ORIGINAL ARTICLE

Improvement in long-term survival with acute kidney recovery after a successful transcatheter aortic valve replacement

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KEY WORDS

acute kidney injury, acute kidney recovery, chronic kidney disease, transcatheter aortic valve replacement

ABSTRACT

INTRODUCTION Chronic kidney disease (CKD) is frequent in patients treated with transcatheter aortic valve replacement. Yet, the procedure can improve kidney function, that is, it can lead to acute kidney recovery (AKR).

OBJECTIVES The aim of the study was to assess kidney function changes after transcatheter aortic valve replacement and their impact on long-term outcomes.

PATIENT AND METHODS In 432 patients (median age, 83 years; female sex, 63.4%), estimated glomerular filtration rate (eGFR) was measured before and after the procedure. Chronic kidney disease was defined as a prior diagnosis or baseline eGFR of less than 60 ml/min/1.73 m^2. Median (interquartile range [IQR]) follow-up was 44.7 (31.2–48) months.

RESULTS Overall, 66.7% of patients had CKD. An increase in eGFR of 10% or greater at 48 hours (median [IQR], 39.8% [26.2%–51.8%]) was observed in 55.2% of patients with CKD and lasted until discharge (31.8% [17.8%–49%]) in 35.8% (the AKR group). In 17.4% of patients (64.3% with CKD), there was a drop in eGFR of 10% or greater at 48 hours, which remained at discharge in 6.5% of patients (the AKI group; median [IQR] eGFR drop, –22.8% [–40.6% to –14.9%] and –22.8% [–37.5% to –16.2%], respectively). There was a stepwise increase in AKR prevalence from CKD stage 1 and 2 (11.5%) to 4 (52%) ($P = 0.03$). In-hospital mortality ($P = 0.01$) was highest with AKI (10.7%); intermediate with CKD but no AKR (6.6%); and lowest with neither CKD nor AKI (1.5%) or with AKR (1%). Estimated 4-year mortality was correspondingly different (46.9%, 47.2%, 25.5%, 35.4%, respectively; $P < 0.001$). The nonperipheral access was associated with more AKI and less AKR. Acute kidney recovery was more frequent with a history of stroke or transient ischemic attack or a newer generation self-expanding valves.

CONCLUSIONS Transcatheter aortic valve replacement led to acute kidney recovery in a substantial number of patients with CKD and an improved 4-year survival.

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INTRODUCTION Chronic kidney disease (CKD) is frequent in patients treated with transcatheter aortic valve replacement (TAVR; 70%)[1] with a stepwise increase in subsequent mortality (early and long-term) with decreasing estimated glomerular filtration rate (eGFR).[1,2] Acute kidney injury (AKI) occurs after successful TAVR in 3.4% to 57% of patients, is more frequent in those with lower baseline eGFR, and adds to an early and 1-year mortality.[3,4] Although CKD is usually irreversible and progressive, an improvement in eGFR of 25% or greater at 48 hours after TAVR was found in every fourth of those with baseline eGFR of 60 ml/min/1.73 m^2 or less.[5] The average increase in eGFR found immediately after TAVR was 8% to 17% and was maintained at 1 and 6 months of follow-up, especially for more advanced CKD stages.[6,7] There are only 2 studies providing conflicting results regarding the long-term clinical impact of acute kidney recovery (AKR) after TAVR: 1) one

WHAT'S NEW?

Chronic kidney disease (CKD), frequent among patients treated with transcatheter aortic valve replacement (TAVR; 70%), has a profound impact on mortality. TAVR can improve kidney function, that is, can lead to acute kidney recovery (AKR). We documented the independent prognostic value of AKR after TAVR in a long-term follow-up implementing AKR definition relying on an increase in estimated glomerular filtration rate (eGFR) that persists till the discharge, which is vital for proper analysis. Successful TAVR led to an increase in eGFR of 10% or greater after the procedure in 55.2% of patients with CKD, lasting until discharge in only 35.8% of patients (AKR). In 17.4% of all patients, there was a drop in eGFR of 10% or greater at 48 hours after TAVR that persisted at discharge in 6.5% of patients (acute kidney injury, AKI). Those with CKD and AKR had improved in-hospital and long-term outcomes that were similar to the most favorable prognosis of those with neither CKD nor AKI. Both phenomena remained predictive even after adjustment for other risk factors.

reported a 10% or greater increase in eGFR at 30 days postprocedure in 42% of those with baseline eGFR of 60 ml/min /1.73 m^2 or less, but without any favorable effect on 30-day-to-12-month mortality (selected patients from PARTNER-1 [Placement of Aortic Transcatheter Valve Trial 1]); and 2) the other reported serum creatinine decrease of 0.3 mg/dl or greater in 37% of patients within 7 days after TAVR that was associated with 13.2% lower 1-year mortality.[8,9] The present report analyzes long-term (>1 year) outcomes of patients with early (48 hours) signs of AKI or AKR that were sustained when analyzed again at discharge along with clinical correlates of AKI or AKR.

PATIENTS AND METHODS Out of 445 consecutive patients treated between August 2009 and October 2017, after excluding patients with failed device implantation (n = 8) or death at day 0 (n = 5), there were 432 patients with TAVR success. All patients were qualified by the Heart Team and signed informed consent, and the study complied with the Declaration of Helsinki and was approved by the local ethics committee.

From the hospital database, we retrospectively retrieved serial eGFR measurements calculated at baseline, at 48 hours after the procedure, and at discharge. Creatinine levels were measured at least once daily during an intensive care unit stay and at the physician's discretion thereafter using the Cobas C501 analyzer (F. Hoffmann-La Roche AG, Basel, Switzerland).

Estimated glomelural filtration rate was calculated by the MDRD equation: eGFR = 186 × (plasma creatinine level [in mg/dl] – 1.154 × (age [in y]) – 0.203. For women, the product of this equation was multiplied by 0.742.[10]

Relative changes in eGFR were calculated as follows: Δ% eGFR = 100% × (eGFR measured at 48 hours post-TAVR and at discharge or the latest results prior to death / baseline) – 100%. AKI was defined as a decrease in eGFR of 10% or greater at 48 hours persisting at the time of discharge; AKR was defined as an increase of 10% or greater at 48 hours persisting at discharge.[9,11] Patients with CKD either had a history of CKD or a decreased baseline eGFR of less than 60 ml/min/1.73 m^2. Patients with CKD were stratified: stage 1 and 2 (eGFR ≥60 ml/min/1.73 m^2); stage 3 (eGFR 30–60 ml/min/1.73 m^2); stage 4 (eGFR 15–30 ml/min/1.73 m^2); and stage 5 (eGFR <15 ml/min/1.73 m^2 plus those treated with renal replacement therapy). We divided patients into the following groups: 1) no CKD and no AKI; 2) AKR in patients with pre-existing CKD; 3) patients with pre-existing CKD and neither AKI nor AKR; and 4) AKI regardless of pre-existing renal function.

Data regarding baseline clinical characteristics, and procedural variables were prospectively gathered. In-hospital outcomes were prospectively collected in accordance with the standardized end-point definitions by VARC-2. All patients were followed on regular periodic visits. Survival status and date of death were obtained from both the National Registry of Population and the valve policlinic. The primary endpoints were all-cause 1-year and 4-year mortality with 100% follow-up at 12 and 24 months, 88.4% at 36 months, and 82.4% at 48 months.

Patients underwent pre- and postprocedural echocardiography for maximal and mean aortic valve gradients, valve area, and left ventricle ejection fraction (LVEF). Electrocardiography-gated computed tomography was used for access site selection and valve sizing (SOMATOM®, Siemens Healthineers, Erlangen, Germany). Coronaries were examined.

The procedure was performed as previously described.[12] TAVR was performed with either a self-expandable supra-annular device, early generation CoreValve or newer generation Evolut R or Evolut PRO (CoreValve ReValving Technology, Medtronic Inc., Minneapolis, Minnesota, United States); Acurate neo (Boston Scientific Corporation, Maple Grove, Minnesota United States); or Engager (Medtronic, Inc.); a balloon expandable early generation Edwards SAPIEN or SAPIEN XT or newer generation SAPIEN 3 (Edwards Lifesciences, Irvine, California); or a new-generation self-expanding intra-annular Lotus Edge Aortic Valve System (Boston Scientific Corporation).[13]

Statistical analysis Categorical data were presented as numbers and frequencies and compared with the χ^2 test or the Fisher exact test. The 1-sample Kolmogorov–Smirnov test was used to verify distribution (normal vs nonuniform) of continuous parameters. Normally distributed variables were compared using the *t* test and the Fisher analysis of variance. The Mann–Whitney test and the Kruskal–Wallis analysis of variance were used for comparisons of variables with nonnormal distributions. All continuous variables were presented as medians and interquartile ranges (IQRs). Demographic, clinical, and procedural characteristics as well

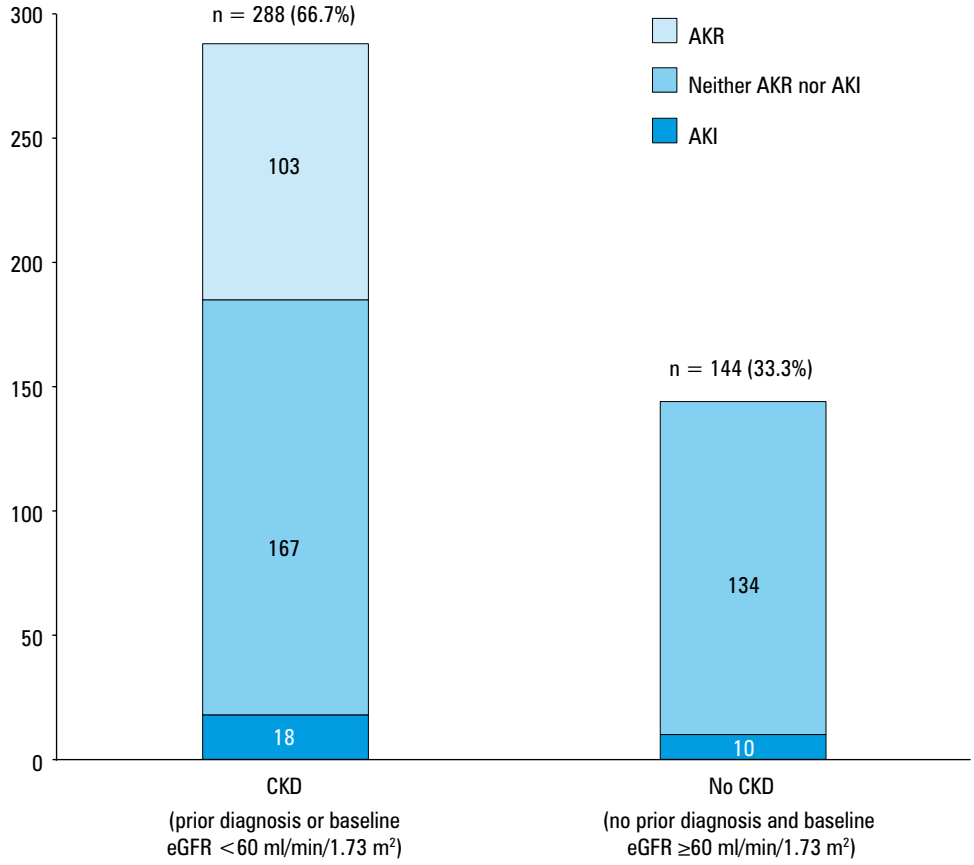

FIGURE 1 Number of patients stratified by chronic kidney disease and acute kidney injury or acute kidney recovery. Abbreviations: AKI, acute kidney injury; AKR, acute kidney recovery; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

as echocardiographic parameters were used to search for independent predictors of AKI or AKR and long-term all-cause mortality. The binary logistic regression was used to search for correlates of AKI or AKR and entry criteria for multivariable model was *P* value of less than 0.15 in the univariable analysis (due to the low assumed incidence of AKI and overall limited study population). Independent long-term all cause-mortality predictors were identified using the Cox proportional hazards regression and entry criteria for multivariable model was a *P* value of less than 0.05 in the univariable analysis. The predictive importance on mortality of the study categories of patients (CKD but neither AKR nor AKI, AKI, and AKR) was analyzed in reference to the prognosis of the no-CKD-and--no-AKI group, in univariable and multivariable analysis. Importantly, predictive importance of AKR occurrence was additionally analyzed in the subset of patients with CKD. Cumulative survival rates were assessed using the Kaplan–Meier analysis, compared with the log-rank test, and adjusted for multiple comparison using the Bonferroni method. A *P* value of less than 0.05 was considered significant. The statistical analysis was performed using the Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, Illinois, United States).

RESULTS We included 432 patients with the median (IQR) age of 82 (77–85) years (range, 40–92 years). Most were female (63.4%), and most (67.6%) were categorized as surgical high-risk.

Overall, 288 patients (66.7%) had CKD, out of whom 26 (9%) had a prior CKD diagnosis, but baseline eGFR of 60 ml/min/1.73 m^2 or greater (stage 1 and 2 CKD). Out of 288 patients with CKD, 159 (55.2%) had an increase in eGFR of 10% or greater at 48 hours and 103 out of those patients (64.8%) had the same value persisting at discharge (the AKR group; 35.8% of those with CKD). There were 75 patients (17.4%) with a decrease in eGFR of 10% or greater at 48 hours and 28 patients (6.5%) with a decrease in eGFR of 10% or greater persisting at discharge (the AKI group; of whom 18 [64.3%] had CKD). Among 167 CKD patients, 58% had neither AKR nor AKI. Finally, there were 134 patients (31%) without CKD who did not have AKI (FIGURE 1).

The baseline eGFR was lowest in patients with CKD (especially those with AKR), intermediate in those with AKI (regardless of baseline kidney function), and highest in those without CKD and without AKI (TABLE 1). The percentage increase in eGFR at 48 hours was greater in those with AKR versus those with an increase in eGFR of 10% or higher at 48 hours that was not sustained at discharge (median [IQR], 39.8% [26.2%–51.8%] vs 30.7% [17.6%–41.7%]; *P* = 0.048, respectively). The percentage decrease in eGFR was similar between those with AKI as compared with those with a decrease in eGFR of 10% or greater at 48 hours that was not sustained at discharge (median [IQR], –22.8% [–40.6% to –14.9%] vs –22.3% [–35.7% to –16.3%]; *P* = 0.43, respectively).

There was a stepwise increase in the rate of AKR from CKD stage 1 and 2 (3 out of 26

TABLE 1 Comparison of baseline demographic and clinical characteristics with pre- and postprocedural echocardiographic parameters in the study groups

Characteristic	No CKD, no AKI (n = 134)	AKR (n = 103)	CKD, no AKR, no AKI (n = 167)	AKI (n = 28)	*P* value
Estimated glomerular filtration rate					
At baseline, ml/min/1.73 m^2	73.1 (67.1–83)	46.3 (37.5–53.6)	46.8 (38.2–55.7)	62.2 (46.4–74.8)	<0.001
At 48 hours, ml/min/1.73 m^2	84.8 (72.1–90)	62.6 (52.3–75.3)[a]	48.5 (33.7–61.3)	40.9 (32.6–60.6)[b]	<0.001
% change at 48 hours	6.3 (0–17.4)	39.8 (26.2–51.8)[a]	2.7 (–7.7 to 19.5)	–22.8 (–40.6 to –14.9)[b]	<0.001
At discharge, ml/min/1.73 m^2	76 (65.3–87)	61.5 (51.1–68.9)[a]	48.9 (38.5–57.3)	41.4 (34.3–57.3)[b]	<0.001
% change at discharge	0 (–8.5 to –11.5)	31.8 (17.8–49)[a]	0.1 (–7.4 to 8.9)	–22.8 (–37.5 to 16.2)[b]	<0.001
Baseline demographic and clinical characteristics					
Surgical high-risk	67 (50)	82 (79.6)	124 (74.3)	19 (67.9)	<0.001
Age, y	81 (76–85)	82 (78–85)	82 (78–86)	81 (75.5–85)	0.04
Female sex	83 (61.9)	68 (66)	107 (64.1)	16 (57.1)	0.82
Body mass index, kg/m^2	26 (23–29)	26.7 (24.3–31.2)	26.7 (24.2–29.4)	28 (25.9–32)[b]	0.02
Diabetes mellitus	40 (29.9)	37 (35.9)	69 (41.3)	14 (50)	0.1
Hypertension	97 (72.4)	84 (81.6)	132 (79)	20 (71.4)	0.3
Dyslipidemia	34 (25.4)	25 (24.3)	43 (25.7)	8 (28.6)	0.97
Previous stroke or TIA	9 (6.7)	25 (24.3)[a]	22 (13.2)	5 (17.9)	0.002
Peripheral vascular disease	18 (13.4)	15 (14.6)	16 (9.6)	3 (10.7)	0.6
Chronic obstructive lung disease	20 (14.9)	9 (8.7)	22 (13.2)	5 (17.9)	0.44
Previous cardiac surgery	26 (19.4)	20 (19.4)	32 (19.2)	7 (25)	0.91
Previous PCI	32 (23.9)	37 (35.9)	53 (31.7)	8 (28.6)	0.22
Previous MI	25 (18.7)	20 (19.4)	42 (25.1)	8 (28.6)	0.4
Atrial fibrillation	27 (20.1)	34 (33)	52 (31.1)	11 (39.3)	0.05
Pacemaker implanted	14 (10.4)	19 (18.4)	29 (17.4)	4 (14.3)	0.28
PCI within 90 days pre-TAVR	11 (8.2)	12 (11.7)	17 (10.2)	5 (17.9)	0.47
Echocardiographic parameters					
Index LVEF <50%	20 (14.9)	30 (29.1)	42 (25.1)	6 (21.4)	0.05
Baseline max AVG, mm Hg	84 (70.3–104.9)	81.6 (66–97)	84.1 (68.2–97.7)	83 (60–92)	0.58
Baseline mean AVG, mm Hg	52 (44–64.2)	50.3 (41.8–61.4)	50 (40.9–63.2)	49 (35.8–53.8)	0.44
Baseline AVA, cm^2	0.7 (0.54–0.8)	0.67 (0.5–0.8)	0.63 (0.53–0.8)	0.71 (0.53–0.86)	0.3
Post-TAVR max AVG, mm Hg	17.5 (12–23.3)	16 (12–20)	16 (12–22)	19 (10.1–28.8)	0.51
Moderate paravalvular leak	32 (23.9)	30 (29.1)	51 (30.5)	10 (35.7)	0.48

Data are presented as number (percentage) or median (interquartile range).

a *P* <0.05 for the comparison of patients with and without AKR (only in patients with CKD)

b *P* <0.05 for the comparison of patients with and without AKI

Abbreviations: AVA, aortic valve area; AVG, aortic valve gradient; LVEF, left ventricular ejection fraction; max, maximal; MI, myocardial infarction; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; others, see FIGURE 1

[11.5%]) to CKD stage 3 (85 out of 230 [37%]), to CKD stage 4 (13 out of 25 [52%]), followed by a drop in the rate of AKR in patients with CKD stage 5 (2 out of 7 [28.6%]; *P* = 0.03). On the other hand, AKI occurred more frequently in CKD stages 1 and 2 (6 out of 26 [23.1%]) and stage 5 (1 out of 7 [14.3%]) as compared to CKD stage 3 (4.8%, 11/230) and stage 4 (0; *P* = 0.004) (FIGURE 2).

Detailed serial values of eGFR (measured at baseline, after the procedure, and at discharge) are presented in Supplementary material (*Figures S1–S3*) and stratified by CKD stages.

Most patients with CKD (without or with AKR) and most with AKI were categorized as surgical high risk (TABLE 1). With regard to body mass index, patients without CKD had the lowest values, those with CKD (without or with AKR) had intermediate values, and those with AKI had the highest values. Diabetes mellitus was more frequent in patients with CKD (but less frequent in those with AKR), with the highest prevalence in those with AKI. Patients with AKR or patients with AKI most often had a history of stroke, transient ischemic attack (TIA), or atrial fibrillation. There were no differences in the severity and etiology of aortic stenosis between the study groups. However, LVEF of less than 50% was more common in patients with CKD and AKI.

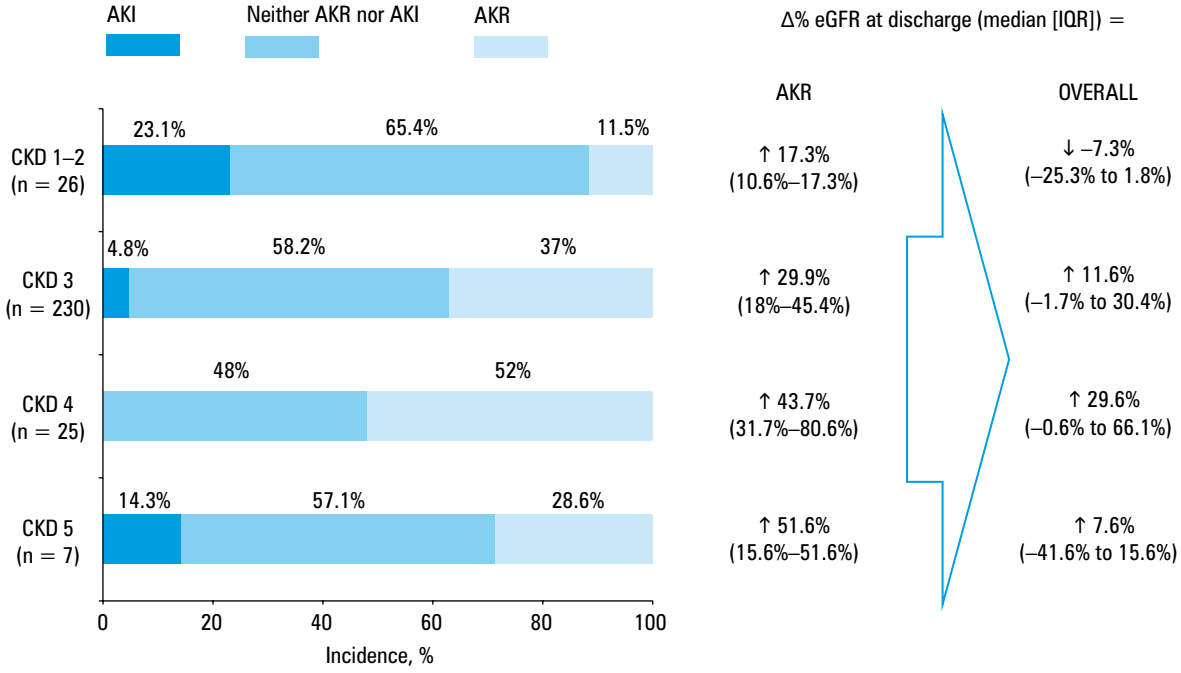

FIGURE 2 The incidence of acute kidney injury or acute kidney recovery in patients at different stages of chronic kidney disease, along with the corresponding percentage estimated glomerular filtration rate value measured at discharge (calculated separately for the acute kidney recovery subgroup and the overall patients group).
Abbreviations: IQR, interquartile range; others, see **FIGURE 1**

The transapical or direct aortic access was used more frequently in patients with AKI and less frequently in patients with AKR (35.7% vs 4.9%; P <0.001; **TABLE 2**). Patients with AKR more often had newer valve types, whereas those with AKI tended to have older valve types. Similarly, patients with CKD who had AKR were treated more often using newer generation of self-expanding valves (41.7% vs 21.4%; P = 0.049; **TABLE 2**). After adjustment for other confounders, the transapical or direct aortic access was associated with more frequent AKI and less frequent AKR. Also, patients with CKD and a history of stroke or TIA were more likely to have AKR (**TABLE 3**).

The median (IQR) follow-up was 44.7 (31.2–48) months. Overall, a combined VARC-2 safety endpoint was recognized in 117 patients (27.1%), with in-hospital and 1-year mortality rates of 3.9% (n = 17) and 17% (n = 58), respectively. Estimated 4-year mortality was 37.2%.

Life-threatening or disabling bleeding more often occurred in patients with AKI and less frequent in those with AKR (**TABLE 4**). In-hospital (P = 0.01) and 1-year mortality (P = 0.002) were highest in those with AKI (10.7% and 28.6%); intermediate in those with CKD but no AKR (6.6% and 18.6%); and lowest in those with neither CKD nor AKI (1.5% and 7.5%) or in those with AKR (1% and 8.7%) (**TABLE 4**). Interestingly, in-hospital and 1-year mortality rates in 28 patients with AKI were similar for those with (n = 18; 64.3%) and without (n = 10; 35.7%) prior CKD (11.1% vs 10% and 27.8% and 30%, respectively).

In a subgroup of 375 patients (86.8%) treated only via the transvascular access, in-hospital (P = 0.03) and 1-year mortality (P = 0.02) remained highest among those with AKI (5.6% and 22.2%); intermediate in those with CKD but not AKR (6.4% and 18.6%); and lowest in patients with neither CKD nor AKI (0.8% and 7.6%) or in those with AKR (1% and 9.2%).

Estimated 4-year mortality rates remained the highest in patients with AKI and lowest in those with neither CKD nor AKI (**FIGURE 3**). Those with CKD and neither AKI nor AKR also had a similarly unfavorable prognosis, unlike patients with AKR whose outcome was significantly better (P = 0.03) and was similar to those with neither CKD nor AKI (P = 0.6). Chronic kidney disease and AKI were both independent correlates of a higher long-term mortality when comparing prognosis to the no-CKD-no-AKI group. Patients with AKR had similar prognosis to the no-CKD-no-AKI group of most favorable outcome (**TABLE 5**). In the analysis of the subgroup of patients with CKD after adjustment for other identified predictors of all-cause 4-year mortality in the multivariable analysis, AKR was associated with improved prognosis (hazard ratio, 0.603; 95% CI, 0.402–0.904; P = 0.01).

DISCUSSION The main findings of this study can be summarized as follows: 1) Successful TAVR led to a substantial (≥10%) increase in eGFR early after the procedure in 55.2% of patients with CKD, but was often transient, lasting until discharge in only 35.8% (AKR) with a substantial median (IQR) eGFR increase of 31.8% (17.8%–49%). 2) Conversely, in 17.4% of all patients after a successful TAVR, there was a drop in eGFR of 10% or greater at 48 hours that persisted at discharge in 6.5% (AKI) with a substantial median (IQR) eGFR decrease of –22.8% (–37.5% to –16.2%).

TABLE 2 Comparison of the procedural characteristics between the study groups

Procedural characteristics	No CKD, no AKI (n = 134)	AKR (n = 103)	CKD, no AKR, no AKI (n = 167)	AKI (n = 28)	*P* value
ASA preloading alone	89 (66.4)	67 (65)	109 (65.3)	17 (60.7)	0.95
ASA plus clopidogrel preloading	29 (21.6)	21 (20.4)	30 (18)	6 (21.4)	0.87
Transfemoral access	109 (81.3)	94 (91.3)[a]	126 (75.4)	17 (60.7)[b]	0.002
Subclavian access	9 (6.7)	4 (3.9)	14 (8.4)	1 (3.6)	
Transaxillary access	1 (0.7)	0	0	0	
Transapical access	13 (9.7)	3 (2.9)	24 (14.4)	7 (25)	
Direct aortic access	2 (1.5)	2 (1.9)	3 (1.8)	3 (10.7)	
Transapical or direct aortic access	15 (11.2)	5 (4.9)[a]	27 (16.2)	10 (35.7)[b]	<0.001
Nominal valve diameter, mm	26 (26–29)	26 (25–29)	26 (26–29)	29 (25.3–29)	0.72
Self-expanding valve	81 (60.4)	74 (71.8)[a]	92 (55.1)	17 (60.7)	0.06
Newer generation valves	46 (34.3)	51 (49.5)	64 (38.3)	9 (32.1)	0.09
Newer generation self-expanding valves	35 (26.1)	43 (41.7)[a]	45 (26.9)	6 (21.4)	0.11
Predilatation	83 (61.9)	62 (60.2)	96 (57.5)	15 (53.6)	0.79
Postdilatation	28 (20.9)	27 (26.2)	35 (21)	7 (25)	0.72
Surgical access	18 (13.4)	19 (18.4)	22 (13.2)	3 (10.7)	0.58
Surgical closure	26 (19.4)	23 (22.3)	35 (21)	4 (14.3)	0.8
Contrast agent volume, ml	200 (150–200)	200 (130–200)	200 (133–200)	200 (100–200)	0.92
Fluoroscopy time, min	29 (20.3–37.9)	28 (22–36.1)	27.9 (20.2–34.9)	27.5 (19.1–46.9)	0.66
Radiation, mGy	1212 (736–2047)	1151.5 (734–2165.8)	1230 (781.3–1863.5)	1252.5 (797.4–2373.5)	0.95

Data are presented as number (percentage) or median (interquartile range).

a *P* <0.05 for the comparison of patients with and without AKR (only in patients with CKD)

b *P* <0.05 for the comparison of patients with and without AKI

Abbreviations: ASA, acetylsalicylic acid; others, see **FIGURE 1**

TABLE 3 Correlates of acute kidney injury or acute kidney recovery

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
AKI						
Body mass index	1.066	0.994–1.143	0.08	1.068	0.988–1.155	0.1
Diabetes mellitus	1.767	0.82–3.809	0.15	1.434	0.63–3.263	0.39
Transapical/direct aortic access	4.22	1.839–9.684	0.001	4.253	1.794–10.083	<0.001
LT/D bleeding	2.327	0.753–7.191	0.14	1.704	0.521–5.574	0.38
AKR[a]						
Stroke or TIA history	1.96	1.063–3.615	0.03	2.032	1.082–3.818	0.03
Transapical or direct aortic access	0.227	0.086–0.599	0.001	0.265	0.098–0.717	0.009
Newer generation self-expanding valves	1.935	1.164–3.218	0.01	1.668	0.998–2.855	0.053

a Analyzed only for the subset of patients with CKD

Abbreviations: HR, hazard ratio; LT/D, life-threatening or disabling; others, see **FIGURE 1**

3) Chronic kidney disease remained a potent risk factor for increased early and long-term mortality; however, patients with CKD and AKR had improved in-hospital and long-term outcomes which were similar to the most favorable prognosis of those with neither CKD nor AKI. 4) Occurrence of AKI was an independent predictor of death, whereas AKR remained predictive of improved long-term survival.

Our results confirm observations indicating higher prevalence of coronary and cerebrovascular diseases in patients with aortic stenosis and concomitant CKD, along with more atrial fibrillation and lower LVEF, all indicating that hemodynamic abnormalities in the setting of aortic stenosis may contribute to renal dysfunction in patients with risk factors for CKD (cardiorenal syndrome).[14]

In a recent study, 52% of TAVR patients with baseline eGFR of 60 ml/min/1.73 m^2 or less had an increase in eGFR of 10% or greater at discharge.[11] In another analysis of 821 patients from

TABLE 4 Comparison of in-hospital events in the study groups according to preceding chronic kidney disease and acute kidney injury or acute kidney recovery occurrence

VARC-2 endpoints	No CKD, no AKI (n = 134)	AKR (n = 103)	CKD, no AKR, no AKI (n = 167)	AKI (n = 28)	*P* value
LT/D bleeding	13 (9.7)	3 (2.9)	11 (6.6)	4 (14.3)	0.1
Major bleeding	24 (17.9)	16 (15.5)	33 (19.8)	3 (10.7)	0.62
Minor bleeding	45 (33.6)	35 (34)	59 (35.3)	13 (46.4)	0.62
Any red blood cell transfusion	42 (31.3)	31 (30.1)	60 (35.9)	14 (50)	0.2
Major vascular complications	30 (22.4)	17 (16.5)	29 (17.4)	3 (10.7)	0.41
Minor vascular complications	44 (32.8)	32 (31.1)	61 (36.5)	14 (50)	0.27
Stroke	2 (1.5)	3 (2.9)	2 (1.2)	1 (3.6)	0.66
New permanent pacemaker	20 (14.9)	14 (13.6)	39 (23.4)	4 (14.3)	0.12
In-hospital mortality	2 (1.5)	1 (1)	11 (6.6)	3 (10.7)	0.01
1-year overall mortality	10 (7.5)	9 (8.7)	31 (18.6)	8 (28.6)	0.002

Data are presented as number (percentage).

Abbreviations: VARC-2, Valve Academic Research Consortium 2; others, see FIGURE 1 and TABLE 3

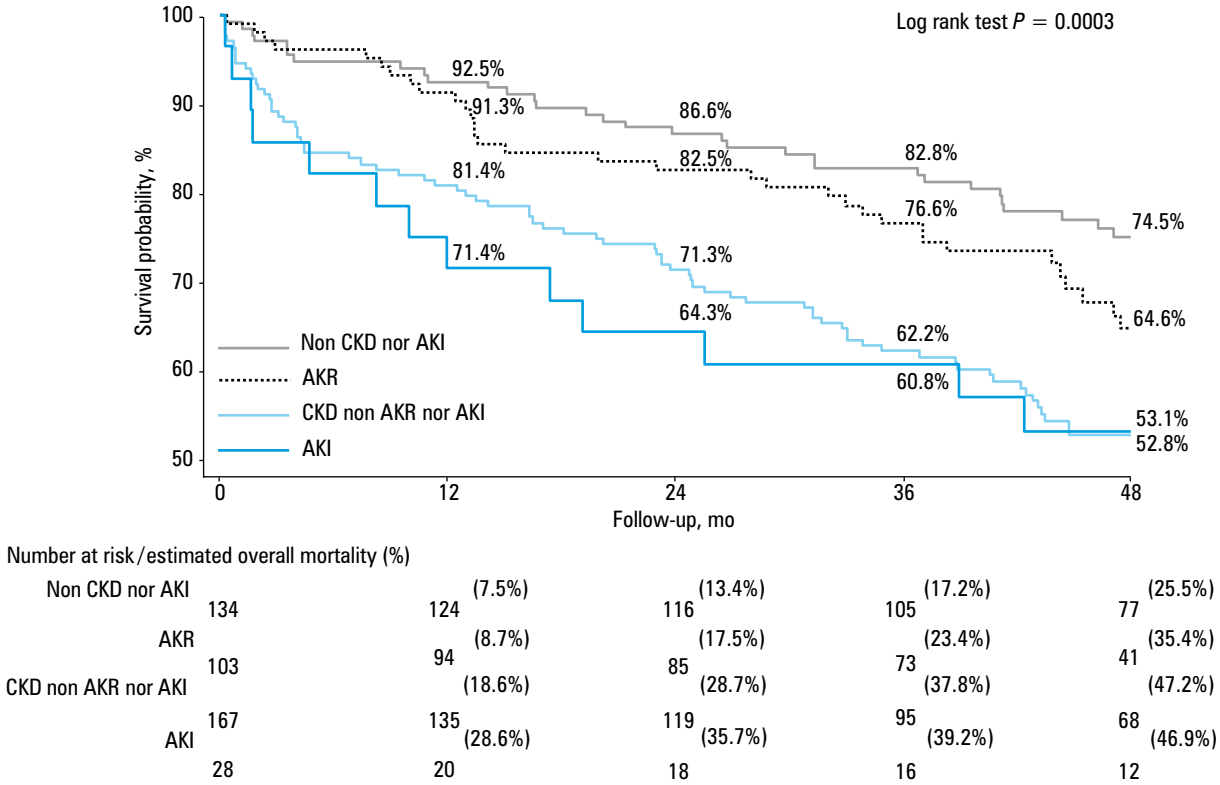

FIGURE 3 Survival curves in the study population
Abbreviations: see FIGURE 1

the PARTNER-1 or the Continued Access Registry, 42% had an improvement in eGFR of 10% or greater at 30 days, whereas 23.9% had a worsening in eGFR of 10% or greater. The increase in eGFR was not associated with improved 1-year outcomes, and worsening of eGFR was associated with increased mortality.[9] In 4 other studies,[5,8,9,11] the clinical effect of AKR was analyzed regardless of a prior CKD diagnosis or a decreased baseline eGFR with only 5.6% of those randomized to TAVR in the PARTNER-1 having creatinine levels higher than 2 mg/dl.[1,9] In another analysis of 204 patients treated with TAVR, serum creatinine decrease of 0.3 mg/dl or greater was identified in 37% of patients within 7 days after TAVR and was associated with an improved 1-year survival; but the analysis included patients without prior CKD and renal improvement was not an independent correlate of a better outcome.[8]

Acute changes in cardiac function have been associated with improved 1-year survival after TAVR; however, this was lost during more prolonged follow-up when the Society of Thoracic Surgeons score became a potent predictor of survival, suggesting that noncardiac comorbidities could mask the beneficial effect of improved

TABLE 5 Predictors of all-cause 4-year mortality

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Male sex	1.568	1.14–2.156	0.006	1.475	1.066–2.041	0.02
Index LVEF <50%	1.739	1.234–2.451	0.002	1.424	0.989–2.05	0.06
Surgical high-risk	1.757	1.206–2.562	0.003	1.398	0.936–2.087	0.1
Atrial fibrillation	1.48	1.063–2.061	0.02	1.256	0.894–1.765	0.19
COPD	1.625	1.085–2.433	0.02	1.363	0.898–2.07	0.15
LT/D bleeding	2.405	1.471–3.934	<0.001	2.552	1.625–4.009	<0.001
CKD but neither AKR nor AKI[a]	2.289	1.514–3.46	<0.001	2.209	1.444–3.380	<0.001
AKI[a]	2.416	1.268–4.604	0.007	2.462	1.283–4.725	0.007
AKR[a]	1.427	0.877–2.321	0.15	–	–	–

a Analyzed in reference to the prognosis of the no-CKD-no-AKI group

Abbreviations: COPD, chronic obstructive pulmonary disease; others, see FIGURE 1 and TABLE 3

cardiac physiology.[15] Our analysis indicated that acute improvement in eGFR could reflect immediate hemodynamic improvement after TAVR that resulted in a better survival during follow-up longer than 1 year to outweigh the deleterious impact of other noncardiac comorbidities seen with a higher STS score or EuroSCORE (eg, hypertension, diabetes mellitus, peripheral and coronary artery disease).[15] Lack of AKR after TAVR may represent irreversibly decreased renal functional reserve to serve as a "failed renal stress test" and a risk factor for future loss of kidney function, cardiovascular disease, and death, rather than playing a causative role.[16]

Patients in whom serum creatinine levels returned to baseline after an episode of AKI are at a lower risk of long-term adverse events as compared with those with a sustained elevation in serum creatinine levels.[16] Currently, in a substantial number of patients, an increase or decrease in eGFR of 10% or greater early after TAVR was transient and did not persist until discharge.

Acute kidney recovery was more likely to occur in patients with more frequent history of stroke or TIA, thus with probably more advanced vascular disease and renal dysfunction due to substantial hemodynamic compromise,[17] as well as in patients treated with newer generation self-expanding valves. Less bulky delivery systems allowed successful peripheral access in patients who had been previously scheduled for a transapical or transaortic procedure; and smaller atheroma dislodgement from the aortic wall and less traumatic aortic valve lumen gain with smaller release of atherosclerotic debris may have lowered the risk of embolization to the renal arteries.[18] On the other hand, self-expanding valves are chosen by operators for patients with a less calcified target site and in that way may indicate patients with a more favorable long-term prognosis because less calcium is associated with less overall burden of atherosclerotic disease. Those with a sustained improvement in eGFR (AKR) had the lowest baseline eGFR (more advanced CKD) and had the greatest early increase in eGRF indicating that aortic stenosis contributed to a baseline decrease in renal function and that hemodynamic improvement was a major mechanism of AKR. Out of 32 patients with advanced CKD (stage 4 and 5), there were 15 (46.9%) with AKR, with an increase in eGFR of 50% at discharge.[19]

Acute kidney injury was more frequent in patients with higher body mass index. It tended to be more frequent in patients with diabetes mellitus, atrial fibrillation, or prior stroke or TIA, indicating importance of the atherothrombotic profile increasing the risk of AKI.[6,18,20] The early (48 hours) percentage decrease in eGFR did not differ between those with sustained or transient renal function worsening, indicating a complex interplay between 1) absolute extent of periprocedural renal injury, 2) magnitude of the initial hemodynamic disturbances in addition to baseline renal function impairment, and 3) extent of renal reparatory potential immediately after TAVR. The incidence of life-threatening or disabling bleeding associated with increased mortality[21] was low but numerically higher in the group of patients with AKI ($P = 0.1$). Hemodynamic disturbances reducing perfusion of the kidneys associated with bleedings were shown to be a strong predictor for AKI,[22] and therefore, might have contributed to the worsening of the kidney function in some patients.

This was a single-center retrospective study with a limited number of patients particularly in the subgroup analysis; however, all data were obtained in a systematic manner. The diagnostic workup of AKI was based solely on eGFR and not on urine output. Glomerular filtration rate was not measured directly and eGFR calculation was based on the serum creatinine level that can be affected by muscle mass, age, sex, or race.[23] Also, there were no data on pharmacological therapy of patients.

A substantial increase in eGFR at 48 hours after TAVR that lasted until discharge was seen in 35.8% of patients with chronic kidney disease, indicating AKR that led to a significantly lower in-hospital and 4-year mortality, thus TAVR may

be the preferred treatment in patients with aortic stenosis and CKD. The described correlates of AKR contribute to a better understanding of the disease mechanisms and thus help to better select candidates for TAVR.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT ŁK conceived the concept of the study. ŁK, KZ, GSM contributed to the design of the research. All authors were involved in data collection. ŁK, KZ, and IK analyzed the data. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST M. Dąbrowski received speaker honoraria from Boston Scientific and personal fees from Boston Scientific, Medtronic and Edwards Lifesciences. AW is a proctor of Medtronic and Edwards Lifesciences and received speaker honoraria from Abbott, Boston Scientific, and Edwards Lifesciences. Other authors declare no conflict of interest.

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