            | <0.001 |
| Angina                                                                | 33 (24)                                                                         | 258 (24)                                                                             | 180 (8)                                                                              | <0.001 |
| Syncope                                                                | 15 (11)                                                                          | 95 (9)                                                                               | 78 (3)                                                                               | <0.001 |
| Heart failure                                                         | 72 (53)                                                                         | 587 (55)                                                                             | 873 (37)                                                                             | <0.001 |
| Admission for heart failure at index echocardiography*†               | 28 (21)                                                                         | 242 (23)                                                                             | 488 (21)                                                                             | 0.19 |
| Hypertension*                                                         | 97 (72)                                                                         | 710 (67)                                                                             | 1670 (71)                                                                            | 0.01 |
| Current smoking*                                                      | 12 (9)                                                                          | 71 (7)                                                                               | 103 (4)                                                                              | 0.005 |
| History of smoking                                                    | 51 (38)                                                                         | 263 (25)                                                                             | 447 (19)                                                                             | <0.001 |
| Dyslipidemia                                                          | 23 (17)                                                                         | 453 (43)                                                                             | 796 (34)                                                                             | <0.001 |
| On statin therapy                                                     | 13 (10)                                                                         | 326 (31)                                                                             | 599 (26)                                                                             | 0.002 |
| Diabetes mellitus                                                     | 32 (24)                                                                         | 244 (23)                                                                             | 526 (22)                                                                             | 0.71 |
| On insulin therapy*                                                   | 11 (8)                                                                          | 47 (4)                                                                               | 105 (4)                                                                              | 0.95 |
| Condition                                                              | Cases  | Controls | p-value | 95% CI       | p-value   |
|-----------------------------------------------------------------------|--------|----------|---------|--------------|-----------|
| Prior myocardial infarction*                                           | 11 (8) | 37 (14)  | 0.10    | 40 (4)       | 235 (10)  | <0.001   |
| Prior percutaneous coronary intervention                              | 26 (19)| 71 (26)  | 0.12    | 77 (7)       | 328 (14)  | <0.001   |
| Prior coronary artery bypass graft                                     | 10 (7) | 35 (13)  | 0.09    | 22 (2)       | 132 (6)   | <0.001   |
| Prior open heart surgery                                               | 12 (9) | 39 (14)  | 0.11    | 36 (3)       | 229 (10)  | <0.001   |
| Prior symptomatic stroke*                                              | 19 (14)| 51 (19)  | 0.23    | 88 (8)       | 345 (15)  | <0.001   |
| Atrial fibrillation or flutter*†                                       | 29 (21)| 71 (26)  | 0.29    | 178 (17)     | 550 (23)  | <0.001   |
| Aortic/peripheral vascular disease*                                    | 12 (9) | 70 (26)  | <0.001  | 58 (5)       | 142 (6)   | 0.50     |
| Years from dialysis introduction                                       | 0.21   |          |         |              |           |
| < 1 year                                                              | 8 (6)  | 25 (9)   |         |              |           |
| ≥ 1 year, < 5 years                                                   | 33 (24)| 83 (31)  |         |              |           |
| ≥ 5 year, < 10 years                                                  | 29 (21)| 58 (21)  |         |              |           |
| ≥ 10 years                                                            | 65 (48)| 104 (39) |         |              |           |
| Anemia*                                                               | 121 (90)| 214 (79)| 0.009   | 508 (48)     | 1274 (54)| <0.001   |
| Liver cirrhosis (Child-Pugh B or C)*                                  | 2 (1)  | 4 (1)    | 1.0     | 4 (0.4)      | 28 (1)    | 0.02     |
| Malignancy                                                            | 15 (11)| 44 (16)  | 0.16    | 116 (11)     | 342 (15)  | 0.004    |
| Malignancy currently under treatment*†                                 | 2 (1)  | 11 (4)   | 0.23    | 22 (2)       | 114 (5)   | <0.001   |
| Chest wall irradiation                                                | 1 (1)  | 1 (0.4)  | 1.0     | 6 (0.6)      | 17 (0.7)  | 0.60     |
| Immunosuppressive therapy                                             | 9 (7)  | 8 (3)    | 0.08    | 22 (2)       | 92 (4)    | 0.006    |
| Chronic lung disease                                                  | 19 (14)| 21 (8)   | 0.045   | 122 (11)     | 238 (10)  | 0.23     |
| Chronic lung disease (moderate or severe)*                            | 5 (4)  | 6 (2)    | 0.52    | 14 (1)       | 87 (4)    | <0.001   |
| Coronary artery disease*                                              | 76 (56)| 119 (44)| 0.02    | 322 (30)     | 627 (27)  | 0.03     |
| Logistic EuroSCORE, %                                                 | 11.3 (7.1-18.9)| 15.9 (8.8-25.1)| <0.001 | 6.6 (4.2-10.6)| 10.8 (6.6-18.3)| <0.001 |
| EuroSCORE II, %                                                       | 2.4 (1.8-4.1)| 2.8 (2.0-4.9)| <0.001 | 2.1 (1.3-3.5)| 3.4 (2.0-5.5)| <0.001 |
### Etiology of aortic stenosis

| Etiology                                      | Degenerative | Congenital (Unicuspid, Bicuspid, Quadricuspid) | Rheumatic | Infective endocarditis | Others |
|-----------------------------------------------|--------------|-----------------------------------------------|-----------|------------------------|--------|
| Etiology of aortic stenosis                   |              |                                               |           |                        |        |
| Degenerative                                  | 130 (96)     | 264 (98)                                      | 844 (79)  | 2141 (91)              |        |
| Congenital                                    | 0            | 4 (1)                                         | 154 (15)  | 100 (4)                |        |
| Rheumatic                                     | 4 (3)        | 1 (0.4)                                       | 49 (5)    | 96 (4)                 |        |
| Infective endocarditis                        | 1 (1)        | 0                                             | 5 (0.5)   | 1 (0.04)               |        |
| Others                                        | 0            | 1 (0.4)                                       | 10 (1)    | 10 (0.4)               |        |

### Echocardiographic variables

| Echocardiographic variables                    | Left ventricular end-diastolic diameter, mm | Left ventricular end-systolic diameter, mm | Left ventricular ejection fraction, % | Left ventricular ejection fraction <40% | Left ventricular ejection fraction <50% | Interventricular septum thickness in diastole, mm | Posterior wall thickness in diastole, mm | Peak aortic jet velocity, m/s | Peak aortic jet velocity ≥5m/s | Peak aortic jet velocity ≥4m/s*† | Peak aortic pressure gradient, mmHg | Mean aortic pressure gradient, mmHg | Aortic valve area (equation of continuity), cm² | Aortic valve area index, cm²/m² | Any combined valvular disease (moderate or severe)*† |
|-----------------------------------------------|---------------------------------------------|--------------------------------------------|-------------------------------------|----------------------------------------|----------------------------------------|-----------------------------------------------|-------------------------------|------------------------------|-------------------------------|----------------------------------|-------------------------------------|-----------------------------|-----------------------------|---------------------------|------------------------------------------------|
| STS-PROM score, %                             | 7.3 (4.8-11.4)                              | 8.9 (5.9-13.0)                             | 0.007                               | 2.5 (1.6-4.1)                          | 3.9 (2.4-6.7)                          | <0.001                                        |                               |                             |                              |                                  |                                     |                             |                             |                           |                                                         |
| Condition                              | Value 1 (n, %) | Value 2 (n, %) | p-value | Value 3 (mean ± SD) | Value 4 (median (IQR)) | p-value |
|----------------------------------------|----------------|----------------|---------|---------------------|------------------------|---------|
| Moderate or severe aortic regurgitation| 35 (26)        | 42 (16)        | 0.01    | 259 (24)            | 455 (19)               | 0.001   |
| Moderate or severe mitral stenosis     | 8 (6)          | 6 (2)          | 0.08    | 43 (4)              | 76 (3)                 | 0.23    |
| Moderate or severe mitral regurgitation| 39 (29)        | 63 (23)        | 0.22    | 188 (18)            | 473 (20)               | 0.09    |
| Moderate or severe tricuspid regurgitation| 21 (16)       | 43 (16)        | 0.92    | 126 (12)            | 438 (19)               | <0.001  |
| Tricuspid regurgitation pressure gradient ≥40 mmHg* | 32 (24) | 48 (18) | 0.16 | 148 (14) | 378 (16) | 0.11 |

Values are number (%), mean ± SD, or median (interquartile range) unless otherwise stated.

* Potential independent variables selected in the Cox proportional hazard models for all-cause death, cardiovascular death and a composite of aortic valve-related death or hospitalization for heart failure.
† Potential independent variables selected in the Cox proportional hazard models for aortic valve-related death, aortic valve-procedure death, sudden death, non-cardiovascular death and hospitalization for heart failure.
‡ Body mass index was calculated as weight in kilograms divided by height in meters squared.
§ Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dl in women and <13.0 g/dl in men).

AVR=aortic valve replacement, STS=Society of Thoracic Surgeons, and PROM=predicted risk of mortality.
Table S2. Baseline Characteristics of Patients in the Initial AVR Group: Dialysis versus Non-dialysis Patients

| Variables                                             | Dialysis patients | Non-dialysis patients | P value |
|-------------------------------------------------------|-------------------|-----------------------|---------|
|                                                       | N=135             | N=1062                |         |
| Age, years                                            | 70.3±8.2          | 73.7±8.9              | <0.001  |
| Age ≥80 years*†                                        | 17 (13)           | 282 (27)              | <0.001  |
| Men*                                                  | 87 (64)           | 420 (40)              | <0.001  |
| Body mass index‡                                       | 20.8±3.1          | 22.5±3.6              | <0.001  |
| Body mass index <22*                                   | 95 (70)           | 527 (50)              | <0.001  |
| Body surface area, m²                                  | 1.49±0.18         | 1.50±0.18             | 0.56    |
| Any symptoms possibly related to aortic stenosis      | 103 (76)          | 802 (76)              | 0.84    |
| Angina                                                | 33 (24)           | 258 (24)              | 0.97    |
| Syncope                                               | 15 (11)           | 95 (9)                | 0.41    |
| Heart failure                                         | 72 (53)           | 587 (55)              | 0.67    |
| Admission for heart failure at index echocardiography*†| 28 (21)           | 242 (23)              | 0.59    |
| Hypertension*                                         | 97 (72)           | 710 (67)              | 0.24    |
| Current smoking*                                      | 12 (9)            | 71 (7)                | 0.34    |
| History of smoking                                    | 51 (38)           | 263 (25)              | 0.001   |
| Dyslipidemia                                          | 23 (17)           | 453 (43)              | <0.001  |
| On statin therapy                                     | 13 (10)           | 326 (31)              | <0.001  |
| Diabetes mellitus                                     | 32 (24)           | 244 (23)              | 0.85    |
| On insulin therapy*                                   | 11 (8)            | 47 (4)                | 0.06    |
| Prior myocardial infarction*                          | 11 (8)            | 40 (4)                | 0.02    |
| Prior percutaneous coronary intervention               | 26 (19)           | 77 (7)                | <0.001  |
| Condition                                      | Cases | Controls | p-value |
|-----------------------------------------------|-------|----------|---------|
| Prior coronary artery bypass graft            | 10 (7)| 22 (2)   | 0.002   |
| Prior open heart surgery                      | 12 (9)| 36 (3)   | 0.002   |
| Prior symptomatic stroke*                     | 19 (14)| 88 (8)   | 0.03    |
| Atrial fibrillation or flutter*†              | 29 (21)| 178 (17)| 0.17    |
| Aortic/peripheral vascular disease*           | 12 (9)| 58 (5)   | 0.11    |
| Serum creatinine, mg/dl                       |       | 0.8 (0.65-1.0) |         |
| Anemia*                                       | 121 (90)| 508 (48) | <0.001  |
| Liver cirrhosis (Child-Pugh B or C)*         | 2 (1)| 4 (0.4)  | 0.14    |
| Malignancy                                    | 15 (11)| 116 (11)| 0.95    |
| Malignancy currently under treatment*†       | 2 (1)| 22 (2)   | 1.0     |
| Chest wall irradiation                        | 1 (1)| 6 (0.6)  | 0.57    |
| Immunosuppressive therapy                    | 9 (7)| 22 (2)   | 0.005   |
| Chronic lung disease                          | 19 (14)| 122 (11)| 0.38    |
| Chronic lung disease (moderate or severe)*    | 5 (4)| 14 (1)   | 0.04    |
| Coronary artery disease*                      | 76 (56)| 322 (30)| <0.001  |
| Logistic EuroSCORE, %                        | 11.3 (7.1-18.9)| 6.6 (4.2-10.6)| <0.001  |
| EuroSCORE II, %                               | 2.4 (1.8-4.1) | 2.1 (1.3-3.5) | 0.71     |
| STS-PROM score, %                             | 7.3 (4.8-11.4)| 2.5 (1.6-4.1)| <0.001  |

**Etiology of aortic stenosis**

| Etiology                                      | Cases | Controls |
|-----------------------------------------------|-------|----------|
| Degenerative                                 | 130 (96)| 844 (79) |
| Congenital (Unicuspid, Bicuspid, Quadricuspid)| 0     | 154 (15) |
| Rheumatic                                    | 4 (3) | 49 (5)   |
| Infective endocarditis                       | 1 (1) | 5 (0.5)  |
### Echocardiographic variables

| Variable                                                                 | Values                          | p-value       |
|--------------------------------------------------------------------------|---------------------------------|---------------|
| Left ventricular end-diastolic diameter, mm                              | 49.6±7.0 46.9±7.1               | <0.001        |
| Left ventricular end-systolic diameter, mm                              | 34.6±8.5 30.6±8.4               | <0.001        |
| Left ventricular ejection fraction, %*                                    | 58.1±13.2 63.4±14.0             | <0.001        |
|   Left ventricular ejection fraction <40%                                 | 16 (12) 87 (8)                  | 0.15          |
|   Left ventricular ejection fraction <50%                                 | 32 (24) 173 (16)                | 0.03          |
| Interventricular septum thickness in diastole, mm                        | 12.4±2.6 11.9±2.3               | 0.02          |
| Posterior wall thickness in diastole, mm                                 | 12.1±2.2 11.5±2.1               | 0.001         |
| Peak aortic jet velocity, m/s                                            | 4.41±0.82 4.74±0.82             | <0.001        |
|   Peak aortic jet velocity ≥5 m/s                                        | 33 (24) 396 (37)                | 0.003         |
|   Peak aortic jet velocity ≥4 m/s*†                                      | 100 (74) 894 (84)               | 0.003         |
| Peak aortic pressure gradient, mmHg                                      | 80±29 93±32                     | <0.001        |
| Mean aortic pressure gradient, mmHg                                      | 49±18 54±20                     | 0.005         |
| Aortic valve area (equation of continuity), cm²                          | 0.69±0.16 0.64±0.17              | 0.009         |
| Aortic valve area index, cm²/m²                                          | 0.46±0.10 0.43±0.12              | 0.01          |
| Any combined valvular disease (moderate or severe)*†                     | 65 (48) 414 (39)                | 0.04          |
|   Moderate or severe aortic regurgitation                                | 35 (26) 259 (24)                | 0.70          |
|   Moderate or severe mitral stenosis                                     | 8 (6) 43 (4)                    | 0.31          |
|   Moderate or severe mitral regurgitation                                | 39 (29) 188 (18)                | 0.002         |
|   Moderate or severe tricuspid regurgitation                             | 21 (16) 126 (12)                | 0.22          |
| Tricuspid regurgitation pressure gradient ≥40 mmHg*                       | 32 (24) 148 (14)                | 0.003         |

Values are number (%), mean ± SD, or median (interquartile range) unless otherwise stated.
* Potential independent variables selected in the Cox proportional hazard models for all-cause death, cardiovascular death and a composite of aortic valve-related death or hospitalization for heart failure.

† Potential independent variables selected in the Cox proportional hazard models for aortic valve-related death, aortic valve-procedure death, non-cardiovascular death and hospitalization for heart failure.

‡ Body mass index was calculated as weight in kilograms divided by height in meters squared.

§ Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dl in women and <13.0 g/dl in men).

AVR=aortic valve replacement, STS=Society of Thoracic Surgeons, and PROM=predicted risk of mortality.
Table S3. Baseline Characteristics in the Entire Cohort and in the Propensity-score Matched Cohort in Dialysis Patients: Initial AVR versus Conservative Groups

| Variables                                      | Dialysis patients | Propensity-score matched cohort |
|------------------------------------------------|-------------------|---------------------------------|
|                                                | Initial AVR | Conservative | P value | Initial AVR | Conservative | P value |
| Age, years                                     | 70.3±8.2 | 74.7±8.4 | <0.001 | 70.7±8.1 | 73.6±8.3 | 0.007 |
| Age ≥80 years*                                  | 17 (13) | 76 (28) | <0.001 | 17 (15) | 19 (17) | 0.72 |
| Men*                                           | 87 (64) | 155 (57) | 0.17 | 72 (63) | 72 (63) | 1.0 |
| Body mass index‡                               | 20.8±3.1 | 20.3±3.9 | 0.24 | 20.7±3.1 | 21.0±2.8 | 0.45 |
| Body mass index <22*                           | 95 (70) | 203 (75) | 0.30 | 80 (70) | 80 (70) | 1.0 |
| Body surface area, m²                          | 1.49±0.18 | 1.45±0.17 | 0.04 | 1.48±0.17 | 1.47±0.16 | 0.72 |
| Any symptoms possibly related to aortic stenosis* | 103 (76) | 95 (35) | <0.001 | 82 (72) | 85 (75) | 0.65 |
| Angina                                         | 33 (24) | 27 (10) | <0.001 | 26 (23) | 14 (12) | 0.04 |
| Syncope                                        | 15 (11) | 10 (4) | 0.007 | 13 (11) | 9 (8) | 0.50 |
| Heart failure                                  | 72 (53) | 71 (26) | <0.001 | 56 (49) | 69 (61) | 0.08 |
| Hypertension                                   | 97 (72) | 190 (70) | 0.76 | 82 (72) | 82 (72) | 1.0 |
| Current smoking                                | 12 (9) | 10 (4) | 0.03 | 9 (8) | 10 (9) | 1.0 |
| History of smoking                             | 51 (38) | 69 (26) | 0.01 | 44 (39) | 52 (46) | 0.28 |
| Dyslipidemia                                   | 23 (17) | 55 (20) | 0.42 | 20 (18) | 21 (18) | 0.86 |
| On statin therapy                              | 13 (10) | 32 (12) | 0.50 | 11 (10) | 12 (11) | 0.83 |
| Diabetes mellitus                              | 32 (24) | 95 (35) | 0.02 | 27 (24) | 46 (40) | 0.007 |
| On insulin therapy                             | 11 (8) | 25 (9) | 0.71 | 9 (8) | 13 (11) | 0.50 |
| Condition                                      | Group 1 | Group 2 | p-value | Group 1 | Group 2 | p-value |
|------------------------------------------------|---------|---------|---------|---------|---------|---------|
| Prior myocardial infarction                    | 11 (8)  | 37 (14) | 0.10    | 11 (10) | 8 (7)   | 0.63    |
| Prior percutaneous coronary intervention        | 26 (19) | 71 (26) | 0.12    | 25 (22) | 22 (19) | 0.62    |
| Prior coronary artery bypass graft              | 10 (7)  | 35 (13) | 0.09    | 10 (9)  | 10 (9)  | 1.0     |
| Prior open heart surgery*                       | 12 (9)  | 39 (14) | 0.11    | 12 (11) | 10 (9)  | 0.65    |
| Prior symptomatic stroke*                       | 19 (14) | 51 (19) | 0.23    | 17 (15) | 13 (11) | 0.43    |
| Atrial fibrillation or flutter                  | 29 (21) | 71 (26) | 0.29    | 24 (21) | 22 (19) | 0.74    |
| Aortic/ peripheral vascular disease             | 12 (9)  | 70 (26) | <0.001  | 28 (25) | 38 (33) | 0.14    |
| Years from dialysis introduction                | 0.21    |         | <0.001  |         |         |         |
| < 1 year                                       | 8 (6)   | 25 (9)  |         | 7 (6)   | 10 (9)  |         |
| ≥ 1 year, < 5 years                            | 33 (24) | 83 (31) |         | 25 (22) | 63 (55) |         |
| ≥ 5 years, < 10 years                          | 29 (21) | 58 (21) |         | 26 (23) | 10 (9)  |         |
| ≥ 10 years                                     | 65 (48) | 104 (39)|         | 56 (49) | 31 (27) |         |
| Anemia*‡                                        | 121 (90)| 214 (79)| 0.009   | 100 (88)| 102 (89)| 0.68    |
| Liver cirrhosis (Child-Pugh B or C) *          | 2 (1)   | 4 (1)   | 1.0     | 1 (0.9)| 0       | 1.0     |
| Malignancy                                     | 15 (11) | 44 (16) | 0.16    | 15 (13) | 18 (16) | 0.57    |
| Malignancy currently under treatment*          | 2 (1)   | 11 (4)  | 0.23    | 2 (2)   | 2 (2)   | 1.0     |
| Chest wall irradiation*                        | 1 (1)   | 1 (0.4)| 1.0     | 1 (0.9)| 0       | 1.0     |
| Immunosuppressive therapy*                     | 9 (7)   | 8 (3)   | 0.08    | 7 (6)   | 4 (4)   | 0.54    |
| Chronic lung disease                           | 19 (14) | 21 (8)  | 0.045   | 16 (14)| 13 (11) | 0.55    |
| Chronic lung disease (moderate or severe) *    | 5 (4)   | 6 (2)   | 0.52    | 4 (4)   | 5 (4)   | 1.0     |
| Logistic EuroSCORE, %                          | 11.3 (7.1-18.9)| 15.9 (8.8-25.1)| <0.001| 11.9 (7.4-20.0)| 13.4 (7.9-23.2)| 0.12|
| EuroSCORE II, %                                | 2.4 (1.8-4.1)| 2.8 (2.0-4.9)| <0.001| 2.5 (1.8-4.3)| 2.9 (2.4-4.7)| 0.01|
| STS-PROM score, %                              | 7.3 (4.8-11.4)| 8.9 (5.9-13.0)| 0.007| 8.4 (5.1-11.5)| 9.5 (6.2-14.9)| 0.02|
### Etiology of aortic stenosis

| Etiology                                           | Degenerative | Congenital (Unicuspid, Bicuspid, Quadricuspid) | Rheumatic | Infective endocarditis | Others |
|----------------------------------------------------|--------------|-----------------------------------------------|-----------|------------------------|--------|
|                                                    | 130 (96)     | 264 (98)                                      | 0         | 1 (1)                  | 0      |
|                                                    | 112 (98)     | 110 (96)                                      | 0         | 0                      | 0      |
|                                                    | 4 (3)        | 4 (1)                                         | 1 (0.4)   | 3 (3)                  | 0      |
|                                                    | 1 (1)        | 0                                             | 1 (0.9)   | 0                      | 0      |
|                                                    | 0            | 1 (0.4)                                       | 0         | 0                      | 1 (0.9) |

### Echocardiographic variables

| Variable                                           | Mean ± SD     | Mean ± SD     | Mean ± SD     | Mean ± SD     | P value |
|----------------------------------------------------|---------------|---------------|---------------|---------------|---------|
| Left ventricular end-diastolic diameter, mm        | 49.6 ± 7.0    | 48.6 ± 7.4    | 49.4 ± 7.1    | 51.8 ± 7.3    | 0.02    |
| Left ventricular end-systolic diameter, mm        | 34.6 ± 8.5    | 34.1 ± 9.0    | 34.6 ± 8.8    | 37.1 ± 9.3    | 0.07    |
| Left ventricular ejection fraction, %              | 58.1 ± 13.2   | 56.4 ± 14.4   | 57.2 ± 13.7   | 54.0 ± 14.8   | 0.04    |
| Left ventricular ejection fraction <40%*           | 16 (12)       | 41 (15)       | 16 (14)       | 23 (20)       | 0.22    |
| Left ventricular ejection fraction <50%            | 32 (24)       | 73 (27)       | 29 (25)       | 37 (32)       | 0.24    |
| Interventricular septum thickness in diastole, mm  | 12.4 ± 2.6    | 11.4 ± 2.2    | 12.2 ± 2.6    | 11.3 ± 2.4    | 0.004   |
| Posterior wall thickness in diastole, mm           | 12.1 ± 2.2    | 11.0 ± 1.8    | 11.9 ± 2.3    | 11.0 ± 1.7    | 0.002   |
| Peak aortic jet velocity, m/s                      | 4.41 ± 0.82   | 3.74 ± 0.80   | 4.21 ± 0.71   | 3.86 ± 0.88   | <0.001  |
| Peak aortic jet velocity ≥5m/s*                    | 33 (24)       | 19 (7)        | 14 (12)       | 14 (12)       | 1.0     |
| Peak aortic jet velocity ≥4m/s                     | 100 (74)      | 111 (41)      | 79 (69)       | 51 (45)       | <0.001  |
| Peak aortic pressure gradient, mmHg                | 80 ± 29       | 59 ± 25       | 73.0 ± 23.1   | 62.6 ± 29.0   | <0.001  |
| Mean aortic pressure gradient, mmHg                | 49 ± 18       | 32 ± 15       | 43.0 ± 14.0   | 32.3 ± 15.0   | <0.001  |
| Aortic valve area (equation of continuity), cm²    | 0.69 ± 0.16   | 0.76 ± 0.16   | 0.70 ± 0.15   | 0.77 ± 0.14   | <0.001  |
| Aortic valve area index, cm²/m²                    | 0.46 ± 0.10   | 0.53 ± 0.12   | 0.47 ± 0.10   | 0.53 ± 0.09   | <0.001  |
| Any combined valvular disease (moderate or severe) *| 65 (48)       | 101 (37)      | 52 (46)       | 56 (49)       | 0.60    |
| Moderate or severe aortic regurgitation            | 35 (26)       | 42 (16)       | 24 (21)       | 28 (25)       | 0.53    |
| Condition                                | Count (%)   | Count (%) | Mean (SD) | Count (%) | Count (%) | Mean (SD) |
|------------------------------------------|-------------|-----------|-----------|-----------|-----------|-----------|
| Moderate or severe mitral stenosis       | 8 (6)       | 6 (2)     | 0.08      | 5 (4)     | 0         | 0.06      |
| Moderate or severe mitral regurgitation  | 39 (29)     | 63 (23)   | 0.22      | 32 (28)   | 37 (32)   | 0.47      |
| Moderate or severe tricuspid regurgitation| 21 (16)     | 43 (16)   | 0.92      | 18 (16)   | 22 (19)   | 0.49      |
| Tricuspid regurgitation pressure gradient ≥40 mmHg | 32 (24) | 48 (18) | 0.16      | 22 (19)   | 24 (21)   | 0.74      |

Values are number (%), mean ± SD, or median (interquartile range) unless otherwise stated.

* Potential independent variables relevant to the choice of initial AVR selected for logistic regression model to develop propensity-score for the choice of initial AVR.

† Body mass index was calculated as weight in kilograms divided by height in meters squared.

‡ Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dl in women and <13.0 g/dl in men).

AVR=aortic valve replacement, STS=Society of Thoracic Surgeons, and PROM=predicted risk of mortality.
| Variables                                           | Non-dialysis patients | Propensity-score matched cohort |
|-----------------------------------------------------|-----------------------|---------------------------------|
|                                                    | Initial AVR group    | Conservative group               |
|                                                    | N=1062                | N=2348                          |
|                                                     | P value               | N=1062                          | P value |
| Age, years                                          | 73.7±8.9              | 80.3±9.4                        | <0.001  | 73.7±8.9              | 76.3±8.9                        | <0.001  |
| Age ≥80 years*                                      | 282 (27)              | 1354 (58)                       | <0.001  | 282 (27)              | 283 (27)                        | 1.0     |
| Men*                                                | 420 (40)              | 781 (33)                        | <0.001  | 420 (40)              | 417 (39)                        | 0.93    |
| Body mass index†                                     | 22.5±3.6              | 21.7±3.9                        | <0.001  | 22.5±3.6              | 22.7±4.1                        | 0.16    |
| Body mass index <22*                                 | 527 (50)              | 1501 (64)                       | <0.001  | 527 (50)              | 507 (48)                        | 0.41    |
| Body surface area, m²                                | 1.50±0.18             | 1.43±0.19                       | <0.001  | 1.50±0.18             | 1.49±0.21                       | 0.12    |
| Any symptoms possibly related to aortic stenosis*    | 802 (76)              | 1005 (43)                       | <0.001  | 802 (76)              | 809 (76)                        | 0.75    |
| Angina                                              | 258 (24)              | 180 (8)                         | <0.001  | 258 (24)              | 173 (16)                        | <0.001  |
| Syncope                                             | 95 (9)                | 78 (3)                          | <0.001  | 95 (9)                | 57 (5)                          | 0.001   |
| Heart failure                                       | 587 (55)              | 873 (37)                        | <0.001  | 587 (55)              | 690 (65)                        | <0.001  |
| Hypertension                                        | 710 (67)              | 1670 (71)                       | 0.1      | 710 (67)              | 782 (74)                        | <0.001  |
| Current smoking                                     | 71 (7)                | 103 (4)                         | 0.005    | 71 (7)                | 91 (9)                          | 0.10    |
| History of smoking                                  | 263 (25)              | 447 (19)                        | <0.001  | 263 (25)              | 234 (22)                        | 0.14    |
| Dyslipidemia                                        | 453 (43)              | 796 (34)                        | <0.001  | 453 (43)              | 413 (39)                        | 0.08    |
| On statin therapy                                   | 326 (31)              | 599 (26)                        | 0.002    | 326 (31)              | 262 (25)                        | 0.002   |
| Diabetes mellitus                                   | 244 (23)              | 526 (22)                        | 0.71     | 244 (23)              | 228 (21)                        | 0.40    |
| On insulin therapy                                  | 47 (4)                | 105 (4)                         | 0.95     | 47 (4)                | 42 (4)                          | 0.59    |
| Condition                                      | Group A | Group B | p-value | Group A | Group B | p-value |
|-----------------------------------------------|---------|---------|---------|---------|---------|---------|
| Prior myocardial infarction                   | 40 (4)  | 235 (10)| <0.001  | 40 (4)  | 78 (7)  | <0.001  |
| Prior percutaneous coronary intervention      | 77 (7)  | 328 (14)| <0.001  | 77 (7)  | 99 (9)  | 0.08    |
| Prior coronary artery bypass graft            | 22 (2)  | 132 (6) | <0.001  | 22 (2.1)| 19 (1.8)| 0.64    |
| Prior open heart surgery*                     | 36 (3)  | 229 (10)| <0.001  | 36 (3)  | 31 (3)  | 0.53    |
| Prior symptomatic stroke*                     | 88 (8)  | 345 (15)| <0.001  | 88 (8)  | 89 (8)  | 0.94    |
| Atrial fibrillation or flutter                | 178 (17)| 550 (23)| <0.001  | 178 (17)| 195 (18)| 0.33    |
| Aortic/peripheral vascular disease            | 58 (5)  | 142 (6) | 0.50    | 58 (5)  | 53 (5)  | 0.63    |
| Anemia*‡                                      | 508 (48)| 1274 (54)| <0.001 | 508 (48)| 508 (48)| 1.0     |
| Liver cirrhosis (Child-Pugh B or C) *         | 4 (0.4) | 28 (1)  | 0.02    | 4 (0.4) | 2 (0.2) | 0.69    |
| Malignancy                                    | 116 (11)| 342 (15)| 0.004   | 116 (11)| 73 (7)  | 0.001   |
| Malignancy currently under treatment*         | 22 (2)  | 114 (5) | <0.001  | 22 (2)  | 12 (1)  | 0.08    |
| Chest wall irradiation*                       | 6 (0.6) | 17 (0.7)| 0.60    | 6 (0.6) | 0       | 0.03    |
| Immunosuppressive therapy*                    | 22 (2)  | 92 (4)  | 0.006   | 22 (2)  | 20 (2)  | 0.76    |
| Chronic lung disease                          | 122 (11)| 238 (10)| 0.23    | 122 (11)| 116 (11)| 0.68    |
| Chronic lung disease (moderate or severe) *   | 14 (1)  | 87 (4)  | <0.001  | 14 (1)  | 10 (0.9)| 0.41    |
| Logistic EuroSCORE, %                         | 6.6 (4.2-10.6)| 10.8 (6.6-18.3)| <0.001| 6.6 (4.2-10.6)| 7.5 (4.8-12.8)| <0.001|
| EuroSCORE II, %                               | 2.1 (1.3-3.5)| 3.4 (2.0-5.5) | <0.001 | 2.1 (1.3-3.5) | 2.5 (1.4-4.1) | <0.001 |
| STS-PROM score, %                             | 2.5 (1.6-4.1)| 3.9 (2.4-6.7) | <0.001 | 2.5 (1.6-4.1) | 2.9 (1.8-4.7) | <0.001 |

**Etiology of aortic stenosis**

| Etiology                      | Group A | Group B | p-value |
|-------------------------------|---------|---------|---------|
| Degenerative                  | 844 (79)| 2141 (91)| <0.001  |
| Congenital (Unicuspid, Bicuspid, Quadricuspid) | 154 (15)| 100 (4)  | 73 (7)  |
| Rheumatic                     | 49 (5)  | 96 (4)  | 20 (2)  |
| Infective endocarditis        | 5 (0.5)| 1 (0.04)| 0       |
| Echocardiographic variables                                      | 10 (1) | 10 (0.4) | 10 (1) | 6 (0.6) |
|---------------------------------------------------------------|--------|----------|--------|---------|
| Left ventricular end-diastolic diameter, mm                   | 46.9±7.1 | 45.0±6.7 | <0.001 | 46.9±7.1 | 46.4±7.2 | 0.17 |
| Left ventricular end-systolic diameter, mm                    | 30.6±8.4 | 29.4±7.2 | <0.001 | 30.6±8.4 | 30.1±7.7 | 0.23 |
| Left ventricular ejection fraction, %                         | 63.4±14.0 | 63.5±12.9 | 0.72    | 63.4±14.0 | 63.9±12.3 | 0.87 |
| Left ventricular ejection fraction <40%*                       | 87 (8)  | 149 (6)  | 0.049   | 87 (8)   | 52 (5)   | 0.002 |
| Interventricular septum thickness in diastole, mm             | 11.9±2.3 | 11.0±2.2 | <0.001  | 11.9±2.3 | 11.7±2.4 | 0.05 |
| Posterior wall thickness in diastole, mm                      | 11.5±2.1 | 10.6±1.9 | <0.001  | 11.5±2.1 | 11.2±2.1 | 0.01 |
| Peak aortic jet velocity, m/s                                 | 4.7±0.82 | 3.8±0.84 | <0.001  | 4.7±0.82 | 4.3±1.00 | <0.001 |
| Peak aortic jet velocity ≥5m/s*                                | 396 (37)| 250 (11) | <0.001  | 396 (37)| 370 (35) | 0.24 |
| Peak aortic jet velocity ≥4m/s                                 | 894 (84)| 1080 (46)| <0.001  | 894 (84)| 672 (63) | <0.001 |
| Peak aortic pressure gradient, mmHg                           | 93±32   | 63±28    | <0.001  | 93±32   | 80±35    | <0.001 |
| Mean aortic pressure gradient, mmHg                           | 54±20   | 36±17    | <0.001  | 54±20   | 46±22    | <0.001 |
| Aortic valve area (equation of continuity), cm²               | 0.64±0.17| 0.75±0.18| <0.001  | 0.64±0.17| 0.73±0.20| <0.001 |
| Aortic valve area index, cm²/m²                               | 0.43±0.12| 0.53±0.13| <0.001  | 0.43±0.12| 0.50±0.13| <0.001 |
| Any combined valvular disease (moderate or severe) *          | 414 (39)| 978 (42) | 0.14    | 414 (39)| 419 (39) | 0.82 |
| Moderate or severe aortic regurgitation                       | 259 (24)| 455 (19) | 0.001   | 259 (24)| 212 (20) | 0.01 |
| Moderate or severe mitral stenosis                            | 43 (4)  | 76 (3)   | 0.23    | 43 (4)  | 33 (3)   | 0.24 |
| Moderate or severe mitral regurgitation                       | 188 (18)| 473 (20)| 0.09    | 188 (18)| 224 (21)| 0.048 |
| Moderate or severe tricuspid regurgitation                    | 126 (12)| 438 (19)| <0.001  | 126 (12)| 157 (15)| 0.048 |
| Tricuspid regurgitation pressure gradient ≥40 mmHg            | 148 (14)| 378 (16)| 0.11    | 148 (14)| 173 (16)| 0.13 |

Values are number (%), mean ± SD, or median (interquartile range) unless otherwise stated.
* Potential independent variables relevant to the choice of initial AVR selected for logistic regression model to develop propensity-score for the choice of initial AVR.
† Body mass index was calculated as weight in kilograms divided by height in meters squared.
‡ Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dl in women and <13.0 g/dl in men).
AVR=aortic valve replacement, STS=Society of Thoracic Surgeons, and PROM=predicted risk of mortality.
Table S5. Clinical Outcomes in the Propensity-score Matched Cohort in Dialysis Patients: Initial AVR versus Conservative Groups

| Event                        | Initial AVR group | Conservative group | HR (95% CI) | P value |
|------------------------------|-------------------|--------------------|-------------|---------|
|                              | Number of patients with at least one event (Cumulative 5-year incidence [%]) | Number of patients with at least one event (Cumulative 5-year incidence [%]) |             |         |
|                              | N=114             | N=114              |             |         |
| All-cause death              | 59 (37.0)         | 74 (66.6)          | 0.69 (0.49-0.98) | 0.037   |
| Cardiovascular death         | 43 (50.5)         | 48 (50.0)          | 0.79 (0.52-1.20) | 0.27    |
| Aortic valve-related death   | 24 (22.6)         | 25 (29.7)          | 0.87 (0.50-1.53) | 0.63    |
| Aortic valve procedure-related death | 23 (21.9) | 2 (2.3) | 10.60 (3.13-66.02) | <0.001  |
| Sudden death                 | 4 (12.9)          | 15 (18.8)          | 0.24 (0.07-0.65) | 0.004   |
| Non-cardiovascular death     | 16 (25.2)         | 26 (33.2)          | 0.52 (0.27-0.96) | 0.036   |
| Hospitalization for heart failure | 10 (32.6) | 13 (20.3) | 0.61 (0.26-1.39) | 0.24    |
| A composite of aortic valve-related death or hospitalization for heart failure | 33 (47.1) | 30 (36.1) | 0.95 (0.58-1.57) | 0.85    |

Number of patients with at least one event was counted through the entire follow-up period, while the cumulative incidence was truncated at 5-year.

Follow-up was commenced on the day of the index echocardiography.

CI=confidence interval, and HR = hazard ratio.
| Event                                      | Initial AVR group | Conservative group | HR (95% CI)          | P value |
|--------------------------------------------|-------------------|--------------------|----------------------|---------|
| All-cause death                            | 170 (18.7)        | 395 (35.8)         | 0.43 (0.36-0.52)     | <0.001  |
| Cardiovascular death                       | 103 (11.3)        | 288 (27.6)         | 0.35 (0.28-0.44)     | <0.001  |
| Aortic valve-related death                 | 41 (4.2)          | 219 (22.2)         | 0.19 (0.13-0.26)     | <0.001  |
| Aortic valve procedure-related death       | 24 (2.3)          | 17 (2)             | 1.35 (0.73-2.55)     | 0.35    |
| Sudden death                               | 23 (3.0)          | 80 (6.6)           | 0.29 (0.18-0.46)     | <0.001  |
| Non-cardiovascular death                   | 67 (8.3)          | 107 (11.4)         | 0.65 (0.47-0.87)     | 0.005   |
| Hospitalization for heart failure          | 87 (10.1)         | 274 (31.0)         | 0.28 (0.22-0.35)     | <0.001  |
| A composite of aortic valve-related death  | 129 (13.9)        | 375 (37.3)         | 0.31 (0.25-0.37)     | <0.001  |

Number of patients with at least one event was counted through the entire follow-up period, while the cumulative incidence was truncated at 5-year. Follow-up was commenced on the day of the index echocardiography.

CI=confidence interval, and HR = hazard ratio.
Table S7. Procedural Characteristics of AVR in the Initial AVR Group: Dialysis versus Non-dialysis Patients

| Combined surgical procedures                              | Dialysis patients (N=131) | Non-dialysis patients (N=1043) | P value |
|------------------------------------------------------------|----------------------------|--------------------------------|---------|
| AVR with coronary artery bypass grafting                   | 52 (40)                    | 236 (23)                       | <0.001  |
| AVR with any valve surgery                                | 25 (19)                    | 154 (15)                       | 0.23    |
| AVR with mitral valve surgery                              | 20 (15)                    | 123 (12)                       | 0.29    |
| Mitral valve replacement                                   | 14 (11)                    | 60 (6)                         | 0.03    |
| Mitral valve repair                                        | 6 (5)                      | 63 (6)                         | 0.56    |
| AVR with tricuspid valve surgery                           | 14 (11)                    | 80 (8)                         | 0.26    |
| Tricuspid valve replacement                                | 0                          | 3 (0.3)                        | 1.0     |
| Tricuspid valve repair                                     | 14 (11)                    | 77 (8)                         | 0.21    |
| AVR with replacement of ascending aorta                    | 4 (3)                      | 91 (9)                         | 0.02    |
| AVR with annular dilatation                                | 1 (0.8)                    | 7 (0.7)                        | 1.0     |
| AVR with maze operation                                    | 7 (5)                      | 61 (6)                         | 1.0     |
| Bioprosthetic valve                                        | 80 (62)                    | 818 (80)                       | <0.001  |
| Mechanical valve                                           | 50 (38)                    | 206 (20)                       |         |
| Unknown                                                    | 1 (0.8)                    | 19 (2)                         |         |

Valve size

| Valve size       | Bioprosthetic valve | Mechanical valve | Unknown |
|------------------|---------------------|------------------|---------|
| 18mm             | 0                   | 1 (0.1)          |         |
| 19mm             | 23 (29)             | 324 (40)         |         |
| 21mm             | 38 (48)             | 302 (37)         |         |
| 23mm             | 13 (16)             | 127 (16)         |         |
| Diameter (mm) | 24 (0) | 25 (6) | 27 (1) | 29 (0) | Unknown (0) |
|--------------|--------|--------|--------|--------|-------------|
| **Mechanical valve** | 1 (0.1) | 45 (6) | 4 (0.5) | 2 (0.2) | 12 (1.5) |

| Diameter (mm) | 16 (6) | 17 (10) | 18 (0) | 19 (30) | 20 (4) | 21 (28) | 22 (2) | 23 (18) | 25 (0) | 27 (0) | 29 (0) | Unknown (0) |
|----------------|--------|---------|--------|---------|-------|--------|-------|--------|-------|--------|-------|-------------|
| **Values**     | 50     | 3 (6)   | 45 (6) | 3 (1.5) | 14 (28)| 1 (2)  | 9 (18)| 0      | 0     | 0      | 0     | 1 (2)       | 3 (1.5) |

Values are number (%).

In the initial AVR group, 1174 of 1197 patients actually underwent surgical AVR or TAVI. In the 1174 patients, TAVI was performed only in 11 non-dialysis patients, who were included in this Table.

Regarding the prosthetic valve types, we did not have information in 20 patients who were operated on in hospitals other than the study participating centers. AVR=aortic valve replacement, and TAVI=transcatheter aortic valve implantation.
Figure S1. Cumulative incidence of surgical AVR or TAVI in the conservative group: dialysis versus non-dialysis patients.
AVR=aortic valve replacement, and TAVI=transcatheter aortic valve replacement.

### Surgical AVR or TAVI

![Graph showing cumulative incidence of surgical AVR or TAVI](image)

Log-rank $P=0.003$

| Interval | 0 day | 30 days | 1 year | 3 years | 5 years |
|----------|-------|---------|--------|---------|---------|
| Dialysis |       |         |        |         |         |
| N of patients with surgical AVR or TAVI | 0     | 18      | 46     | 50      |
| N of patients at risk | 270   | 245     | 141    | 41      | 6       |
| Cumulative incidence | 0%    | 9.4%    | 33.1%  | 45.7%   |

Non-Dialysis

| Interval | 0 day | 30 days | 1 year | 3 years | 5 years |
|----------|-------|---------|--------|---------|---------|
| N of patients with surgical AVR or TAVI | 1     | 130     | 385    | 491     |
| N of patients at risk | 2348  | 2222    | 1734   | 897     | 210     |
| Cumulative incidence | 0.04% | 6.5%    | 22.9%  | 37.3%   |
Figure S2. Propensity score-matched cohort in dialysis and non-dialysis patients for the sensitivity analysis.

We used logistic regression model to develop propensity-score for the choice of initial AVR with 15 independent variables relevant to the choice of initial AVR listed in Supplementary Table 3. Patients in the conservative group were matched to those in the initial AVR group using a 1:1 greedy matching technique.

AS=aortic stenosis, and AVR=aortic valve replacement.
Figure S3. Cumulative incidence of all-cause death and sudden death in the propensity-score matched cohort in (A) dialysis patients and (B) non-dialysis patients: initial AVR versus conservative strategies. AVR=aortic valve replacement.

(A) Dialysis patients
(B) Non-dialysis patients

**All-cause death**

Log-rank P<0.001

| Interval | 0 day | 30 days | 1 year | 3 years | 5 years |
|----------|-------|---------|--------|---------|---------|
| **Initial AVR group** | | | | | |
| N of patients with event | 7 | 60 | 118 | 148 | |
| N of patients at risk | 1062 | 1048 | 980 | 672 | 236 |
| Cumulative incidence | 0.7% | 5.8% | 11.8% | 15.7% | |
| **Conservative group** | | | | | |
| N of patients with event | 19 | 127 | 246 | 320 | |
| N of patients at risk | 1062 | 1022 | 888 | 629 | 289 |
| Cumulative incidence | 1.8% | 12.3% | 24.8% | 35.8% | |

**Sudden death**

Log-rank P<0.001

| Interval | 0 day | 30 days | 1 year | 3 years | 5 years |
|----------|-------|---------|--------|---------|---------|
| **Initial AVR group** | | | | | |
| N of patients with event | 2 | 10 | 15 | 17 | |
| N of patients at risk | 1062 | 1048 | 980 | 672 | 236 |
| Cumulative incidence | 0.2% | 1.0% | 1.6% | 3.0% | |
| **Conservative group** | | | | | |
| N of patients with event | 2 | 11 | 13 | 12 | |
| N of patients at risk | 1062 | 1022 | 888 | 629 | 289 |
| Cumulative incidence | 0.2% | 1.2% | 2.8% | 6.6% | |
Figure S4. Cumulative incidences of (A) all-cause death and (B) hospitalization for heart failure after surgical AVR in the initial AVR group in dialysis patients: mechanical valve versus bioprosthetic valve.
Follow-up was commenced on the day of surgical AVR.
AVR=aortic valve replacement.

(A) All-cause death

![Graph showing cumulative incidences of (A) all-cause death and (B) hospitalization for heart failure after surgical AVR in the initial AVR group in dialysis patients: mechanical valve versus bioprosthetic valve.](image)

| Interval      | 0 day | 30 days | 1 year | 3 years | 5 years |
|---------------|-------|---------|--------|---------|---------|
| **Bioprosthetic** |       |         |        |         |         |
| No of patients with event | 5 | 16 | 23 | 28 |     |
| No of patients at risk   | 80 | 73 | 52 | 27 | 5 |
| Cumulative incidence     | 6.4% | 24.9% | 37.3% | 60.8% |     |
| **Mechanical**            |       |         |        |         |         |
| No of patients with event | 5 | 16 | 23 | 28 |     |
| No of patients at risk   | 50 | 45 | 29 | 16 | 5 |
| Cumulative incidence     | 10.0% | 34.0% | 50.3% | 70.4% |     |
(B) Hospitalization for heart failure

![Graph showing cumulative incidence of hospitalization for heart failure over time after surgical AVR. Log-rank P=0.83.]

| Interval | 0 day | 30 days | 1 year | 3 years | 5 years |
|----------|-------|---------|--------|---------|---------|
| Bioprosthetic | | | | | |
| N of patients with event | 6 | 26 | 50 | 69 | |
| N of patients at risk | 80 | 74 | 52 | 26 | 4 |
| Cumulative incidence | 7.5% | 32.7% | 64.4% | 91.7% | |
| Mechanical | | | | | |
| N of patients with event | 5 | 21 | 34 | 44 | |
| N of patients at risk | 50 | 45 | 29 | 16 | 5 |
| Cumulative incidence | 10.0% | 42.0% | 70% | 89.1% | |
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