Late Adverse Cardiorenal Events of Catheter Procedure-Related Acute Kidney Injury After Transcatheter Aortic Valve Implantation

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Data regarding the longitudinal effect of catheter procedure-related acute kidney injury (AKI) on clinical outcomes are limited. This study aimed to assess the late adverse cardiorenal events of AKI following transcatheter aortic valve implantation (TAVI). A total of 2,518 patients who underwent TAVI, excluding in-hospital deaths, were enrolled from the Japanese multicenter registry. The definition of AKI was determined using the Valve Academic Research Consortium-2 criteria. The incidence, predictors, major adverse renal and cardiac events (MARCE), and all-cause mortality of AKI were evaluated. MARCE included readmission for renal and heart failure (HF), hemodialysis requirement, and cardiovascular-renal death during the follow-up period. The incidence of AKI was 9.7% in the entire cohort. The significant predictive factors of AKI were men, diabetes mellitus, hypertension, chronic kidney disease, low albumin, overdose of contrast media, nontransfemoral approach, transfusion, vascular complications, and new pacemaker implantation. The rates of HF readmission and future hemodialysis were significantly higher in patients with AKI than in those without AKI (19.7% vs 9.0%, p <0.001, 3.3% vs 0.4%, p <0.001, respectively). Cox regression multivariate analysis showed that AKI occurrence was an independent predictive factor for the incremental risk of both MARCE and late mortality up to 4 years (hazard ratio [HR] 1.59, 95% confidence interval [CI] 0.75 to 1.20, p <0.001, HR 2.18, 95% CI 1.70 to 2.79; p <0.001, respectively). In conclusion, AKI occurrence was significantly associated with late adverse cardiorenal events after TAVI. Adequate clinical management can be expected to reduce AKI-related late phase cardiorenal damage even after successful TAVI. **(Am J Cardiol 2020;133:89–97)**

There is general agreement that the occurrence of acute kidney injury (AKI) is associated with an increased risk of early and late mortality in patients who undergo several catheter interventions.[1-3] Similar trends are also confirmed after transcatheter aortic valve implantation (TAVI) for severe aortic stenosis patients.[4-6] The procedure of TAVI has been established and simplified in this decade, whereas periprocedural complications are still a clinical issue; the incidence of AKI, one such complication, is reported approximately ranging from 10% to 50% after TAVI.[4-9] Cardiorenal syndrome encompasses a spectrum of disorders in the heart and kidneys, wherein dysfunction in one organ may cause dysfunction in the other organ.[10-11] AKI is one of the principal parts of a malignant cycle of cardiorenal syndrome. The clinical question arises whether catheter procedure-related AKI is a direct cause of worsening renal function and heart failure (HF) that is related to the subsequent risk of increased cardiac and renal death. Although a worse prognosis of AKI after invasive treatments is widely known in the literature,[1-6] the longitudinal effects of catheter procedure-related AKI on clinical outcomes, such as the incidence of HF readmission, future requirement of hemodialysis, and detailed information regarding reason of death

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are not fully elucidated. Especially in the TAVI cohort, little is known regarding the late adverse cardiac and renal events in patients with AKI. The aim of this study was to investigate the clinical impact of the periprocedural AKI on long-term clinical outcomes using data from the Japanese multicenter registry.

Methods

Data were extracted from the Optimized CathEter vAlvular iNtervention (OCEAN)-TAVI registry.[12-13] The OCEAN-TAVI registry is an ongoing multicenter registry collecting data from 14 Japanese medical centers including Kishiwada Tokusyukai Hospital.[12-13] A total of 2,588 patients underwent baseline, peri-, and postoperative data collection before undergoing TAVI between October 2013 and May 2017. All patients who underwent TAVI in each center were considered in the initial inclusion in this registry. The decision to perform TAVI was made by consensus within the heart team in each center. We initially excluded 70 patients with in-hospital death. The remaining 2,518 patient's data were retrospectively examined between the patients complicated with AKI and without AKI after TAVI. Conventional data collection included baseline patient characteristics, laboratory data, echocardiographic data, procedural variables, and clinical outcomes in terms of mortality, HF rehospitalization, and future requirement of hemodialysis during the follow-up period. The hemodialysis status was defined as chronic renal impairment requiring regular blood dialysis, excluding transit blood dialysis in both procedure-related phase and terminal stage. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2. Information regarding the occurrence and/or causes of death was obtained from the treating hospital or by contacting the patient's family members. Data reported on the internet-based system were checked via self-audit by sites. Data committee members also confirmed the completeness and consistency of the database and regularly sent queries to each center when necessary. This study protocol was approved by the local institutional review board and was registered with the University Hospital Medical Information Network (no.: UMIN000020423). Written informed consent was obtained from all patients before undergoing TAVI.

The information regarding the TAVI procedure has been previously described in detail.[12-13] Two devices are available in Japan, the Edwards SAPIEN-XT and SAPIEN-3 (Edwards Lifesciences, Irvine, CA) as a balloon-expandable prosthesis and the Medtronic CoreValve and Evolut-R System (Medtronic, Minneapolis, MN) as self-expandable. The local TAVI team member decided on the indication, therapeutic approach including approach route, and postprocedural management. Periprocedural and postprocedural complications, and post discharge events were evaluated according to the Valve Academic Research Consortium-2 (VARC-2) criteria.[14] According to the VARC-2 criteria, AKI was defined as an increase in serum creatinine (SCr) of at least 0.3 mg/dl or a relative increase of at least 50% within 48 hours from baseline following TAVI. Causes of death were categorized into cardiovascular and noncardiovascular. The definition of cardiovascular mortality was also applied to the VARC-2 criteria. As the composite clinical endpoint, major adverse renal and cardiac events (MARCE) was evaluated according to the following definitions: rehospitalization of HF, requirement of hemodialysis, and cardiac death. We also subcategorized the AKI group into 3 groups of AKI stages 1 to 3 according to the VARC-2 criteria. All statistical analyses were performed using IBM SPSS statistics v22 (SPSS, Inc., Chicago, IL), R software packages (version 3.0.1; R Development Core team), and Stata 14 (Stata Corp., College Station, TX). Continuous variables are expressed as mean ± standard deviation and median with interquartile ranges. Differences were tested using the unpaired Student's t test or Mann-Whitney U test depending on the variable distribution. Baseline and procedural outcomes were compared between the AKI and non-AKI groups. The univariate and multivariate logistic regression analyses were performed to obtain the odds ratio of each variable for predicting the AKI. The amount of contrast media (CM) was corrected according to the baseline renal function, which was determined per the eGFR and SCr per body weight in accordance with previous research.[6] A multivariate analysis was performed using the baseline clinical characteristics and other variables with a univariate p value <0.10. The univariate and multivariate Cox regression analyses were also performed to determine the hazard ratio (HR) for predicting MARCE and long-term mortality of AKI. The Kaplan-Meier curve was used to estimate the cumulative mortality rate, and differences were assessed with the log-rank test. The statistical tests were all 2-sided, and a p value <0.05 was considered statistically significant.

Results

AKI occurred in 243 of 2,518 patients (9.7%). The patient baseline characteristics are shown in Table 1. The proportion of men patients was 30.5%, and the mean age was 84.3 ± 5.2 years. Several baseline characteristics differed between the AKI and non-AKI groups. The baseline SCr value was higher and eGFR was lower in the AKI group than in the non-AKI group (1.39 ± 0.8 mg/dl vs 0.99 ± 0.4 mg/dl, p <0.001, 51.6 ± 19.4 ml/min/1.73 m^2 vs 52.7 ± 19.1 ml/min/1.73 m^2, p = 0.04, respectively). As a result, the prevalence of CKD was significantly higher in the AKI group than in the non-AKI group (83.1% vs 68.0%, p <0.001). The procedural characteristics are given in Table 2. Although the total amount of CM was similar in the CM/eGFR and CM × SCr/body weight ratios were significantly higher in the AKI group than in the non-AKI group (3.4 ± 2.8 vs 2.4 ±1.8, p <0.001, 3.0 ± 2.3 vs 2.2 ± 1.3, p <0.001). The rates of procedural complications such as disabling stroke, bleeding, transfusion, and vascular complications were significantly higher in the AKI group than in the non-AKI group (all p <0.05).

The results of the univariate and multivariate analysis for predicting AKI are presented in Table 3. In the univariate analysis, clinical frailty scale (CFS), peripheral artery disease, prior stroke, baseline hemoglobin value, use of diuretics, low left ventricle ejection fraction, general anesthesia, postprocedural disabling stroke were significantly related to AKI occurrence. However, all these factors were attenuated in the multivariate model. In contrast, men

Table 1
Baseline patient characteristics

Variable	Overall (n = 2,518)	Acute kidney injury		p value
		Yes (n = 243)	No (n = 2,275)	
Age (years)	84.3 ± 5.2	84.1 ± 5.7	84.4 ± 5.2	0.07
Men	769 (30.5%)	98 (40.3%)	671 (29.5%)	0.001
Body mass index (kg/m^2)	22.2 ± 3.7	22.5 ± 3.6	22.2 ± 3.6	0.68
Clinical frailty scale	3.9 ± 1.2	4.2 ± 1.3	3.9 ± 1.2	0.04
New York Heart Association class III/IV	1272 (50.5%)	135 (55.6%)	1137 (50.0%)	0.11
Hypertension	1934 (76.8%)	203 (83.5%)	1731 (76.1%)	0.005
Diabetes mellitus	542 (21.5%)	74 (30.5%)	468 (20.6%)	0.001
Dyslipidemia	1083 (43.0%)	112 (46.1%)	971 (42.7%)	0.31
Chronic kidney disease	1749 (69.5)	202 (83.1%)	1547 (68.0%)	<0.001
Coronary artery disease	915 (36.3%)	100 (41.2%)	815 (35.8%)	0.11
Peripheral artery disease	353 (14.0%)	67 (27.6%)	286 (12.6%)	<0.001
Pulmonary disease	366 (14.5%)	38 (15.6%)	328 (14.4%)	0.63
Prior stroke	285 (11.3%)	44 (18.1%)	241 (10.6%)	0.001
Prior coronary artery bypass graft	159 (6.3%)	18 (7.4%)	141 (6.2%)	0.49
Liver disease	75 (3.0%)	8 (3.3%)	67 (2.9%)	0.69
Society of thoracic surgeons predicted risk of mortality score (%)	6.5 (4.5-9.4)	8.4 (4.6-12.2)	6.3 (4.0-8.7)	<0.001
Hemoglobin (g/dl)	11.3 ± 1.7	10.9 ± 1.7	11.3 ± 1.7	0.92
Albumin (g/dl)	3.8 ± 0.5	3.6 ± 0.5	3.8 ± 0.5	0.99
Serum creatinine (mg/dl)	1.0 ± 0.5	1.39 ± 0.8	0.99 ± 0.4	<0.001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	51.6 ± 19.4	41.7 ± 19.6	52.7 ± 19.1	0.04
Echocardiographic data				
Aortic valve area (cm^2)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.15
Index aortic valve area (cm^2/m^2)	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.16
Peak velocity (m/s)	4.6 ± 0.8	4.5 ± 0.8	4.6 ± 0.8	0.44
Mean gradient (mm Hg)	50.7 ± 18.2	49.7 ± 19.1	50.7 ±18.2	0.55
Left ventricle ejection fraction (%)	59.3 ± 12.6	57.6 ± 14.4	59.5 ±12.4	0.001
Left ventricle ejection fraction <40%	222 (8.8%)	35 (14.4%)	187 (8.2%)	0.002
Aortic regurgitation grade 3/4	266 (10.6%)	26 (10.7%)	240 (10.5%)	0.91
Mitral regurgitation grade 3/4	278 (11.0%)	35 (14.4%)	243 (10.7%)	0.09
Medication				
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	1344 (53.4%)	125 (51.4%)	1219 (53.6%)	0.54
Beta blocker	859 (34.1%)	91 (37.4%)	768 (33.8%)	0.26
Diuretic	1341 (53.3%)	152 (62.6%)	1189 (52.3%)	0.002
Tolvaptan	179 (8.0%)	22 (9.8%)	157 (7.8%)	0.30

Values are numbers (%), mean ± SD, or median (interquartile range).

sex, diabetes mellitus, hypertension, CKD, serum albumin value, CM/eGFR ratio, nontransfemoral approach, transfusion, vascular complications, and new pacemaker implantation were maintained as independent predictive factors of AKI (all p <0.05).

The 1-year clinical follow-up rate was 99.5% in the overall cohort. During a median follow-up period of 693 days (interquartile range 389 to 871), a total of 423 deaths occurred. Hemodialysis was introduced in 17 patients (0.7%). Among them, all-cause mortality after the introduction of dialysis was 52.9% (n = 9 of 17). HF readmission occurred in 254 patients (10.1%). A new-onset postoperative high degree atrioventricular block requiring permanent pacemaker implantation during hospitalization occurred in 8.3% of the patients (n = 210 of 2,518) and it was observed more frequently in the AKI group than in the non-AKI group (11.9% vs 8.8%; p <0.05). In total, 137 patients (5.4%) underwent urgent TAVI. Urgent TAVI was significantly more common in the AKI group than in the non-AKI (10.7% vs 4.9%; p 0.001). All these incidences were significantly higher in patients with AKI than in those without AKI (Figure 1). The Kaplan-Meier curves showed significant differences in terms of all-cause death between the AKI and non-AKI groups after TAVI (Figure 2). The incidence of MARCE was also significantly elevated in the AKI group than in the non-AKI group (Figure 2). The subanalysis of all-cause mortality in the AKI stages 1 to 3 is shown in Figure 3. An incremental cumulative 4-year mortality was found across the 3 groups (Figure 3) (49.3% vs 48.5%, vs 75.5%, respectively, p 0.005). The Cox regression multivariate model analyzed for the predictive clinical factors of MARCE after TAVI (Table 4). The occurrence of AKI was one of the significant factors for predicting MARCE (HR 1.86, 95% confidence interval [CI] 1.41 to 2.44, p <0.001). The other independent predictive factors of MARCE were men sex (HR 1.52, 95% CI 1.21 to 1.90, p <0.001), CFS (HR 1.10, 95% CI 1.01 to 1.19, p = 0.036), CKD (HR 1.61, 95% CI 1.23 to 2.10, p <0.001), and mitral regurgitation grade 3/4 (HR 1.79, 95% CI 1.38 to 2.33, p <0.001). The Cox regression multivariate model also analyzed for the association between all-cause mortality and clinical findings (Table 5). AKI was significantly associated

Table 2
Procedural patient characteristics

Variable	Overall (n = 2,518)	Acute kidney injury		p value
		Yes (n = 243)	No (n = 2,275)	
Periprocedural variables				
Procedure time (min)	80.8 ± 45.5	98.4 ± 76.1	76.1 ± 37.5	<0.001
Fluoroscopy time (min)	21.4 ± 11.1	21.1 ± 11.1	20.7 ± 11.2	0.03
General anesthesia	1915 (76.1%)	208 (85.6%)	1707 (75.0%)	<0.001
Nonelective	137 (5.4%)	26 (10.7%)	111 (4.9%)	<0.001
Contrast media dose (ml)	105.0 (75.0-144.0)	100.0 (60.5-139.5)	106.0 (72-140)	0.50
Contrast media/estimated glomerular filtration rate ratio	2.5 ± 1.9	3.4 ± 2.8	2.4 ± 1.8	<0.001
Contrast media × serum creatinine/body weight ratio	2.3 ± 1.5	3.0 ± 2.3	2.2 ± 1.3	<0.001
Valve type				
Balloon-expandable valve	2187 (86.9%)	215 (88.5%)	1972 (86.7%)	0.49
Self-expandable valve	331 (13.1%)	28 (11.5%)	303 (13.3%)	
Approach route				
Transfemoral approach	2125 (84.4%)	153 (63.0%)	1972 (86.7%)	<0.001
*Nontransfemoral approach	393 (15.6%)	90 (37.0%)	303 (13.3%)	
Postprocedural variables				
Serum creatinine within 48 hours (mg/dl)	0.04 ± 0.3	0.66 ± 0.8	-0.02 ± 0.1	<0.001
Disabling stroke	32 (1.3%)	7 (2.9%)	25 (1.1%)	0.02
Acute coronary obstruction	23 (0.9%)	1 (0.4%)	22 (1.0%)	0.39
All bleeding	570 (22.6%)	98 (40.3%)	472 (20.7%)	<0.001
Transfusion	693 (27.5%)	113 (46.5%)	580 (25.5%)	<0.001
All vascular complication	216 (8.6%)	33 (13.6%)	183 (8.0%)	0.003
Major vascular complication	97 (3.9%)	22 (9.1%)	75 (3.3%)	<0.001
Hospital stay after procure (day)	13.1 (7.0-15.0)	25.1 (11.0-26.0)	11.8 (7.0-14.0)	<0.001
New pacemaker implantation	210 (8.3%)	29 (11.9%)	181(8.0%)	0.04
Intensive care unit stay (day)	2.1 (1.0-2.0)	4.9 (1.0-6.0)	1.9 (1.0-2.0)	<0.001

Values are numbers (%), mean ± SD, or median (interquartile range).
* Other approaches included transiliac, transsubclavian, and direct aortic approach.

with increased risk of mortality after TAVI (HR 1.61, 95% CI 1.23 to 2.11, p <0.001). The other clinical factors of significantly increased mortality after TAVI were men sex, body mass index, CFS, pulmonary disease, liver disease, serum hemoglobin value, and serum albumin value (all p <0.05).

Discussion

The results of our study demonstrated the clinical impact of AKI on the long-term cardiac adverse events after TAVI. Although the longitudinal clinical effect of catheter-related AKI has not been well established, the occurrence of AKI significantly increased the rates of HF readmission, future hemodialysis, cardiac death, and all-cause mortality. AKI-related complications negatively affect both cardiac and renal function; this supports the concept of cardiorenal syndrome.[10-11] Even after a successful TAVI procedure, we should pay attention to the subsequent risk of AKI. Physicians need to make an effort to reduce this complication and improve the patient care pathway in the future. The most important clinical point is to predict and prevent AKI during TAVI. Advances in operator experience and devices have reduced procedural complications after TAVI. In fact, we have previously reported decreased complication rates, including AKI, in both the short- and long-term after the introduction of TAVI.[13] The AKI rate reported in this study (9.7%) is comparable to that of previous studies.[4-9] Nonmodifiable factors such as pre-existing men sex, diabetes mellitus, hypertension, CKD, low albumin status, and nontransfemoral approach should be understood as potential risk factors for AKI following TAVI. The low albumin status is newly identified, whereas the remaining factors have been confirmed through past data.[4-9] The modifiable factors are considered procedural complications with transfusion, vascular complications and new pacemaker implantation. Transfusion during the procedure is a well-known factor related to AKI occurrence in the literature.[9] These periperiprocedural complications should be minimized. Previous reports emphasize the importance of corrected CM volume based on the kidney function for predicting the risk of AKI after percutaneous coronary intervention and TAVI.[6,15] Especially in advanced CKD patients, CM volume should be strictly controlled to prevent AKI after TAVI. Multiple approaches should be adapted to decrease the risk of AKI in patients undergoing TAVI. Hemodynamic instability, or hypotension with reduction in renal blood flow due to a high degree atrioventricular block after TAVI may cause AKI. We considered that new pacemaker implantation was a significant predictive factor of AKI because of such hemodynamic changes. Whether catheter procedure-related AKI is a sensitive marker reflecting a worse prognosis or is directly linked to heart and renal damage is still under debate. A national percutaneous coronary intervention registry data from the United States revealed a longitudinal increased risk of death, renal injury including hemodialysis, and myocardial infarction in patients complicated with AKI.[16] However, these data lack the association between

Table 3
Univariate and multivariate regression analysis for the association between AKI and clinical findings

	Univariate analysis			Multivariate analysis		
Explanatory variables	OR	95% CI	p value	OR	95% CI	p value
Baseline characteristics						
Age (per 1 year increase)	0.99	0.97-1.01	0.40			
Men	1.62	1.23-2.12	0.001	1.93	1.40-2.65	<0.001
Body mass index (per 1.0 m^2 increase)	1.02	0.99-1.07	0.12			
Clinical frailty scale (per 1 scale increase)	1.21	1.09-1.34	<0.001	1.06	0.94-1.20	0.32
New York Heart Association class III/IV	1.25	0.96-1.63	0.10			
Diabetes mellitus	1.69	1.26-2.26	<0.001	1.48	1.07-2.04	0.018
Hypertension	1.60	1.12-2.27	0.009	1.48	1.02-2.16	0.041
Chronic kidney disease	2.32	1.64-3.28	<0.001	1.58	1.08-2.32	0.020
Peripheral artery disease	2.65	1.95-3.60	<0.001	1.40	0.99-1.99	0.060
Prior stroke	1.87	1.31-2.66	0.001	1.46	0.98-2.16	0.061
Laboratory data						
Hemoglobin (per 1.0 g/dl increase)	0.86	0.79-0.93	<0.001	0.95	0.87-1.07	0.35
Albumin (per 1.0 g/dl increase)	0.50	0.39-0.64	<0.001	0.63	0.46-0.87	0.004
Medication						
Diuretics	1.53	1.16-2.00	0.002	1.19	0.88-1.62	0.26
Echocardiographic data						
Left ventricle ejection fraction <40%	1.88	1.27-2.77	0.001	1.21	0.77-1.90	0.40
Aortic regurgitation grade 3/4	1.02	0.66-1.56	0.94			
Mitral regurgitation grade 3/4	1.41	0.96-2.06	0.080	1.21	0.79-1.85	0.38
Procedural variables						
General anesthesia (for local anesthesia)	1.98	1.37-2.86	<0.001	0.70	0.46-1.05	0.09
Nonelective	2.34	1.49-3.66	<0.001	1.68	0.99-2.86	0.06
Contrast media volume (per 1.0 ml increase)	1.00	0.99-1.00	0.50			
Contrast media/estimated glomerular filtration rate ratio (per 1.0 increase)	1.20	1.13-1.27	<0.001	1.16	1.09-1.23	<0.001
Balloon-expandable valve	1.18	0.78-1.78	0.43			
Nontransfemoral approach	3.83	2.87-5.10	<0.001	3.29	2.34-4.62	<0.001
Procedural complications						
Disabling stroke	2.67	1.14-6.23	0.02	2.23	0.88-5.67	0.09
Transfusion	2.54	1.94-3.33	<0.001	1.50	1.10-2.05	0.011
Vascular complication	1.80	1.21-2.67	0.004	2.10	1.35-3.28	0.001
New pacemaker implantation	1.57	1.03-2.38	0.03	1.97	1.26-3.09	0.003

CI = confidence interval; OR = odds ratio.

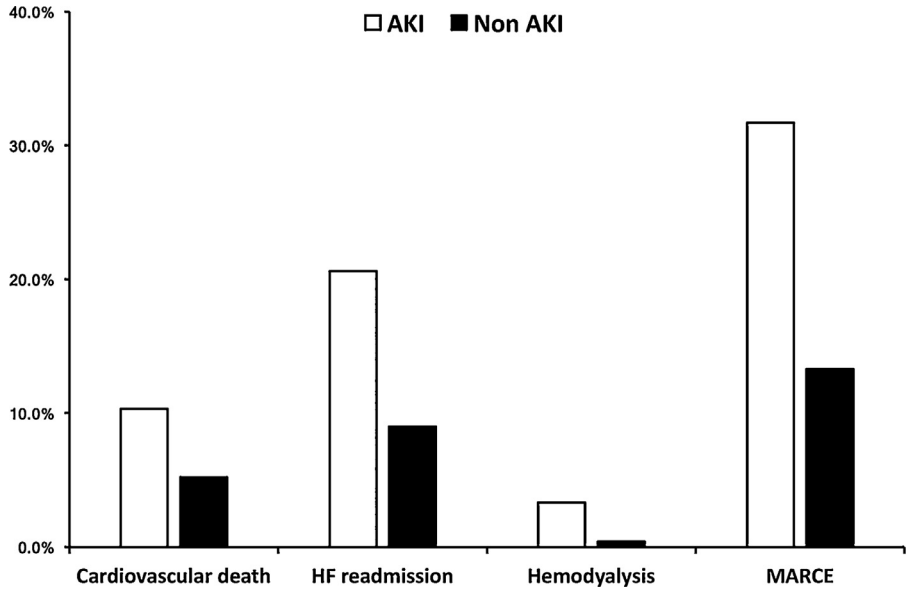
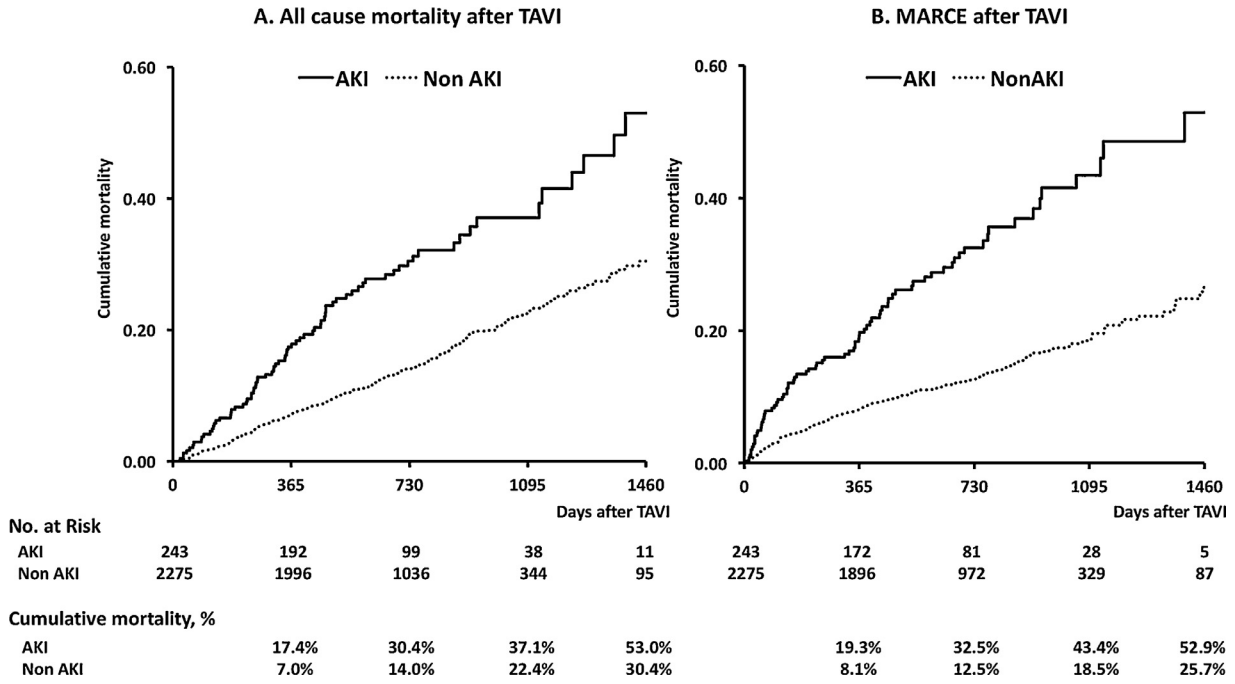
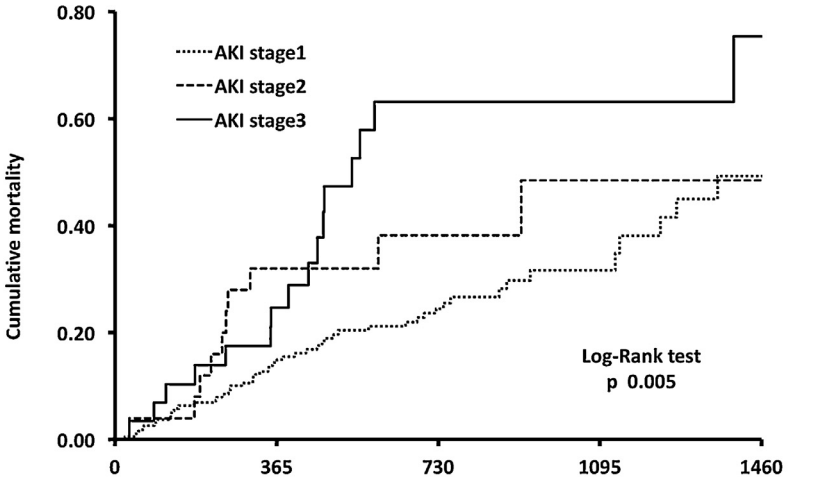


Figure 1. The incidence of cardiovascular death, hemodialysis requirement, HF readmission, and MARCE in the AKI and non-AKI groups. The percentage of cardiovascular death was 9.5% (n = 23 of 243) and 5.0% (n = 114 of 2,275); that of hemodialysis, 3.3% (n = 8 of 243) and 0.4% (n = 9 of 2,275); that of HF readmission, 20.6% (n = 50 of 243) and 9.0% (n = 204 of 2,275); and that of MARCE, 31.7% (n = 77 of 243) versus 13.3% (n = 303 of 2,275), respectively.



No. at Risk										
AKI	243	192	99	38	11	243	172	81	28	5
Non AKI	2275	1996	1036	344	95	2275	1896	972	329	87
Cumulative mortality, %										
AKI		17.4%	30.4%	37.1%	53.0%		19.3%	32.5%	43.4%	52.9%
Non AKI		7.0%	14.0%	22.4%	30.4%		8.1%	12.5%	18.5%	25.7%

Figure 2. Kaplan-Meier curves showing cumulative mortality of AKI and non-AKI patients in terms of all-cause mortality (*A*) and MARCE (*B*).



No. at Risk				
AKI stage1	155	84	28	6
AKI stage2	16	8	4	1
AKI stage3	21	7	5	2
Cumulative mortality, %				
AKI stage1	14.4%	24.5%	31.7%	49.3%
AKI stage2	32.0%	38.2%	48.5%	48.5%
AKI stage3	24.7%	63.2%	63.2%	75.5%

Figure 3. Kaplan-Meier curves showing cumulative mortality of AKI stage 1-3 patients in terms of all-cause mortality.

AKI and future HF risk. Our study additionally clarified the higher rates of HF readmission in patients with AKI. The worsened clinical effect of AKI obviously revealed higher rates of HF readmission and hemodialysis, causing MARCE. This finding suggests that caution regarding the future risk of MARCE caused by AKI is warranted in patients undergoing invasive catheter interventions. Indications for TAVI are drastically expanding, as a lower risk of cardiac surgery has been reported in a pivotal randomized trial.[17] The TAVI procedure is an established method and is definitely effective in stabilizing AS. The majority of patients receive the survival advantage owing to the hemodynamic improvements after procedure. Nonetheless, the physicians always consider the risk-benefit

Table 4
The Cox regression analysis for the clinical predictive factors of major adverse real and cardiac event after TAVI

	Univariate analysis			Multivariate analysis		
Explanatory variables	HR	95% CI	p value	HR	95% CI	p value
Age (per 1 year increase)	1.03	1.01-1.05	0.016	1.01	0.99-1.03	0.30
Men	1.43	1.16-1.77	0.001	1.52	1.21-1.90	<0.001
Body mass index (per 1.0 m^2 increase)	0.99	0.96-1.02	0.36			
Clinical frailty scale (per 1 scale increase)	1.17	1.08-1.27	<0.001	1.10	1.01-1.19	0.036
New York Heart Association class III/IV	1.57	1.28-1.93	<0.001	1.14	0.91-1.42	0.24
Hypertension	1.27	0.99-1.64	0.064	1.17	0.90-1.52	0.23
Diabetes mellitus	1.47	1.18-1.84	0.001	1.23	0.97-1.56	0.093
Chronic kidney disease	2.01	1.56-2.59	<0.001	1.61	1.23-2.10	<0.001
Peripheral artery disease	1.57	1.22-2.03	<0.001	0.99	0.75-1.31	0.94
Pulmonary disease	1.01	0.80-1.27	0.97			
Prior stroke	1.19	0.87-1.61	0.27			
Prior coronary artery bypass graft	1.70	1.22-2.37	0.002	1.38	0.98-1.94	0.069
Liver disease	1.67	1.01-2.75	0.045	1.41	0.85-2.35	0.19
Society of thoracic surgeons predicted risk of mortality score	1.04	1.03-1.04	<0.001	1.01	0.99-1.02	0.11
Hemoglobin	0.88	0.82-0.93	<0.001	0.94	0.88-1.01	0.092
Albumin	0.53	0.43-0.65	<0.001	0.73	0.58-0.92	0.007
Left ventricle ejection fraction <40%	2.03	1.52-2.71	<0.001	1.30	0.94-1.78	0.11
Aortic regurgitation grade 3/4	0.89	0.63-1.26	0.51			
Mitral regurgitation grade 3/4	2.19	1.69-2.83	<0.001	1.79	1.38-2.33	<0.001
Nontransfemoral approach	1.50	1.17-1.91	0.001	1.27	0.98-1.66	0.076
Acute kidney injury	2.70	2.10-3.47	<0.001	1.86	1.41-2.44	<0.001

HR = hazard ratio.

Table 5
The Cox regression analysis for the association between all-cause mortality and clinical findings

	Univariate analysis			Multivariate analysis		
Explanatory variables	HR	95% CI	p value	HR	95% CI	p value
Age (per 1 year increase)	1.01	0.99-1.03	0.16			
Men	1.71	1.41-2.08	<0.001	1.98	1.60-2.44	<0.001
Body mass index (per 1.0 m^2 increase)	0.93	0.91-0.96	<0.001	0.95	0.92-0.97	0.001
Clinical frailty scale (per 1 group increase)	1.27	1.18-1.37	<0.001	1.17	1.08-1.27	<0.001
New York Heart Association class III/IV	1.63	1.34-1.98	<0.001	1.16	0.94-1.43	0.16
Hypertension	0.91	0.73-1.14	0.43			
Diabetes mellitus	1.26	1.01-1.56	0.04	1.07	0.86-1.35	0.54
Chronic kidney disease	1.40	1.13-1.75	0.003	1.23	0.98-1.55	0.076
Peripheral artery disease	1.61	1.28-2.04	<0.001	1.09	0.84-1.42	0.51
Pulmonary disease	1.31	1.02-1.67	0.03	1.28	1.04-1.58	0.023
Prior stroke	1.11	0.83-1.49	0.49			
Prior coronary artery bypass graft	1.21	0.85-1.72	0.30			
Liver disease	2.62	1.77-3.88	<0.001	2.22	1.49-3.31	<0.001
Society of thoracic surgeons predicted risk of mortality score	1.04	1.03-1.04	<0.001	1.01	0.9-1.02	0.077
Hemoglobin	0.84	0.79-0.89	<0.001	0.92	0.86-0.99	0.016
Albumin	0.37	0.31-0.44	<0.001	0.53	0.43-0.65	<0.001
Left ventricle ejection fraction <40%	1.39	1.01-1.91	0.041	0.80	0.57-1.13	0.21
Aortic regurgitation grade $^3/_4$	1.08	0.80-1.48	0.61			
Mitral regurgitation grade $^3/_4$	1.31	0.98-1.74	0.068	1.09	0.81-1.47	0.56
Nontransfemoral approach	1.24	0.98-1.58	0.078	0.99	0.77-1.29	0.98
Acute kidney injury	2.18	1.70-2.79	<0.001	1.61	1.23-2.11	<0.001

balance of the invasive therapy that contains the iatrogenic problem with periprocedural complications. When the target of TAVI for AS patients shifted broadly, it is clinically important to know and manage the early and subsequent late risk of AKI following TAVI.

Several study limitations should be addressed. AKI is considered as a transient effect in some patients; previous reports have identified a subgroup of patients who recovered from renal impairment within the acute phase after TAVI.[18-19] Unfortunately, we have no laboratory data regarding the dynamic change in the acute phase (1 week and 1 month) that confirms kidney function recovery. Therefore, recovery from kidney damage in the acute phase is undetermined. The 1-year clinical follow-up rate was

99.5% and systematic queries are provided by the data manager, whereas information regarding hemodialysis requirement, HF readmission, and causes of death were self-reported from individual centers. Thus, missing data and under-reported clinical events are inevitable.

Authors' Contributions

Yuya Adachi: Conceptualization, Methodology, Software, Formal analysis, Visualization. Masanori Yamamoto: Data curation, Writing - Review and Editing, Supervision. Tetsuro Shimura: Resources, Data curation. Ryo Yamaguchi: Resources, Data curation. Ai Kagase: Resources, Data curation. Takahiro Tokuda: Resources, Data curation. Satoshi Tsujimoto: Resources, Data curation. Yutaka Koyama: Resources, Data curation. Toshiaki Otsuka: Software, Validation, Formal analysis. Fumiaki Yashima: Investigation, Data curation. Norio Tada: Resources, Investigation, Data curation. Toru Naganuma: Resources, Investigation, Data curation. Motoharu Araki: Resources, Investigation, Data curation. Futoshi Yamanaka: Resources, Investigation, Data curation. Shinichi Shirai: Resources, Investigation, Data curation. Kazuki Mizutani: Resources, Investigation, Data curation. Minoru Tabata: Resources, Investigation, Data curation. Hiroshi Ueno: Resources, Investigation, Data curation. Kensuke Takagi: Resources, Investigation, Data curation. Yusuke Watanabe: Resources, Investigation, Data curation, Supervision. Kentaro Hayashida: Investigation, Supervision, Project administration, Funding acquisition.

Disclosures

Drs. Yamamoto, Tada, Naganuma, Shirai, Mizutani, and Watanabe are clinical proctors for Edwards Lifesciences and Medtronic. Drs. Araki, Tabata, Takagi, Higashimori, and Hayashida are clinical proctors of Edwards Lifesciences. Dr. Ueno is a clinical proctor for Medtronic. The remaining authors have nothing to disclose.

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