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Original article

Impact of Acute Kidney Injury on Short- and Long-term Outcomes After Transcatheter Aortic Valve Implantation

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ABSTRACT

Introduction and objectives: Acute kidney injury (AKI) is frequently observed after transcatheter aortic valve implantation (TAVI) and is associated with higher mortality. However, the impact of AKI on long-term outcomes remains controversial. Therefore, we sought to evaluate the impact of AKI on short- and long-term outcomes following TAVI using the Valve Academic Research Consortium 2 criteria.
Methods: Consecutive patients (n = 794) with severe aortic stenosis who underwent TAVI were included in a multicenter Brazilian registry. Logistic regression analysis was used to identify predictors of AKI. Four-year outcomes were determined as Kaplan-Meier survival curves, and an adjusted landmark analysis was used to test the impact of AKI on mortality among survivors at 12 months.
Results: The incidence of AKI after TAVI was 18%. Independent predictors of AKI were age, diabetes mellitus, major or life-threatening bleeding and valve malpositioning. Acute kidney injury was independently associated with higher risk of all-cause death (adjusted HR, 2.8; 95%CI, 2.0-3.9; $P < .001$) and cardiovascular mortality (adjusted HR, 2.9; 95%CI, 1.9-4.4; $P < .001$) over the entire follow-up period. However, when considering only survivors at 12 months, there was no difference in both clinical endpoints (adjusted HR, 1.2; 95%CI, 0.5-2.4; $P = .71$, and HR, 0.7; 95%CI, 0.2-2.1; $P = .57$, respectively).
Conclusions: Acute kidney injury is a frequent complication after TAVI. Older age, diabetes, major or life-threatening bleeding, and valve malpositioning were independent predictors of AKI. Acute kidney injury is associated with worse short- and long-term outcomes. However, the major impact of AKI on mortality is limited to the first year after TAVI.

Impacto del daño renal agudo en el seguimiento a corto y a largo plazo tras el implante percutáneo de válvula aórtica

Palabras clave:
Estenosis aórtica
Daño renal agudo
Implante percutáneo de válvula aórtica
Mortalidad
Edad avanzada
Valve Academic Research Consortium

RESUMEN

Introducción y objetivos: El daño renal agudo (DRA) ocurre con frecuencia tras el implante percutáneo de válvula aórtica (TAVI) y se asocia con una mayor mortalidad. Sin embargo, el impacto del DRA en la evolución a largo plazo continúa siendo controvertida. Por dicho motivo se evalúa el impacto del DRA el resultado a corto y largo plazo tras el TAVI usando los criterios *Valve Academic Research Consortium 2*.
Métodos: Se incluyeron 794 pacientes consecutivos con estenosis aórtica grave en un registro multicéntrico brasileño. Para la identificación de los predictores de DRA se utilizó el análisis de regresión logística. La supervivencia a 4 años se determinó mediante las curvas de Kaplan-Meier y para determinar el impacto del DRA en la mortalidad entre los supervivientes a 12 meses se usó un análisis de punto de referencia ajustado.
Resultados: La incidencia de DRA tras el TAVI fue del 18%. Los predictores independientes de DRA fueron: edad, diabetes mellitus, hemorragia mayor o amenazante para la vida y la malaposición valvular. El DRA se asoció independientemente con un riesgo mayor de muerte total (HR ajustada = 2,8; IC95%, 2,0-3,9;

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p < 0,001) y cardiovascular (HR ajustada = 2,9; IC95%, 1,9-4,4; p < 0,001) durante el periodo de seguimiento completo. Sin embargo, cuando se consideró solo los supervivientes a 12 meses, no hubo diferencias en ambos objetivos clínicos (HR ajustada = 1,2; IC95%, 0,5-2,4; p = 0,71, y HR = 0,7; IC95%, 0,2-2,1; p = 0,57, respectivamente).

Conclusiones: El DRA es una complicación frecuente tras el TAVI. La edad avanzada, la diabetes, la hemorragia mayor o amenazante para la vida y la malaposición valvular eran factores predictivos de DRA. El DRA se asoció con el pronóstico a corto y largo plazo, sin embargo, el impacto del DRA sobre la mortalidad se limitó al primer año tras el TAVI.

Abbreviations

AKI: acute kidney injury
TAVI: transcatheter aortic valve implantation

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is now a well-established treatment for inoperable, high and intermidiate surgical risk patients with symptomatic severe aortic stenosis.[1–7] Acute kidney injury (AKI) is frequently observed after TAVI, with rates ranging from 3% to 50% depending on the definition used.[8–16]

The occurrence of AKI following TAVI has been associated with the presence of comorbidities, the administration of contrast medium, the need for rapid pacing with subsequent hypotension,[17] and the occurrence of postprocedural complications, such as bleeding and vascular complications.[13]

Acute kidney injury following TAVI is associated with poorer short- and mid-term outcomes,[9] prolonged hospital stay and, consequently, increased financial health care system cost.[18,19] However, conflicting evidence is available regarding the impact of AKI on long-term clinical outcomes.[10,13] Additionally, previous studies have used heterogeneous definitions of AKI, and have only assessed short- and mid-term clinical outcomes.[9,10] Moreover, the vast majority of previous research dichotomized AKI as present or absent and did not stratify this complication according to its different stages, even though a few studies have shown that the risk of death and complications increases with higher AKI severity.[19,20] Therefore, our study aimed to evaluate the clinical impact of AKI and its different stages on short- and long-term clinical outcomes following TAVI using the Valve Academic Research Consortium 2 (VARC-2) criteria.[21] We also aimed to identify the independent predictors of AKI after TAVI, in an attempt to better define risk assessment for this increasing population.

METHODS

Study Population

From January 2008 to January 2015, 819 consecutive patients with symptomatic severe aortic stenosis underwent TAVI and were included in a multicenter Brazilian registry.[22] Twenty-two sites from different regions of Brazil participated in the study. For each patient, baseline characteristics, procedure details, and follow-up data were collected and recorded in a web-based case report form designed especially for this registry. To better understand the predictors and prognostic role of AKI following TAVI, we excluded 25 patients who died in the first 24 hours after the procedure. Finally, 794 participants were included in this analysis. Informed written consent was obtained from the patients included prospectively. The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by each institution's ethics committee.

Procedure

The self-expandable CoreValve (Medtronic, Minneapolis, Minnesota, United States), the balloon-expandable SAPIEN XT (Edwards Lifesciences, Irvine, California, United States) or the Inovare (Braile Biomédica, São José do Rio Preto, São Paulo, Brazil) prosthesis were used. Transcatheter aortic valve implantation procedures were performed according to standard techniques. The type of anesthesia used and access site were left to the operator's discretion. Transfemoral vascular access was the first-choice approach. When transfemoral access was not feasible, transapical or transarterial approaches (transubclavian, direct transaortic, transapical or transcarotid) were used according to the preference of the Heart Team.

Clinical Endpoints and Definitions

Patients were followed up and all adverse events were adjudicated by an independent committee, according to the VARC-2 definitions. The definition of AKI was based on the AKIN (Acute Kidney Injury Network) criteria as follows: stage 1 (increase in serum creatinine to 150%-199% compared with baseline or increase of 0.3 mg/dL or urine output < 0.5 mL/kg/h for > 6 but < 12 h); stage 2 (increase in serum creatinine to 200%-299% compared with baseline or urine output < 0.5 mL/kg/h for > 12 but < 24 h); stage 3 (increase in serum creatinine to > 300% compared with baseline or serum creatinine of > 4.0 mg/dL with an acute increase of at least 0.5 mg/dL or urine output < 0.3 mL/kg/h for > 24 h or anuria for > 12 h or renal replacement therapy). The baseline serum creatinine was measured at the hospital admission before the procedure and daily thereafter, up to 1 week or less if the patient was discharged before this period. In comparison with the original VARC definitions, the timing for the diagnosis of AKI was extended from 72 hours to 7 days. Chronic kidney disease was defined as estimated glomerular filtration rate < 60 mL/min. The definition of valve malpositioning included valve migration, valve embolization, and ectopic valve deployment.[21] Device success was defined as the absence of procedural mortality and correct positioning of a single prosthetic heart valve into the proper anatomical location and intended performance of the prosthetic heart valve (mean aortic valve gradient < 20 mmHg and no moderate or severe aortic valve regurgitation).[21] The present study reports data on clinical outcomes at 30 days, 1 year, over the entire length of follow-up (up to 4 years), and starting at 1 year of follow-up (landmark analysis).

Statistical Analysis

The baseline clinical and procedural characteristics of the study population are presented according to AKI status. Continuous

variables are reported as mean ± standard deviation, or median and [interquartile range], and were compared using the Student *t* test or the Mann-Whitney test, as appropriate. Categorical variables are reported as frequencies and percentages, and were compared using the Pearson chi-square test.

Kaplan-Meier survival curves were created using different stages of AKI as a cutoff and the outcomes were compared using a log-rank test. Once AKI was associated with multiple factors including patient comorbidities, the procedure itself and its complications, a landmark survival analysis was used to explore the clinical impact of AKI on short- and long-term outcomes starting from 30 days and 1 year after the index procedure, respectively. Cox proportional hazards models were used to test the impact of AKI on all-cause death and cardiovascular mortality. Variables were selected if $P < .2$ in a bivariate analysis, and all variables with $P < .05$ remained in the model. The variables included in the models were age, sex, New York Heart Association functional class, chronic obstructive pulmonary disease, peripheral vascular disease, aortic balloon valvuloplasty, left ventricular ejection fraction, moderate or severe mitral regurgitation, pulmonary hypertension, access site (femoral vs nonfemoral), transoesophageal echocardiogram, predilatation, AKI, myocardial infarction, stroke, major or life-threatening bleeding, major vascular complication, and valve malpositioning.

A stepwise logistic regression analysis including all variables with *P* value < .2 in the univariate analysis was used to identify the predictors of AKI and 30-day all-cause and cardiovascular mortality. The variables tested in the models were age, chronic kidney disease, body mass index, diabetes mellitus, peripheral vascular disease, systemic hypertension, porcelain aorta, diuretics use, contrast media volume, creatinine clearance, valve malpositioning, major or life-threatening bleeding, and major vascular complications. All statistical tests were 2-sided, and the criterion for statistical significance was $P < .05$. All statistical analyses were performed using SPSS statistical software version 20.0.

RESULTS

Baseline Clinical Characteristics

The baseline characteristics of the study population are illustrated in Table 1. The overall mean age was 81.5 ± 7.3 years, 50.6% were women, 32.0% diabetics, the mean Society of Thoracic Surgeons score was 10.3 ± 7.9, and the mean EuroSCORE was 20.6 ± 14.7. The mean left ventricular ejection fraction was 58.6 ± 15% and the mean aortic gradient was 49 ± 15 mmHg. The preprocedural estimated glomerular filtration rate was 48.4 ± 22.1 mL/min and 77.1% of the patients had chronic kidney disease.

The incidence of AKI following TAVI was 18% (143/794). Of these, 11.1% (88) were classified as AKI stage 1, 2.4% (19) as stage 2, and 4.5% (36) as stage 3. Demographic characteristics were similar between patients with and without AKI (Table 1). The only exception was the Society of Thoracic Surgeons score, which was higher among patients with AKI (11.5 ± 8.3 vs 10 ± 7.7; $P = .04$). Length of hospital stay was significantly higher among patients with AKI (19.3 ± 29.1 days vs 11.2 ± 20.9 days; $P < .001$).

Procedural Characteristics and Complications

Transcatheter aortic valve implantation was performed via transfemoral access in most patients (93.6%), with CoreValve being the device most commonly used (72.9%). Most patients underwent general anesthesia. Procedural characteristics are shown in Table 2. We observed a higher prevalence of nontransfemoral access and predilatation among patients who developed AKI. The mean total contrast media used was 187 ± 110 mL, with a nonsignificant trend toward less contrast use in the group who developed AKI (175 ± 73 vs 190 ± 116; $P = .09$). However, the amount of contrast media received was higher among patients with valve malpositioning (276 ± 219 mL vs 183 ± 100 mL; $P = .028$) in comparison with those without valve malpositioning.

Device success rate was lower and valve malpositioning was more frequently observed in patients who developed AKI following TAVI (Table 2).

Table 1
Baseline Clinical Characteristics of the Study Population According to AKI Status

	Overall	AKI (+)	AKI (–)	*P*[*]
	(N = 794)	(n = 143)	(n = 651)	
Age, y	81.5 ± 7.3	82.4 ± 6.7	81.4 ± 7.4	.12
Female	402 (50.6)	72 (50.3)	330 (50.7)	.94
BMI, kg/m²	26.3 ± 4.7	26.2 ± 4.7	26.8 ± 4.8	.20
NYHA functional class III or IV	650 (81.9)	118 (82.5)	532 (81.7)	.82
CAD	466 (58.7)	83 (58)	383 (58.8)	.86
Previous stroke	65 (8.2)	10 (7.0)	55 (8.4)	.56
COPD	150 (18.9)	26 (18.2)	124 (19.0)	.83
Diabetes mellitus	254 (32.0)	52 (36.4)	202 (31.0)	.19
PVD	136 (17.1)	31 (21.7)	105 (16.1)	.11
Hypertension	598 (75.3)	114 (79.7)	484 (74.3)	.18
Porcelain aorta	60 (7.6)	15 (10.5)	45 (6.9)	.14
CKD	612 (77.1)	117 (81.8)	495 (76.0)	.13
eGFR				.26
30-60 mL/min	453 (58.6)	85 (59.9)	368 (58.3)	
< 30 mL/min	143 (18.5)	31 (21.8)	112 (17.7)	
LVEF	58.6 ± 15	58.7 ± 14.5	58.6 ± 15.0	.96
LVEF < 35%	76 (9.7)	11 (7.9)	65 (10.1)	.58
AVA, cm²	0.70 ± 0.20	0.67 ± 0.19	0.64 ± 0.18	.22
Mean gradient, mmHg	49 ± 15	50 ± 15	49 ± 16	.48
Logistic EuroSCORE, %	20.6 ± 14.7	21.3 ± 15.2	20.4 ± 14.6	.53
STS score, %	10.3 ± 7.9	11.5 ± 8.3	10 ± 7.7	.04
eGFR, mL/min	48.4 ± 22.1	46.0 ± 22.6	48.9 ± 22.0	.16
Use of diuretics	495 (62.3)	98 (68.5)	394 (61.0)	.09
ACE inhibitors or ARB	400 (50.4)	75 (52.4)	325 (49.9)	.58

ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; AVA, aortic valve area; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVD, peripheral vascular disease; STS, Society of Thoracic Surgeons.
Data are expressed as No. (%) or mean ± standard deviation.
[*] *P* values were obtained from the comparison between patients with and those with no AKI.

Predictors of Acute Kidney Injury

On multivariate analysis, the independent predictors of AKI were age, diabetes mellitus, major or life-threatening bleeding, and valve malpositioning (Table 3), the latter being the strongest (odds ratio [OR], 4.90; 95% confidence interval [95%CI], 2.42-9.92; $P < .001$) predictor.

Impact of Acute Kidney Injury on Short-term Outcomes

At 30 days, patients with AKI had higher rates of all-cause death (21% vs 2.9%; OR, 7.84; 95%CI, 3.70-16.58; $P < .001$] and cardiovascular mortality (18.2% vs 2.3%; OR, 8.55; 95%CI, 3.80-19.38; $P < .001$) than those without AKI. When an adjusted logistic

Table 2
Procedural Characteristics and Complications According to AKI Status

	Overall	AKI (+)	AKI (–)	P[a]
	(N = 794)	(n = 143)	(n = 651)	
Type of prosthesis				.74
CoreValve	579 (72.9)	106 (74.1)	473 (72.7)	
SAPIEN XT	193 (24.3)	32 (22.4)	161 (24.7)	
Inovare	22 (2.8)	5 (3.5)	17 (2.6)	
Contrast media volume, mL[b]	187 ± 110	175 ± 73	190 ± 116	.09
Q (1) (< 120 mL)	128 (22.3)	20 (19.6)	108 (22.8)	.86
Q (2) (120-149 mL)	84 (14.6)	17 (16.7)	67 (14.2)	
Q (3) (150-219 mL)	217 (37.7)	39 (38.2)	178 (37.6)	
Q (4) (≥ 220 mL)	146 (25.4)	26 (25.5)	120 (25.4)	
Access site				.03
Transfemoral	743 (93.6)	128 (89.5)	615 (94.5)	
Other	51 (6.4)	15 (10.5)	36 (5.5)	
General anesthesia	723 (91.1)	136 (95.1)	587 (90.2)	.06
Predilatation	384 (48.4)	80 (55.9)	304 (46.7)	.04
Postdilatation	297 (37.4)	48 (33.6)	249 (38.2)	.29
TEE guidance	646 (81.4)	122 (85.3)	524 (80.5)	.18
Device success[c]	634 (79.8)	90 (62.9)	544 (83.6)	< .001
Aortic regurgitation[d]	54 (7.4)	8 (6.2)	6 (7.7)	.58
Mean gradient, ≥ 20 mmHg	30 (5.1)	5 (4.9)	25 (5.2)	.90
Valve malpositioning	39 (4.9)	18 (12.6)	21 (3.2)	< .001
Multiple valve implants	37 (4.7)	16 (11.2)	21 (3.2)	< .001
Left ventricle perforation	8 (1.0)	3 (2.1)	5 (0.8)	.16
Conversion to open surgery	7 (0.9)	3 (2.1)	4 (0.6)	.11

AKI, acute kidney injury; Other, transapical and transarterial; Q, quartiles; TEE, transesophageal echocardiogram.
Data are expressed as No. (%) or mean ± standard deviation.
[a] *P* values were obtained from the comparison between patients with and those with no AKI.
[b] Data obtained from 575 patients (102 patients with AKI and 473 without AKI).
[c] According to Valve Academic Research Consortium 2 criteria.
[d] Moderate/severe aortic regurgitation.

Table 3
Multivariate Predictors of AKI in Patients Who Underwent TAVI

Variable	Multivariate	P
	OR (95%CI)	
Age	1.03 (1.00-1.06)	.044
Diabetes mellitus	1.53 (1.02-2.30)	.038
Bleeding*	3.30 (2.11-5.15)	< .001
Valve malpositioning	4.90 (2.42-9.92)	< .001
BMI	1.04 (0.98-1.09)	.19
Peak aortic gradient	1.01 (1.00-1.02)	.20
eGFR	0.99 (0.98-1.00)	.17
Contrast media volume	1.00 (1.00-1.00)	.25
Peripheral vascular disease	1.02 (0.56-1.84)	.95
Hypertension	1.14 (0.64-2.04)	.65
Porcelain aorta	1.53 (0.68-3.43)	.30
Use of diuretics	1.22 (0.74-2.01)	.44
Major vascular complications	0.97 (0.39-2.37)	.94

95%CI, 95% confidence interval; AKI, acute jidney injury; BMI, body mass index; eGFR, estimated glomerular filtration rate; OR, odds ratio; TAVI, transcatheter aortic valve implantation.
* Major or life-threatening bleeding.

regression model was used, AKI remained independently associated with 30-day all-cause mortality (OR, 2.71; 95%CI, 1.53-4.79; *P* = .001) and cardiovascular mortality (OR, 2.43; 95%CI, 1.32-4.46; *P* = .004).

Among patients with AKI, the 30-day all-cause death was 9.1% (OR, 3.33; 95%CI, 1.41-7.85) for those in stage 1, 36.8%(OR, 19.40; 95%CI, 6.87-54.78) in stage 2, and 41.7% (OR, 23.76; 95%CI, 10.63-53.12) in stage 3 (*P* < .001); 30-day cardiovascular mortality was 5.7% (OR, 2.55; 95%CI, 0.91-7.21), 36.8% (OR, 24.73; 95%CI, 8.54-71.64) and 38.9% (OR, 26.98; 95%CI, 11.61-62.71), in stages 1, 2 and 3, respectively (*P* < .001).

At 1-year of follow-up, we observed higher rates of all-cause (hazard ratio [HR], 4.17; 95%CI, 2.60-6.70; *P* < .001) and cardiovascular mortality (HR, 5.34; 95%CI, 2.98-9.57; *P* < .001) among patients with AKI compared with those without AKI (Figure 1).

When only survivors at 30 days were considered in the landmark analysis, AKI remained associated with higher risk of all-cause (HR, 2.86; 95%CI, 1.55-5.28; *P* < .001) and cardiovascular mortality (HR, 4.04; 95%CI, 1.56-10.48; *P* < .001) (Figure 1).

Long-term Outcomes

The presence of AKI was associated with a 3-fold increase in the risk of all-cause mortality (HR, 3.06; 95%CI, 2.06-4.55; *P* < .001) and a 4-fold increase in the risk of cardiovascular mortality (HR, 4.24; 95%CI, 2.52-7.12; *P* < .001) at 4 years of follow-up (Figure 2). Importantly, we observed a stepwise increase in all-cause and cardiovascular mortality according to different stages of AKI over the entire length of follow-up (Figure 3). Acute kidney injury remained independently associated with all-cause (adjusted HR, 2.8; 95%CI, 2.0-3.9; *P* < .001) and cardiovascular mortality (adjusted HR, 2.9; 95%CI, 1.9-4.4; *P* < .001) mortality, after adjustment for possible confounding variables (Table 4).

However, when considering only survivors at 12 months (428/794) in the landmark analysis, there was no difference in all-cause death (HR, 1.20; 95%CI, 0.60-2.39; *P* = .58) or cardiovascular mortality (HR, 1.35; 95%CI, 0.46-3.95; *P* = .4) among patients with and without AKI (Figure 2). Even after adjustment for important covariates, AKI was not associated with higher all-cause (adjusted HR, 1.2; 95%CI, 0.5-2.6; *P* = .71) and cardiovascular (adjusted HR, 0.7; 95%CI, 0.2-2.1; *P* = .57) mortality.

DISCUSSION

The present study has 3 main findings: *a)* age, diabetes mellitus, major or life-threatening bleeding and valve malpositioning were independent predictors of AKI; *b)* AKI was associated with increased short- and long-term all-cause and cardiovascular mortality with a stepwise increase in mortality with higher AKI severity; and *c)* however, in the landmark analysis starting at 1-year of follow-up, AKI was not associated with worse outcomes, indicating that its negative impact on outcomes is limited to the first year after TAVI.

In our study, AKI was a frequent (18%) complication after TAVI, which is consistent with 2 previous meta-analyses.[9,15] However, none of them included studies that used the updated VARC-2 criteria, which extends the timing for AKI diagnosis from 72 hours to 7 days following TAVI. Koifman et al.,[23] showed that there was approximately 10% of disagreement between the AKIN and RIFLE (Risk, Injury, Failure, Loss, End-stage) definitions, which suggests that postprocedural AKI may be misdiagnosed depending on the definition used, especially considering that peak levels of creatinine usually occur after 72 hours of the procedure.[13,17,23]

In accordance with previous reports, our study suggests that nontransfemoral TAVI is associated with increased risk of AKI.[12,17,24,25] We believe that this association is related to the higher occurrence of major vascular complications, bleeding, and need for blood transfusion with the use of alternative transarterial or transapical approaches, which are risk factors for AKI.[25,26]

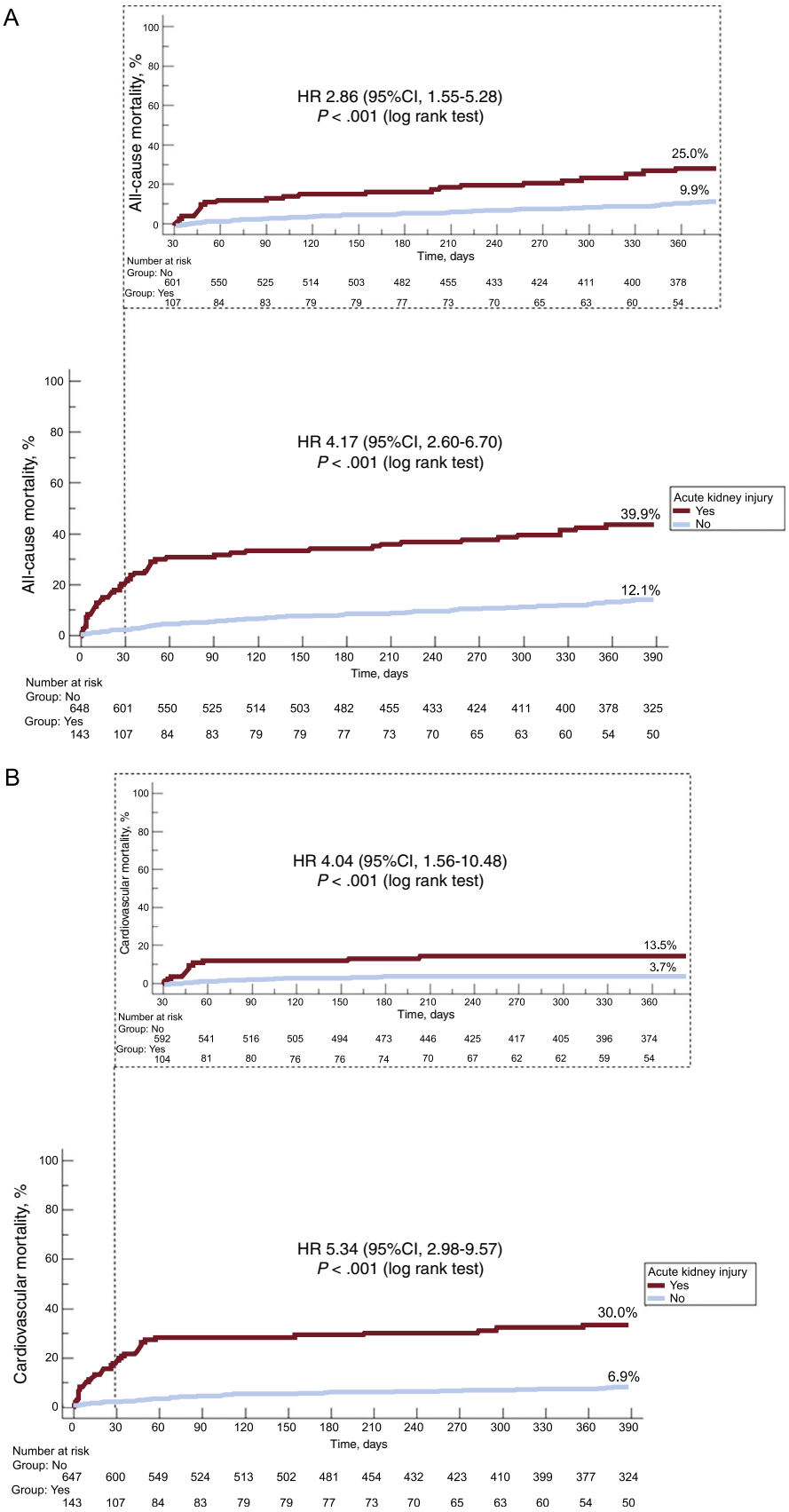

Figure 1. Kaplan-Meier curves for all-cause (A) and cardiovascular mortality (B) according to acute kidney injury status during the first year of follow-up and the unadjusted landmark analysis with follow-up starting at 30 days of all-cause mortality (A) and cardiovascular mortality (B). 95%CI, 95% confidence interval; HR, hazard ratio.

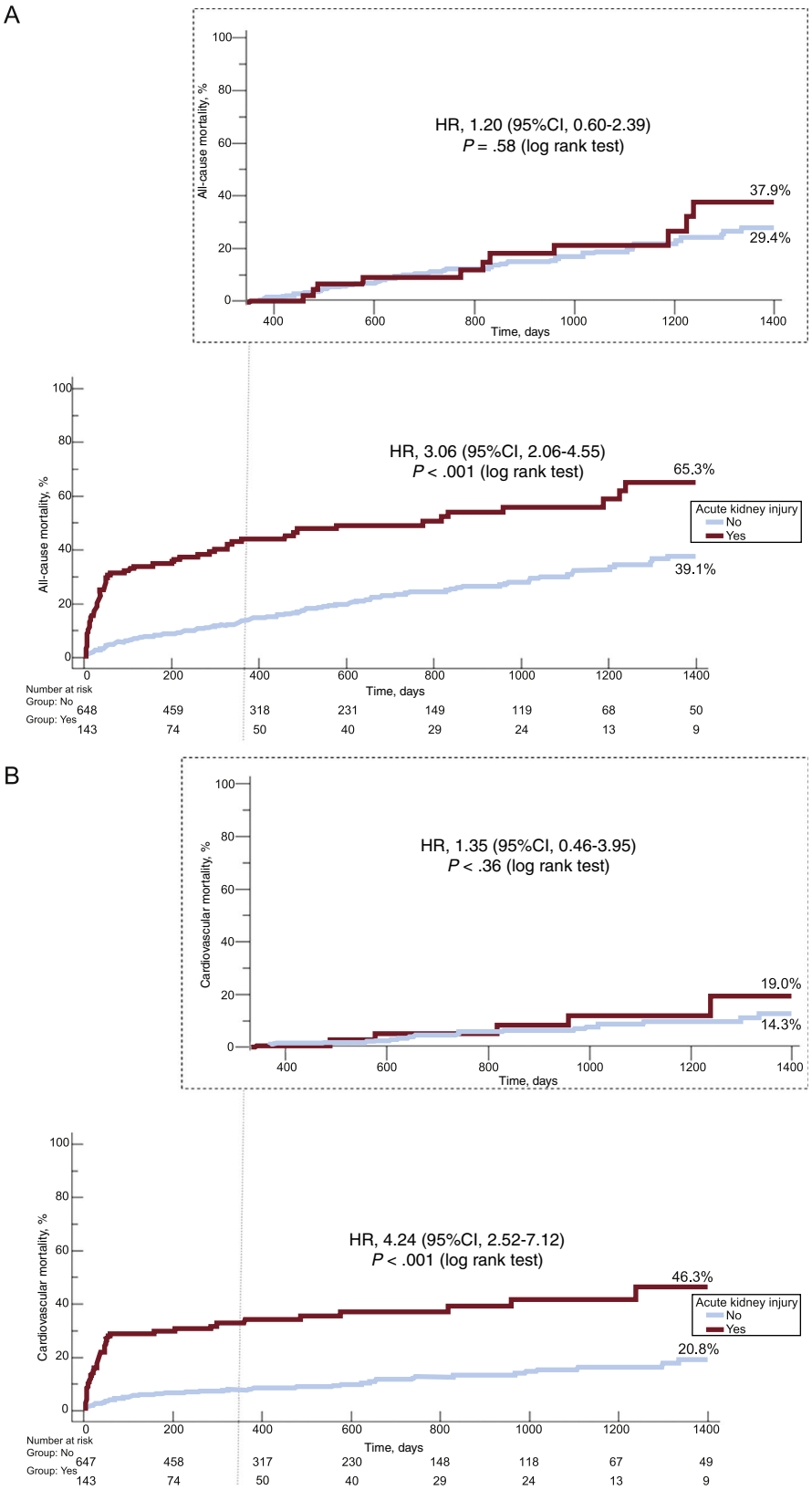

Figure 2. Kaplan-Meier curves for all-cause (A) and cardiovascular mortality (B) according to acute kidney injury status, over the entire length of follow-up and the unadjusted landmark analysis with follow-up starting at 1 year of all-cause mortality (A) and cardiovascular mortality (B). 95%CI, 95% confidence interval; HR, hazard ratio.

Age, diabetes mellitus, and life-threatening bleeding are well known risk factors for the development of AKI after TAVI.[10,17,27–29] However, to our knowledge, this is the first time that valve malpositioning has been shown to be an independent predictor of AKI. We suggest that the following factors may underlie this association. First, the amount of contrast media used in patients with valve malpositioning was, on average, 50% higher. Second, longer duration of the procedure, longer runs of ventricular pacing

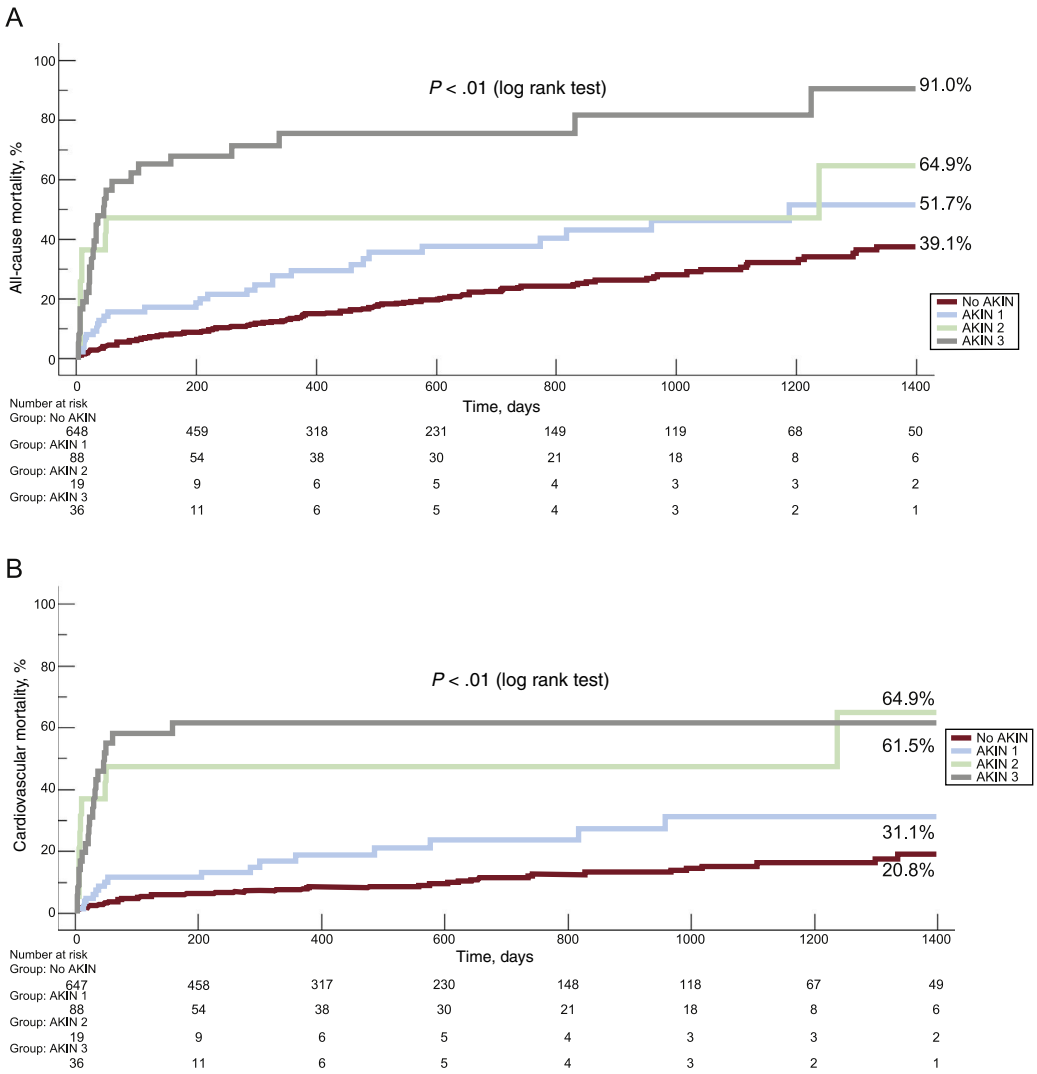

Figure 3. Kaplan-Meier curves for all-cause mortality (A) and cardiovascular mortality (B) according to acute kidney injury network criteria (AKIN 1, AKIN 2 and AKIN 3) over the entire length of follow-up. AKIN, Acute Kidney Injury Network.

Table 4
Predictors of Long-term All-cause Death and Cardiovascular Mortality

Models	Variables	HR (95%CI)	*P*
All-cause death			
	AKI	2.8 (2.0-3.9)	.001
	COPD	2.33 (1.6-3.3)	.001
	Aortic balloon valvuloplasty	2.2 (1.34-3.6)	.002
	NYHA functional class III or IV	2.0 (1.18-3.4)	.001
	Major stroke	1.98 (1.3-3.0)	.002
	Major or life-threatening bleeding	1.95 (1.4-2.8)	.01
Cardiovascular mortality			
	AKI	2.9 (1.9-4.4)	<.001
	Major stroke	3.1 (1.9-4.9)	<.001
	Valve malpositioning	2.7 (1.5-4.7)	.001
	Major vascular complications	2.5 (1.6-4.2)	<.001
	NYHA functional class III or IV	2.3 (1.1-4.7)	.028
	COPD	1.8 (1.1-2.8)	.008
	PVD	1.8 (1.1-2.8)	.013
	Female sex	0.65 (0.44-0.97)	.035

95%CI, 95% confidence interval; AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; HR, hazard ratio; PVD, peripheral vascular disease.

and sustained hemodynamic instability may provoke systemic inflammatory response syndrome, which appears to be a predictor of AKI and is associated with unfavorable outcomes.[24,30,31] We can speculate that second-generation devices, some of which are fully repositionable and retrievable,[32,33] will reduce the incidence of valve malpositioning and consequently, postprocedural AKI. Furthermore, the reduced profile of the newer delivery systems will probably reduce the rates of vascular and bleeding complications and may, therefore, also reduce the incidence of AKI.

Our findings suggest that AKI is associated with higher all-cause and cardiovascular mortality during short- (30-day landmark analysis) and long-term follow-up. However, an exploratory adjusted landmark analysis starting at 1-year of follow-up did not show differences in either all-cause death and cardiovascular mortality rates when comparing patients with and without AKI. A report by Généreux et al.,[13] demonstrated that significant AKI (stages 2 or 3) was associated with an increase in short-term all-cause mortality, but not after a 30-day landmark analysis. Similarly, Barbanti et al.[10] showed no significant impact of AKI on cardiovascular mortality after 30 days. Therefore, our study provides new insights as it shows that the major negative impact of AKI on mortality is limited to the first year after the procedure.

Importantly, our results showed that all stages of AKI (1, 2, and 3) had an effect on short- and long-term all-cause death and

cardiovascular mortality, with a stepwise increase in mortality with higher AKI severity. This is consistent with previous findings, with even a small increase in creatinine levels ($\geq$ 0.3 mg/dL) being associated with worse prognosis.[11,26] This finding highlights the clinical importance of adopting preventive measures for postprocedural AKI in a high-risk population of elderly patients undergoing TAVI.

Limitations

Our study has several limitations. First, data was self-reported by each center and, therefore, the occurrence of AKI might have been underreported, since on-site source document verification was randomly performed in only 20% of cases. Second, some patients may have been discharged from hospital earlier than 7 days; however, in our population, only 1% of the patients were discharged before this period. Third, although we appropriately adjusted for imbalance in baseline characteristics, residual confounding from unmeasured variables cannot be excluded and a cause and effect relationship between AKI and outcomes cannot be determined.

CONCLUSIONS

AKI is a frequent complication following TAVI. Older age, diabetes, major or life-threatening bleeding, and valve malpositioning are independent predictors of AKI. Acute kidney injury is associated with all-cause death and cardiovascular mortality, with a stepwise increase in mortality with higher AKI severity. However, the major impact of AKI on mortality is limited to the first year after TAVI. Our results suggest that all efforts should be made to identify patients at risk, reduce procedural complications and adopt preventive measures for postprocedural AKI.

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CONFLICTS OF INTEREST

F.S. de Brito Jr, D.A. Siqueira, and M.A. Perin are proctors from Edwards LifeSciences and Medtronic. L.A. Carvalho, and R. Sarmento-Leite are proctors from Medtronic.

WHAT IS KNOWN ABOUT THE TOPIC?

- Acute kidney injury is frequently observed after TAVI and is associated with poorer short- and mid-term outcomes. However, there is conflicting evidence on the impact of AKI on long-term clinical outcomes.

WHAT DOES THIS STUDY ADD?

- Our study provides new insights as it shows that the major negative impact of AKI on mortality is limited to the first year after the procedure.

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