ORIGINAL RESEARCH

Severe Aortic Stenosis in Dialysis Patients

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***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

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Accompanying Appendix S1, Data S1, Tables S1 through S7, and Figures S1 through S4 are available at http://jaha.ahajournals.org/content/6/7/e004961/DC1/embed/inline-supplementary-material-1.pdf

*The CURRENT AS Registry Investigators are listed in Appendix S1.

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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.

to be an independent risk factor for death in hemodialysis patients.[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).[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.[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.[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

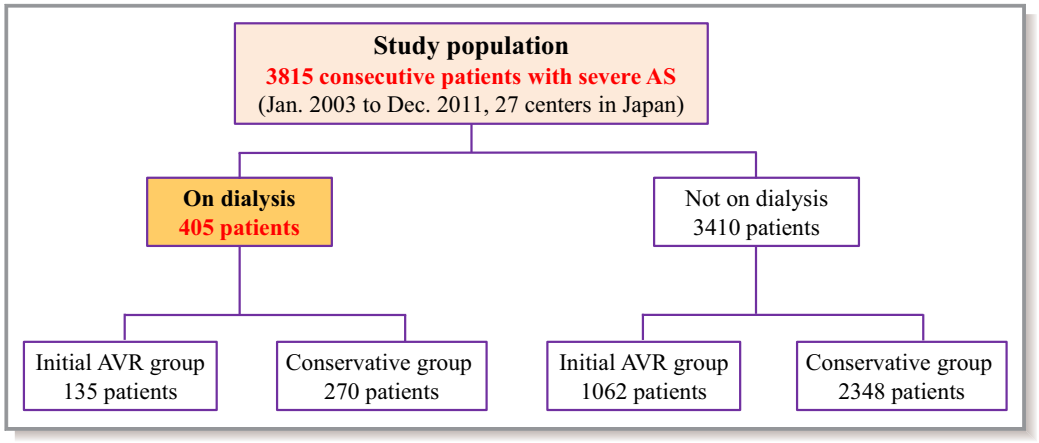


Figure 1. Study flow chart. AS indicates aortic stenosis; AVR, aortic valve replacement.

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 or 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 χ^2 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, m^2	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)	0.27
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			
<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			<0.001
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), cm^2	0.74±0.17	0.72±0.19	0.03
Aortic valve area index, cm^2/m^2	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

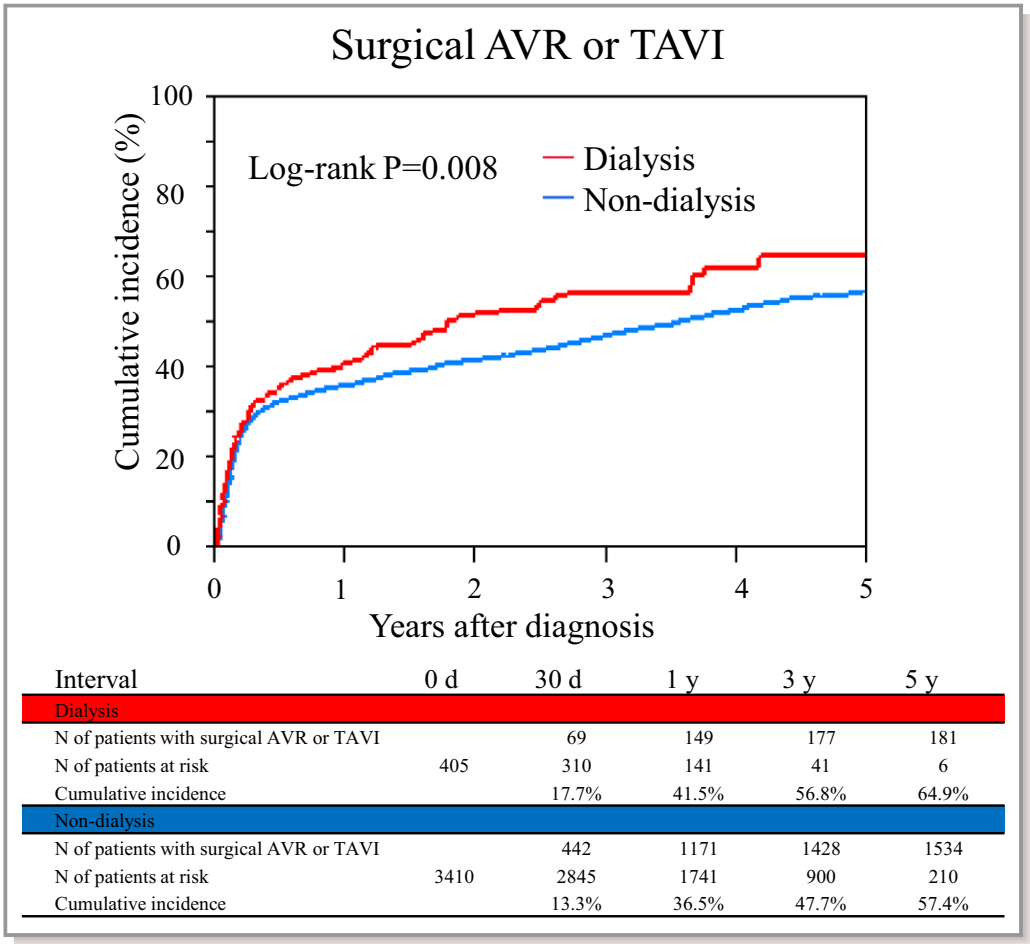
Values are number (%), mean±SD, or median (interquartile range) unless otherwise stated. AVR indicates aortic valve replacement; PROM, predicted risk of mortality; STS, Society of Thoracic Surgeons.

*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).



Interval	0 d	30 d	1 y	3 y	5 y
Dialysis					
N of patients with surgical AVR or TAVI		69	149	177	181
N of patients at risk	405	310	141	41	6
Cumulative incidence		17.7%	41.5%	56.8%	64.9%
Non-dialysis					
N of patients with surgical AVR or TAVI		442	1171	1428	1534
N of patients at risk	3410	2845	1741	900	210
Cumulative incidence		13.3%	36.5%	47.7%	57.4%

Figure 2. Cumulative incidence of surgical AVR or TAVI: dialysis vs nondialysis patients. Follow-up was commenced on the day of the index echocardiography. AVR indicates aortic valve replacement; TAVI, transcatheter aortic valve implantation.

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).

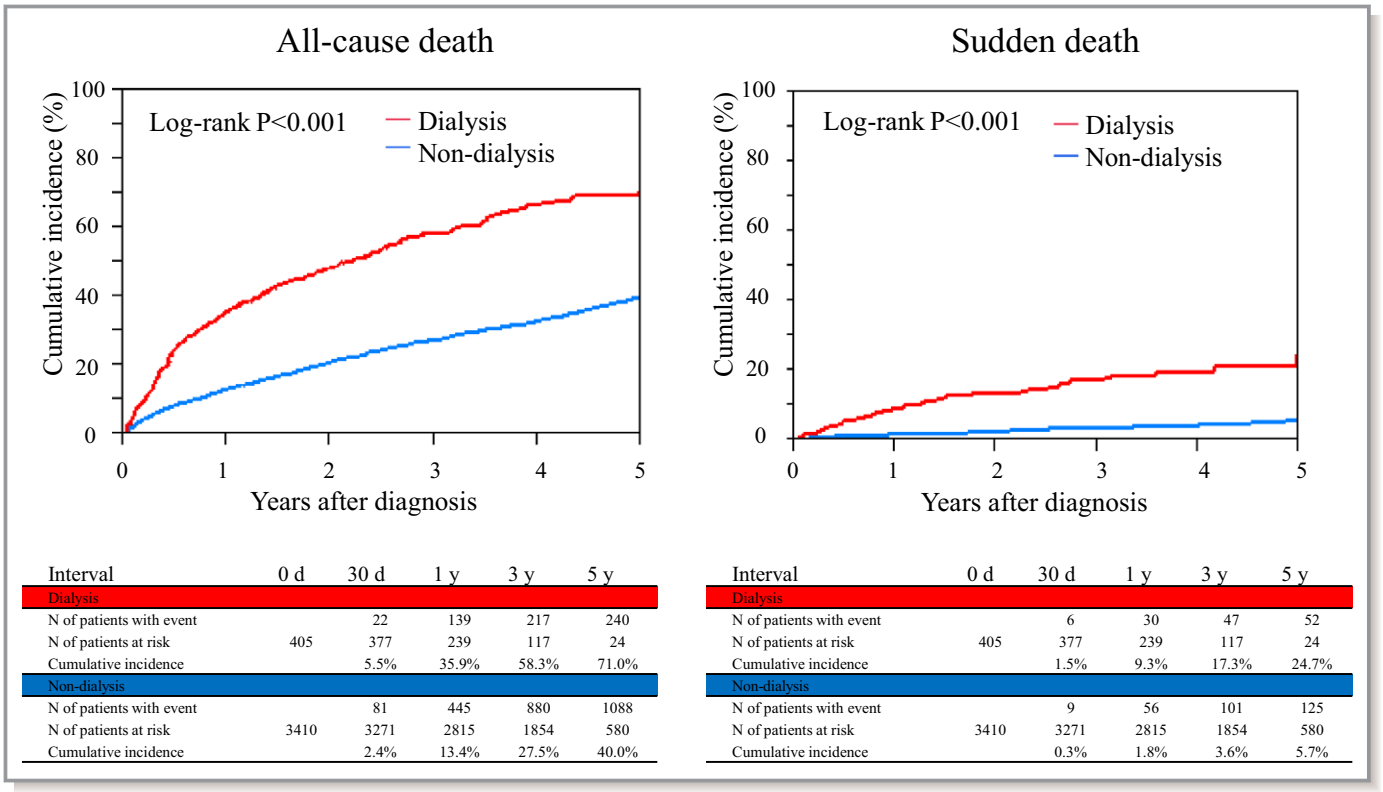
In both hemodialysis and nonhemodialysis patients, cumulative 5-year incidence of all-cause death was significantly lower in the initial AVR group than in the conservative group (Table 4 and Figure 4). However, the effect size of the initial

Table 2. Clinical Outcomes: Dialysis VS Nondialysis Patients

	Dialysis Patients	Nondialysis Patients				
	Number of Patients With at Least 1 Event (Cumulative 5-Y Incidence [%])	Number of Patients With at Least 1 Event (Cumulative 5-Y Incidence [%])				
	N=405	N=3410	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
All-cause death	248 (71.0)	1201 (40.0)	2.69 (2.34–3.08)	<0.001	2.76 (2.35–3.25)	<0.001
Cardiovascular death	183 (59.5)	769 (27.8)	3.07 (2.60–3.60)	<0.001	3.18 (2.62–3.86)	<0.001
Aortic valve–related death	107 (36.1)	502 (19.2)	2.69 (2.17–3.31)	<0.001	3.10 (2.41–3.98)	<0.001
Aortic valve procedure–related death	32 (9.9)	49 (1.9)	7.02 (4.44–10.93)	<0.001	6.74 (4.17–10.91)	<0.001
Sudden death	52 (24.7)	144 (5.7)	4.70 (3.38–6.43)	<0.001	4.80 (3.23–7.14)	<0.001
Noncardiovascular death	65 (28.5)	432 (16.9)	2.00 (1.52–2.57)	<0.001	2.05 (1.52–2.77)	<0.001
Hospitalization for heart failure	57 (31.9)	755 (29.2)	0.96 (0.72–1.24)	0.76	0.84 (0.63–1.13)	0.26
A composite of aortic valve–related death or hospitalization for heart failure	136 (51.6)	936 (34.1)	1.78 (1.48–2.12)	<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



Interval	0 d	30 d	1 y	3 y	5 y
Dialysis					
N of patients with event		22	139	217	240
N of patients at risk	405	377	239	117	24
Cumulative incidence		5.5%	35.9%	58.3%	71.0%
Non-dialysis					
N of patients with event		81	445	880	1088
N of patients at risk	3410	3271	2815	1854	580
Cumulative incidence		2.4%	13.4%	27.5%	40.0%

Interval	0 d	30 d	1 y	3 y	5 y
Dialysis					
N of patients with event		6	30	47	52
N of patients at risk	405	377	239	117	24
Cumulative incidence		1.5%	9.3%	17.3%	24.7%
Non-dialysis					
N of patients with event		9	56	101	125
N of patients at risk	3410	3271	2815	1854	580
Cumulative incidence		0.3%	1.8%	3.6%	5.7%

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.

Table 3. Baseline Characteristics in Dialysis and Nondialysis Patients: Initial AVR VS Conservative Groups

Variables	Dialysis Patients			Nondialysis Patients		
	Initial AVR Group (N=135)	Conservative Group (N=270)	*P* Value	Initial AVR Group (N=1062)	Conservative Group (N=2348)	*P* Value
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*†	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‡	20.8±3.1	20.3±3.9	0.24	22.5±3.6	21.7±3.9	<0.001
Body mass index <22*	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*†	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*†	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*§	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*†	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	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*†	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^2	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)*†	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.

*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, noncardiovascular 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).

Table 4. Clinical Outcomes in Dialysis and Nondialysis Patients: Initial AVR VS Conservative Groups

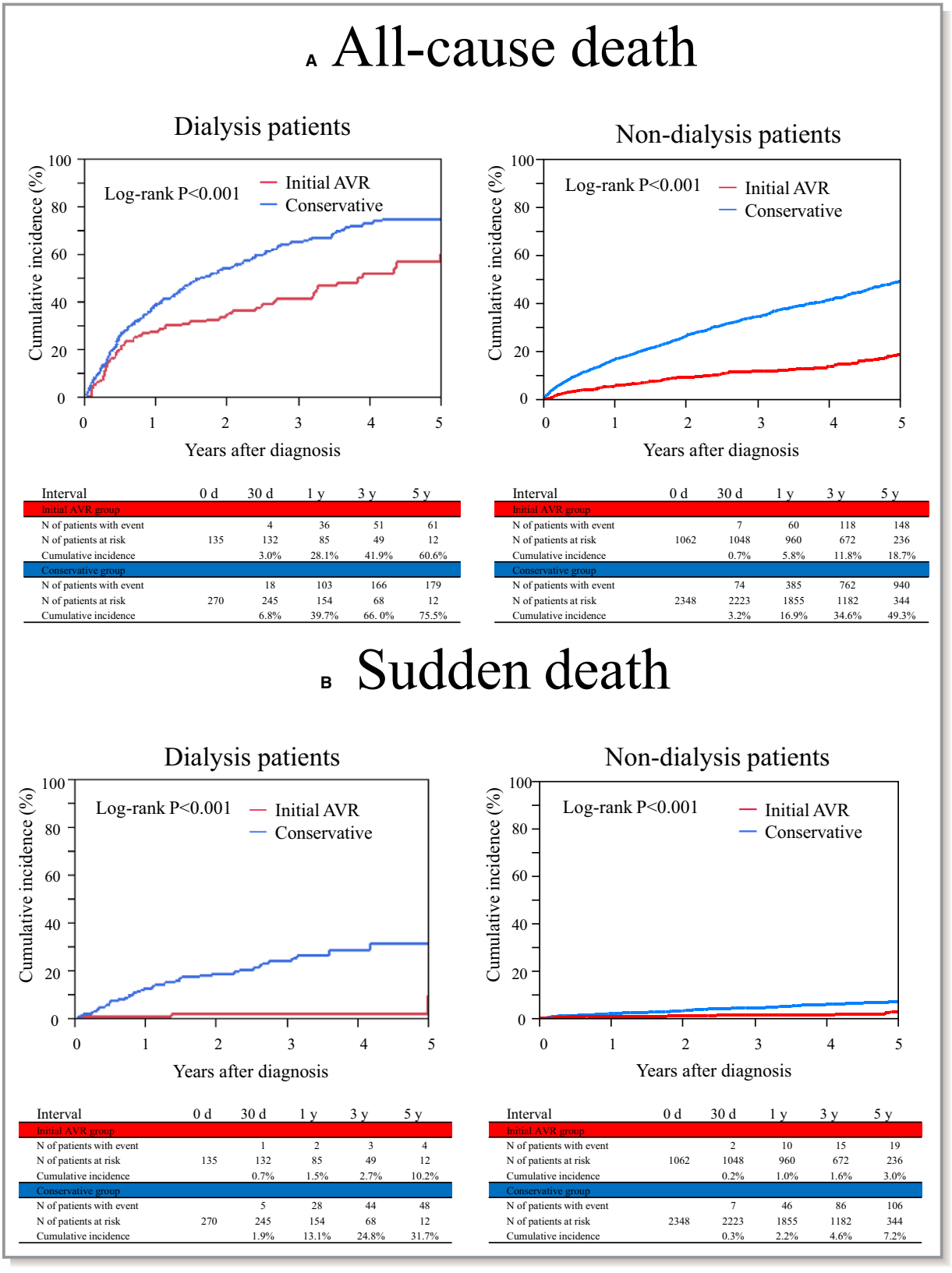
	Initial AVR Group	Conservative Group					
	Number of Patients With at Least 1 Event (Cumulative 5-Y Incidence [%])	Number of Patients With at Least 1 Event (Cumulative 5-Y Incidence [%])					
	Dialysis: N=135 Nondialysis: N=1062	Dialysis: N=270 Nondialysis: N=2348	Unadjusted HR (95% CI)	*P* Value	Adjusted 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.

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



Interval	0 d	30 d	1 y	3 y	5 y
Initial AVR group					
N of patients with event		4	36	51	61
N of patients at risk	135	132	85	49	12
Cumulative incidence		3.0%	28.1%	41.9%	60.6%
Conservative group					
N of patients with event		18	103	166	179
N of patients at risk	270	245	154	68	12
Cumulative incidence		6.8%	39.7%	66. 0%	75.5%

Interval	0 d	30 d	1 y	3 y	5 y
Initial AVR group					
N of patients with event		7	60	118	148
N of patients at risk	1062	1048	960	672	236
Cumulative incidence		0.7%	5.8%	11.8%	18.7%
Conservative group					
N of patients with event		74	385	762	940
N of patients at risk	2348	2223	1855	1182	344
Cumulative incidence		3.2%	16.9%	34.6%	49.3%

Interval	0 d	30 d	1 y	3 y	5 y
Initial AVR group					
N of patients with event		1	2	3	4
N of patients at risk	135	132	85	49	12
Cumulative incidence		0.7%	1.5%	2.7%	10.2%
Conservative group					
N of patients with event		5	28	44	48
N of patients at risk	270	245	154	68	12
Cumulative incidence		1.9%	13.1%	24.8%	31.7%

Interval	0 d	30 d	1 y	3 y	5 y
Initial AVR group					
N of patients with event		2	10	15	19
N of patients at risk	1062	1048	960	672	236
Cumulative incidence		0.2%	1.0%	1.6%	3.0%
Conservative group					
N of patients with event		7	46	86	106
N of patients at risk	2348	2223	1855	1182	344
Cumulative incidence		0.3%	2.2%	4.6%	7.2%

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

	Dialysis Patients	Nondialysis Patients				
	Number of Patients With at Least 1 Event (Cumulative 5-Y Incidence [%])	Number of Patients With at Least 1 Event (Cumulative 5-Y Incidence [%])	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
	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.

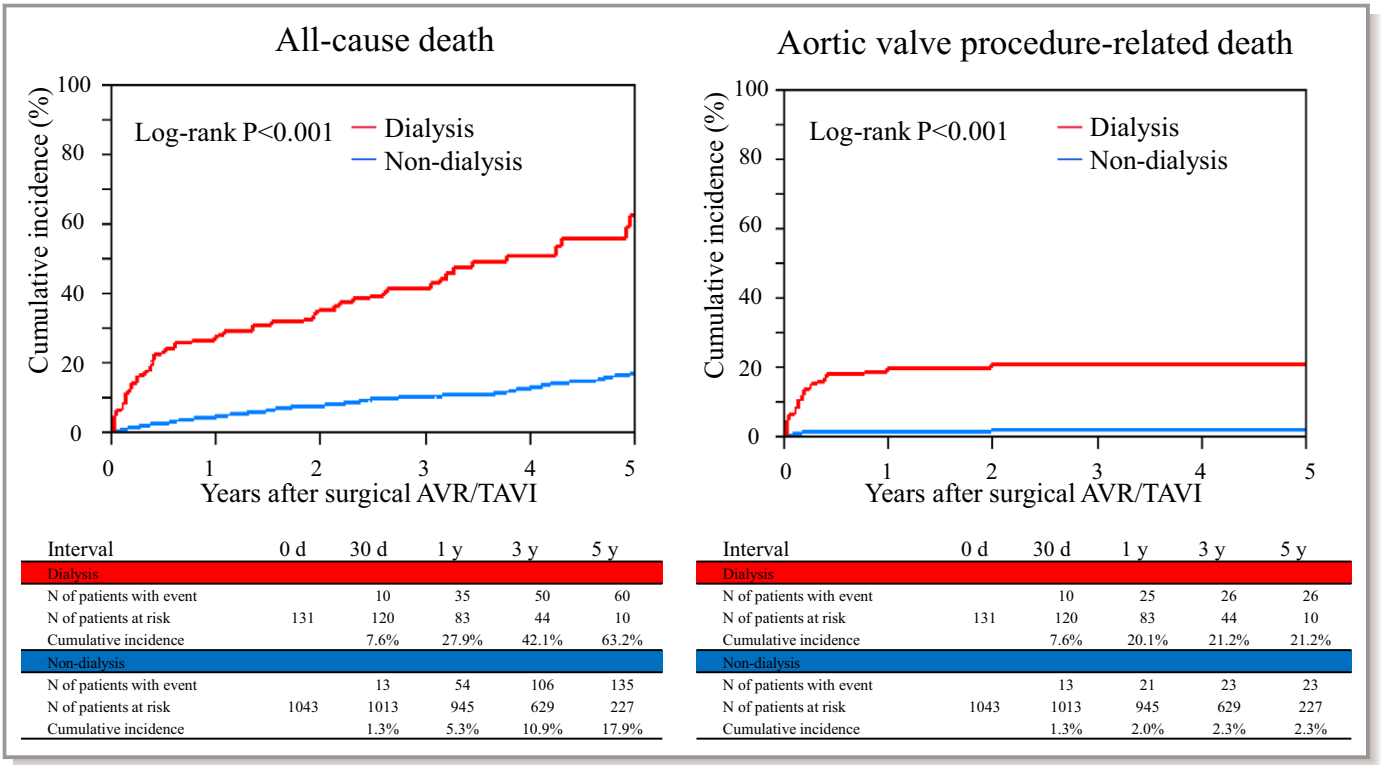
more often underwent AVR combined with coronary artery bypass grafting and less often AVR combined with replacement of ascending aorta than nonhemodialysis patients. A bioprosthetic valve was less often used in hemodialysis patients than in nonhemodialysis patients (Table S7). Hemodialysis patients were 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



Interval	0 d	30 d	1 y	3 y	5 y
Dialysis					
N of patients with event		10	35	50	60
N of patients at risk	131	120	83	44	10
Cumulative incidence		7.6%	27.9%	42.1%	63.2%
Non-dialysis					
N of patients with event		13	54	106	135
N of patients at risk	1043	1013	945	629	227
Cumulative incidence		1.3%	5.3%	10.9%	17.9%

Interval	0 d	30 d	1 y	3 y	5 y
Dialysis					
N of patients with event		10	25	26	26
N of patients at risk	131	120	83	44	10
Cumulative incidence		7.6%	20.1%	21.2%	21.2%
Non-dialysis					
N of patients with event		13	21	23	23
N of patients at risk	1043	1013	945	629	227
Cumulative incidence		1.3%	2.0%	2.3%	2.3%

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.

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.

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 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.

Disclosures

None.

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Supplemental Material

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A clinical event committee

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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]

Table S1. Baseline Characteristics of Dialysis and Non-dialysis Patients: Initial AVR versus Conservative Groups

Variables	Dialysis patients			Non-dialysis patients		
	Initial AVR group N=135	Conservative group N=270	P value	Initial AVR group N=1062	Conservative group N=2348	P value
Age, years	70.3±8.2	74.7±8.4	<0.001	73.7±8.9	80.3±9.4	<0.001
Age ≥80 years*†	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‡	20.8±3.1	20.3±3.9	0.24	22.5±3.6	21.7±3.9	<0.001
Body mass index <22*	95 (70)	203 (75)	0.30	527 (50)	1501 (64)	<0.001
Body surface area, m^2	1.49±0.18	1.45±0.17	0.04	1.50±0.18	1.43±0.19	<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*†	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
History of smoking	51 (38)	69 (26)	0.01	263 (25)	447 (19)	<0.001
Dyslipidemia	23 (17)	55 (20)	0.42	453 (43)	796 (34)	<0.001
On statin therapy	13 (10)	32 (12)	0.50	326 (31)	599 (26)	0.002
Diabetes mellitus	32 (24)	95 (35)	0.02	244 (23)	526 (22)	0.71
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 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

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
Etiology of aortic stenosis			0.05			<0.001
Degenerative	130 (96)	264 (98)		844 (79)	2141 (91)	
Congenital (Unicuspid, Bicuspid, Quadricuspid)	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						
Left ventricular end-diastolic diameter, mm	49.6±7.0	48.6±7.4	0.20	46.9±7.1	45.0±6.7	<0.001
Left ventricular end-systolic diameter, mm	34.6±8.5	34.1±9.0	0.60	30.6±8.4	29.4±7.2	<0.001
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 <40%	16 (12)	41 (15)	0.36	87 (8)	149 (6)	0.049
Left ventricular ejection fraction <50%	32 (24)	73 (27)	0.47	173 (16)	315 (13)	0.03
Interventricular septum thickness in diastole, mm	12.4±2.6	11.4±2.2	<0.001	11.9±2.3	11.0±2.2	<0.001
Posterior wall thickness in diastole, mm	12.1±2.2	11.0±1.8	<0.001	11.5±2.1	10.6±1.9	<0.001
Peak aortic jet velocity, m/s	4.41±0.82	3.74±0.80	<0.001	4.74±0.82	3.89±0.84	<0.001
Peak aortic jet velocity ≥5m/s	33 (24)	19 (7)	<0.001	396 (37)	250 (11)	<0.001
Peak aortic jet velocity ≥4m/s*†	100 (74)	111 (41)	<0.001	894 (84)	1080 (46)	<0.001
Peak aortic pressure gradient, mmHg	80±29	59±25	<0.001	93±32	63±28	<0.001
Mean aortic pressure gradient, mmHg	49±18	32±15	<0.001	54±20	36±17	<0.001
Aortic valve area (equation of continuity), cm^2	0.69±0.16	0.76±0.16	<0.001	0.64±0.17	0.75±0.18	<0.001
Aortic valve area index, cm^2/m^2	0.46±0.10	0.53±0.12	<0.001	0.43±0.12	0.53±0.13	<0.001
Any combined valvular disease (moderate or severe)*†	65 (48)	101 (37)	0.04	414 (39)	978 (42)	0.14

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 N=135	Non-dialysis patients N=1062	P value
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, m^2	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

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			<0.001
Degenerative	130 (96)	844 (79)	
Congenital (Unicuspid, Bicuspid, Quadricuspid)	0	154 (15)	
Rheumatic	4 (3)	49 (5)	
Infective endocarditis	1 (1)	5 (0.5)	

Others	0	10 (1)	
Echocardiographic variables			
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), cm^2	0.69±0.16	0.64±0.17	0.009
Aortic valve area index, cm^2/m^2	0.46±0.10	0.43±0.12	0.01
Any combined valuvular 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 group N=135	Conservative group N=270	P value	Initial AVR group N=114	Conservative group N=114	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, m^2	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

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 year, < 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			0.05			0.20
Degenerative	130 (96)	264 (98)		112 (98)	110 (96)	
Congenital (Unicuspid, Bicuspid, Quadricuspid)	0	4 (1)		0	3 (3)	
Rheumatic	4 (3)	1 (0.4)		1 (0.9)	0	
Infective endocarditis	1 (1)	0		1 (0.9)	0	
Others	0	1 (0.4)		0	1 (0.9)	
Echocardiographic variables						
Left ventricular end-diastolic diameter, mm	49.6±7.0	48.6±7.4	0.20	49.4±7.1	51.8±7.3	0.02
Left ventricular end-systolic diameter, mm	34.6±8.5	34.1±9.0	0.60	34.6±8.8	37.1±9.3	0.07
Left ventricular ejection fraction, %	58.1±13.2	56.4±14.4	0.25	57.2±13.7	54.0±14.8	0.04
Left ventricular ejection fraction <40%*	16 (12)	41 (15)	0.36	16 (14)	23 (20)	0.22
Left ventricular ejection fraction <50%	32 (24)	73 (27)	0.47	29 (25)	37 (32)	0.24
Interventricular septum thickness in diastole, mm	12.4±2.6	11.4±2.2	<0.001	12.2±2.6	11.3±2.4	0.004
Posterior wall thickness in diastole, mm	12.1±2.2	11.0±1.8	<0.001	11.9±2.3	11.0±1.7	0.002
Peak aortic jet velocity, m/s	4.41±0.82	3.74±0.80	<0.001	4.21±0.71	3.86±0.88	<0.001
Peak aortic jet velocity ≥5m/s*	33 (24)	19 (7)	<0.001	14 (12)	14 (12)	1.0
Peak aortic jet velocity ≥4m/s	100 (74)	111 (41)	<0.001	79 (69)	51 (45)	<0.001
Peak aortic pressure gradient, mmHg	80±29	59±25	<0.001	73.0±23.1	62.6±29.0	<0.001
Mean aortic pressure gradient, mmHg	49±18	32±15	<0.001	43.0±14.0	32.3±15.0	<0.001
Aortic valve area (equation of continuity), cm^2	0.69±0.16	0.76±0.16	<0.001	0.70±0.15	0.77±0.14	<0.001
Aortic valve area index, cm^2/m^2	0.46±0.10	0.53±0.12	<0.001	0.47±0.10	0.53±0.09	<0.001
Any combined valvular disease (moderate or severe) *	65 (48)	101 (37)	0.04	52 (46)	56 (49)	0.60
Moderate or severe aortic regurgitation	35 (26)	42 (16)	0.01	24 (21)	28 (25)	0.53

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.

Table S4. Baseline Characteristics in the Entire Cohort and in the Propensity-score Matched Cohort in Non-dialysis Patients: Initial AVR versus Conservative Groups

Variables	Non-dialysis patients			Propensity-score matched cohort		
	Initial AVR group N=1062	Conservative group N=2348	P value	Initial AVR group N=1062	Conservative group 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, m^2	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)	0.01	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

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			<0.001			<0.001
Degenerative	844 (79)	2141 (91)		844 (79)	963 (91)	
Congenital (Unicuspid, Bicuspid, Quadricuspid)	154 (15)	100 (4)		154 (15)	73 (7)	
Rheumatic	49 (5)	96 (4)		49 (5)	20 (2)	
Infective endocarditis	5 (0.5)	1 (0.04)		5 (0.5)	0	

Others	10 (1)	10 (0.4)		10 (1)	6 (0.6)	
Echocardiographic variables						
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
Left ventricular ejection fraction <50%	173 (16)	315 (13)	0.03	173 (16)	129 (12)	0.006
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	4.74±0.82	3.89±0.84	<0.001	4.74±0.82	4.36±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), cm^2	0.64±0.17	0.75±0.18	<0.001	0.64±0.17	0.73±0.20	<0.001
Aortic valve area index, cm^2/m^2	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

	Initial AVR group Number of patients with at least one event (Cumulative 5-year incidence [%]) N=114	**Conservative group** Number of patients with at least one event (Cumulative 5-year incidence [%]) N=114	HR (95% CI)	P value
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.

Table S6. Clinical Outcomes in the Propensity-score Matched Cohort in Non-dialysis Patients: Initial AVR versus Conservative Groups

	Initial AVR group Number of patients with at least one event (Cumulative 5-year incidence [%]) N=1062	**Conservative group** Number of patients with at least one event (Cumulative 5-year incidence [%]) N=1062	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 or hospitalization for heart failure	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
Tricaupid 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			
Bioprosthetic valve	80	818	
18mm	0	1 (0.1)	
19mm	23 (29)	324 (40)	
21mm	38 (48)	302 (37)	
23mm	13 (16)	127 (16)	

24mm	0	1 (0.1)
25mm	5 (6)	45 (6)
27mm	1 (1)	4 (0.5)
29mm	0	2 (0.2)
Unknown	0	12 (1.5)
Mechanical valve	50	206
16mm	3 (6)	8 (4)
17mm	5 (10)	32 (16)
18mm	0	16 (8)
19mm	15 (30)	60 (29)
20mm	2 (4)	4 (2)
21mm	14 (28)	41 (20)
22mm	1 (2)	8 (4)
23mm	9 (18)	26 (13)
25mm	0	3 (1.5)
27mm	0	3 (1.5)
29mm	0	2 (1)
Unknown	1 (2)	3 (1.5)

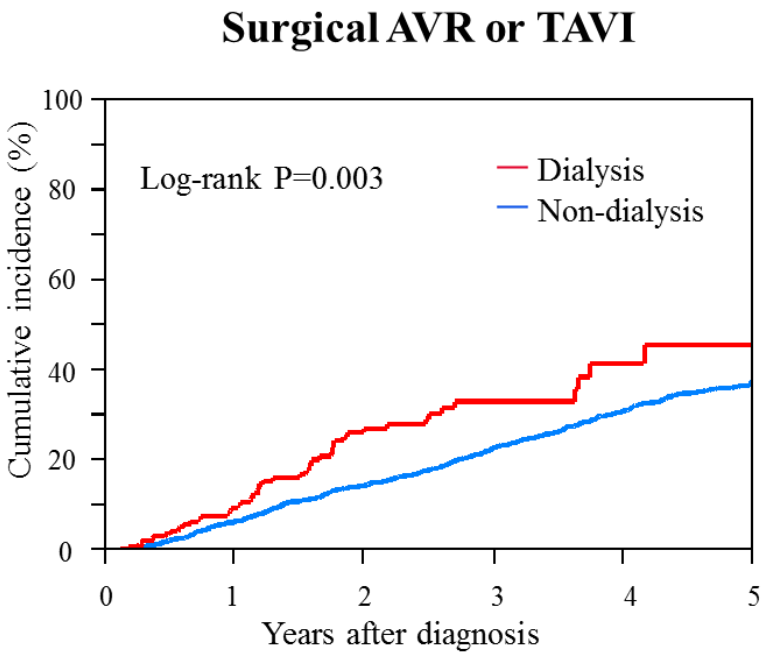
Values are number (%).

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.



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					
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.

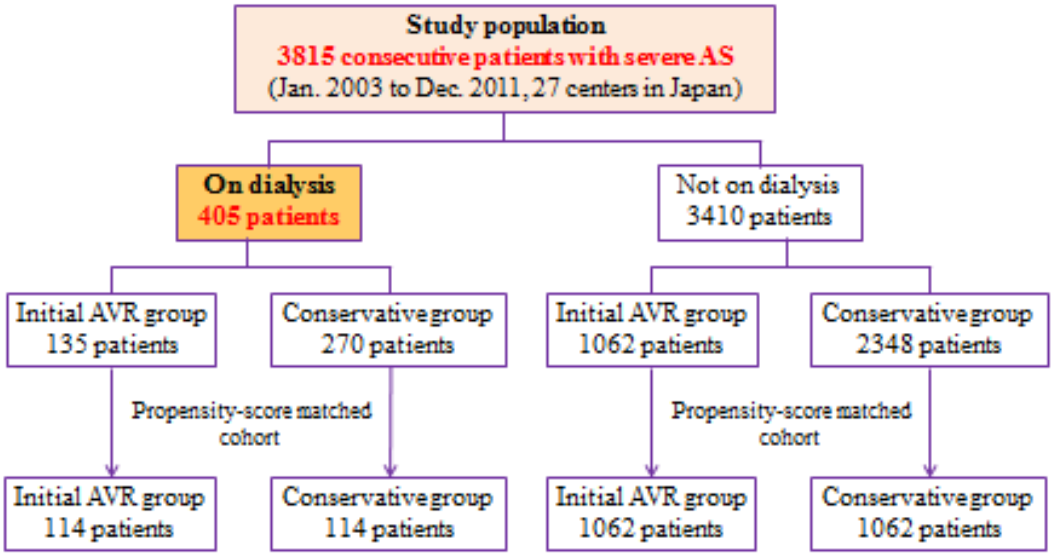
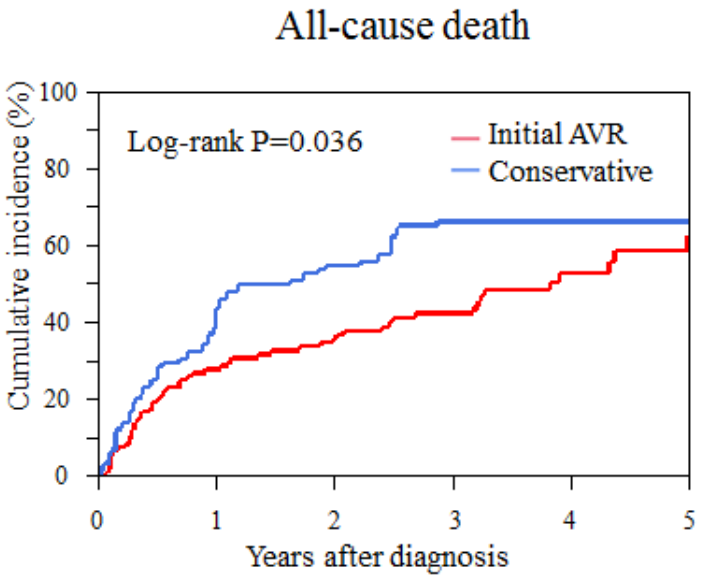
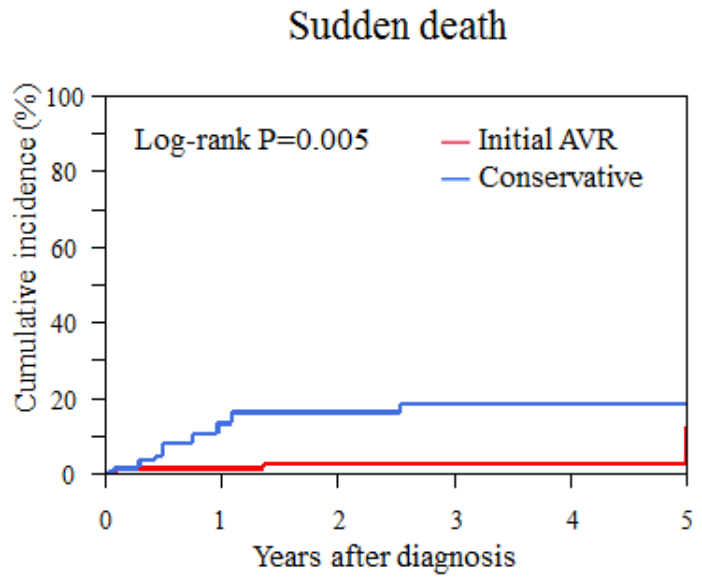


Figure S3. Cumulative incidence of all-cause death and sudden death in the propensity-score matched cohort in (A) dialysis patients and (B) non-dialysis patients: initial AVR versus conservative strategies.
AVR=aortic valve replacement.

(A) Dialysis patients

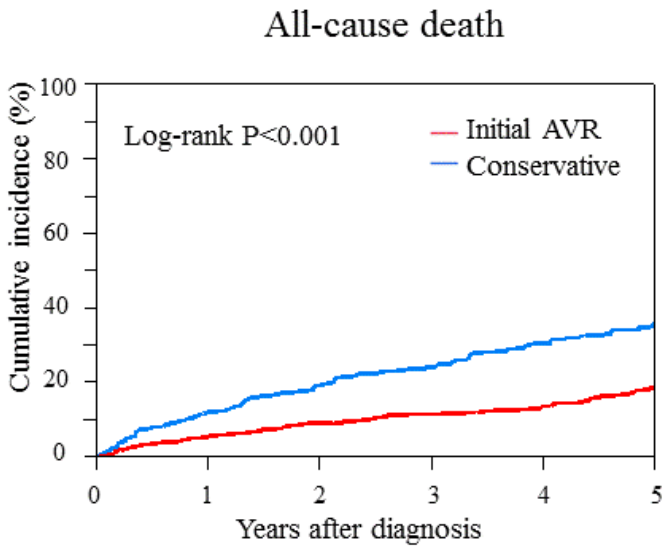


Interval	0 day	30 days	1 year	3 years	5 years
Initial AVR group					
N of patients with event		4	31	45	54
N of patients at risk	114	111	74	44	9
Cumulative incidence		3.5%	28.1%	57.3%	37.0%
Conservative group					
N of patients with event		7	48	72	72
N of patients at risk	114	104	61	26	7
Cumulative incidence		6.2%	43.7%	66.6%	66.6%

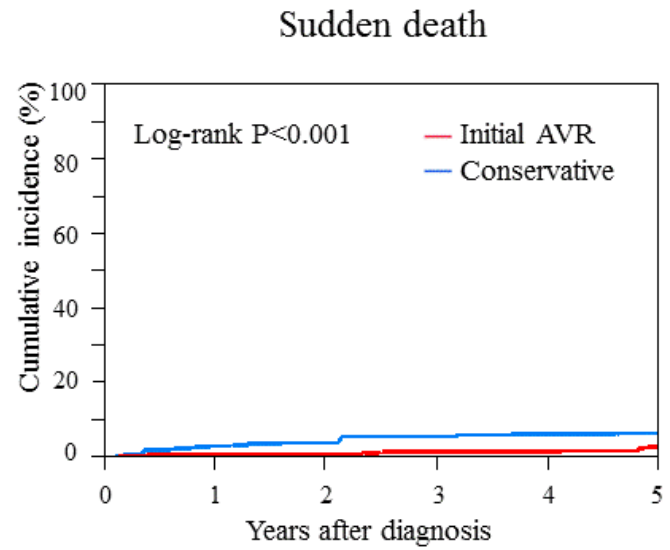


Interval	0 day	30 days	1 year	3 years	5 years
Initial AVR group					
N of patients with event		1	2	3	4
N of patients at risk	114	111	74	44	7
Cumulative incidence		0.9%	1.8%	3.2%	12.9%
Conservative group					
N of patients with event		2	12	15	15
N of patients at risk	114	104	61	26	7
Cumulative incidence		1.8%	13.7%	18.8%	18.8%

(B) Non-dialysis patients



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	960	672	236
Cumulative incidence		0.7%	5.8%	11.8%	18.7%
Conservative group					
N of patients with event		19	127	244	320
N of patients at risk	1062	1022	888	629	289
Cumulative incidence		1.8%	12.3%	24.3%	35.8%



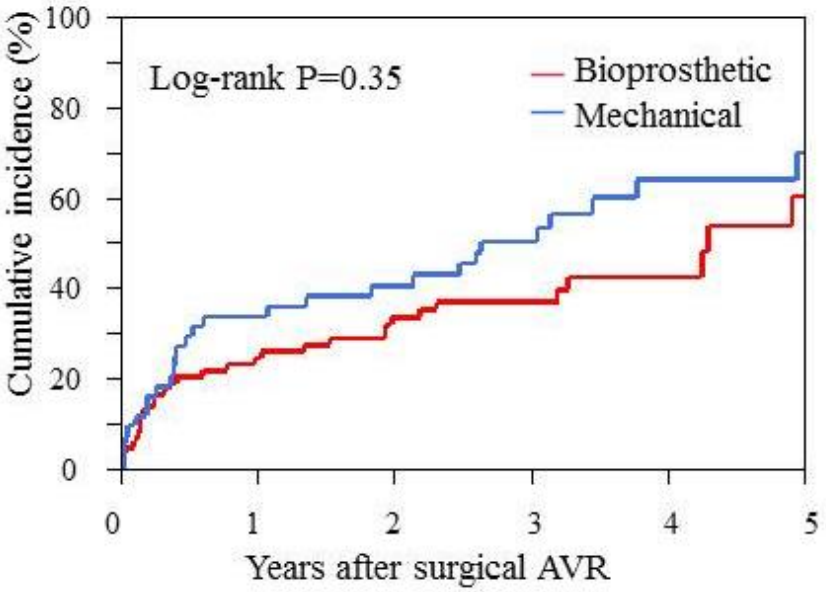
Interval	0 day	30 days	1 year	3 years	5 years
Initial AVR group					
N of patients with event		2	10	15	19
N of patients at risk	1062	1048	960	672	236
Cumulative incidence		0.2%	1.0%	1.6%	3.0%
Conservative group					
N of patients with event		2	31	53	57
N of patients at risk	1062	1022	888	629	289
Cumulative incidence		0.2%	3.2%	5.8%	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.

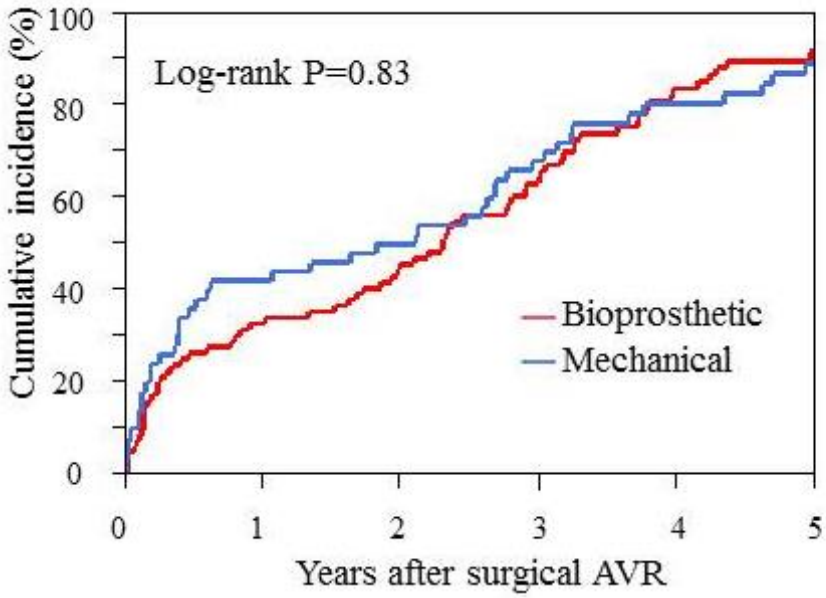
AVR=aortic valve replacement.

(A) All-cause death



Interval	0 day	30 days	1 year	3 years	5 years
Bioprosthetic					
N of patients with event		5	19	27	32
N of patients at risk	80	73	52	27	5
Cumulative incidence		6.4%	24.9%	37.3%	60.8%
Mechanical					
N of patients with event		5	16	23	28
N of patients at risk	50	45	29	16	5
Cumulative incidence		10.0%	34.0%	50.8%	70.4%

(B) Hospitalization for heart failure



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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