Recovery of Kidney Dysfunction After Transcatheter Aortic Valve Implantation (from the Northern New England Cardiovascular Disease Study Group)

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Acute Kidney Recovery (AKR) is a potential benefit of transcatheter aortic valve implantation (TAVI). We determined the incidence and predictors of AKR in a multicenter prospective registry of TAVI. After excluding patients on dialysis or who died within 48 hours postprocedure, we reviewed 1,502 consecutive patients underwent TAVI in Northern New England from 2012 to 2017. Patients were categorized into 3 groups based on the change in postprocedure estimated glomerular filtration rate (eGFR): Acute Kidney Injury (AKI, decrease in eGFR >25%), AKR (increase in eGFR >25%) or no change in kidney function on discharge creatinine following TAVI. We then focused in patients with baseline chronic kidney disease (CKD defined as eGFR ≤60 ml/min; n = 755) and developed multivariate predictor models to determine the clinical and procedural variables associated with AKR. For the TAVI cohort (n = 1,502), the overall incidence of AKR was 17.8%. AKR was threefold higher in patients with eGFR ≤60 ml/min as compared to those with eGFR >60 ml/min (26.6% vs 8.9%, p < 0.001). In the CKD population, hospital complications were similar among patients with no change in renal function and AKR; patients with AKI had a higher rate of hospital mortality, pacemaker implantation, length of hospitalization, and transfusions. Using multivariable logistic regression, moderate to severe lung disease, eGFR < 50 ml/min and previous aortic valve surgery were found to be independent predictors of AKR. Patients with diabetes mellitus, baseline anemia, and Society of thoracic surgeons score >6.1 were less likely to develop AKR. In conclusion, AKR occurred in 1 of 4 of all TAVI patients with baseline CKD and was a more frequent phenomena than AKI. Patients with decreased lung function, previous aortic valve surgery and worse baseline renal function were more likely to demonstrate AKR, whereas patients with diabetes mellitus, baseline anemia, and higher Society of thoracic risk scores were less likely to see improvements in renal function after TAVI. **(Am J Cardiol 2019;123:426−433)**

Early experience with transcatheter aortic valve implantation (TAVI) focused upon feasibility, safety, and improved mortality compared to medical therapy.[1] We have recently described a secondary benefit of TAVI that may portend clinical significance: acute kidney recovery (AKR).[2] We hypothesized that chronic severe aortic stenosis can lead to chronic left ventricular pressure overload, high left ventricular filling pressures, systemic venous congestion, and decreased renal blood flow, causing type II cardiorenal syndrome. Thus, TAVI mediated correction of aortic stenosis with potential improvement in cardiac output[3,4] may lead to improvement in renal plasma flow and filtration fraction,[5] a decrease in renal congestion and subsequent improvement in renal function in patients after TAVI. This improvement would be manifest as an acute improvement in estimated glomerular filtration rate (eGFR) especially among patients with evidence of chronic kidney disease (CKD). In our previous single center study, we demonstrated that one-third of patients underwent TAVI had 25% or more improvement in their eGFR within 48 hours of the procedure. Our work complements an analysis of the PARTNER trial demonstrating improvement in post-TAVI renal function at later time points (30 days and 1 year).[6] We sought to expand upon previous single center registry designs to confirm and obtain a robust, generalizable estimate of AKR in the first large, multicenter prospective registry and to identify the clinical and procedural variables associated with the development of AKR.

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See page 432 for disclosure information.

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Methods

We examined data from the Northern New England Cardiovascular Disease Study Group (NNECDSG). The NNECDSG is a multicenter, voluntary, regional collaborative of 7 interventional cardiology and cardiac surgery programs in northern New England. Registry data are validated against hospital billing data every 2 years for complete capture of cases and to ensure the accuracy of data for vital status at discharge. The NNECDSG registry collects data on patient characteristics including co-morbidities, cardiac history, cardiac anatomy and function, procedural indication, priority, process, and hospital outcomes.

One thousand five hundred fifty-three consecutively enrolled patients underwent clinically indicated TAVI 2012 to 2017 and were at intermediate, high, or extreme risk for surgical aortic valve replacement determined based on Society for Thoracic Surgeons (STS) mortality risk score as well as independent evaluation by the heart team. All patients had complete baseline and discharge renal function data except for 2 patients that were excluded from the analysis. As we sought to determine changes in kidney function at the time of discharge, patients were excluded if they had baseline end-stage renal disease on dialysis (n = 40) or died within 48 hours (n = 14; Figure 1). We then focused on patients with baseline CKD (defined as eGFR ≤60 ml/min) for the multivariable analysis: thus, the predictors of AKR are identified after excluding 747 patients without baseline CKD**;** Figure 1).

Detailed data on demographics, past medical history, coronary anatomy and function, procedural indications, and hospital outcomes were collected using a standardized reporting form as previously described for the STS/ACC TVT Registry; all data definitions were as detailed in the TVT data dictionary.[7] All data are verified by chart review until hospital discharge by a dedicated quality assurance nurse. Access approach, TAVI valve choice, hydration protocols, and contrast limits were left to the discretion of the operator. The definitions applied in this analysis were consistent throughout the study period. There is no standardized definition of AKR as it is a newly described phenomena: AKR has been previously defined by our group as a positive change in eGFR of ≥25% at 48 hours after TAVI.[2] As the Northern New England Cardiovascular Study Group did not have access to uniform 48 hours renal function assessment, we utilized a variation on this definition of eGFR ≥25% at hospital discharge. We used a definition of AKI to mirror that of AKR: eGFR reduction of ≥25% at hospital discharge.

All patients underwent TAVI received either balloon expandable Edwards SAPIEN transcatheter heart valve (Edwards Lifesciences, Irvine, California) or self-expandable Medtronic CoreValve (Medtronic Incorporation, Minneapolis, Minnesota) for clinical indications. The prosthesis sizes were determined using preprocedural echocardiographic and multislice computed tomography angiogram findings. The TAVI devices were delivered through femoral, apical, subclavian, or transaortic approaches, with the femoral approach comprising over 80% of the cohort. Presence or absence of baseline CKD was determined from the baseline eGFR calculated using the CKD Epidemiology Collaboration equation.[8] Patients with eGFR ≤60 ml/min/1.73 m^2 were considered to have CKD and received hydration protocol to potentially reduce AKI as per individual institutional protocols.

The incidence of AKR and AKI after TAVI was calculated. Hospital and 30-day all-cause mortality were compared

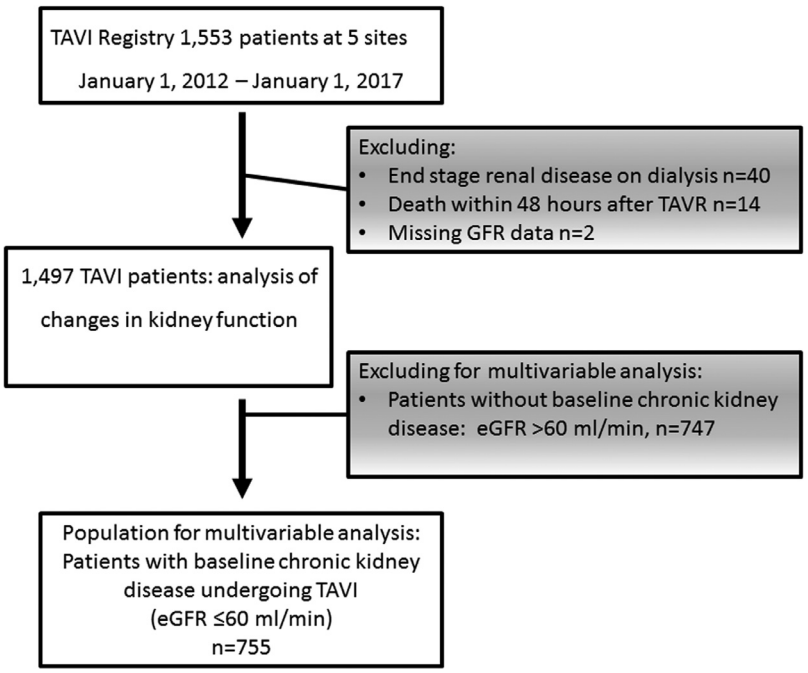

Figure 1. Patient flow diagram and study design. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; TAVI = transcatheter aortic valve implantation.

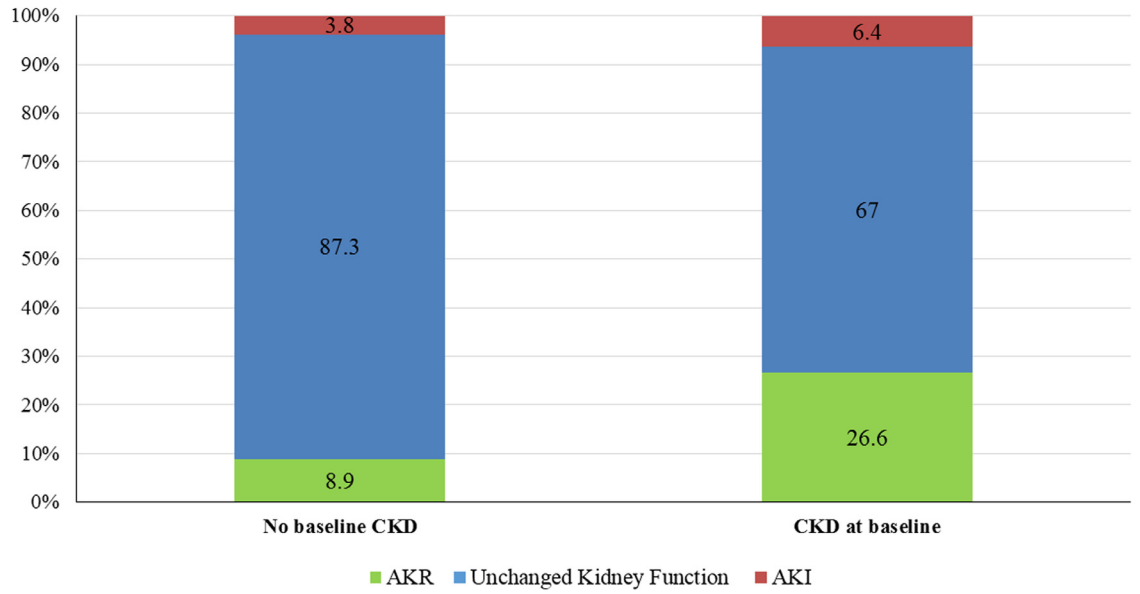

Figure 2. Dynamic acute kidney changes among 1,502 consecutive patients who underwent TAVI. AKI = acute kidney injury; AKR = acute kidney recovery; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; TAVI = transcatheter aortic valve implantation.

among 3 groups. Length of stay in each group was recorded. Frequency of renal failure requiring dialysis, rate of permanent pacemaker requirement post-TAVI, major bleeding complication, packed red blood cell transfusion, transient ischemic attack, and stroke were also compared. Variables were summarized using means, standard deviations, or percentages. Overall group comparisons of baseline demographics and medical histories, baseline laboratory and medications, echocardiographic, and procedural characteristics were conducted. These measures were subsequently compared between patients with AKR (≥25% improvement in eGFR) and AKI (≥25% worsening in eGFR) where in both cases the unchanged renal function patients served as the reference group in all multivariate logistic regression models. Categorical variables were reported as percent with a chi-square test and continuous variables as median values tested using the Wilcoxon rank sum test. The initial models utilized variables, which were observed to have a $p < 0.10$ overall from the demographics and medical history, labs, and medications and procedural data. A multivariable model was generated for predictors of AKR among patients with CKD (eGFR ≤60 cc/min) using univariate predictors with p value <0.10. This included age, contrast volume, clinical presentation, body mass index, diabetes mellitus, heart failure within 2 weeks, baseline GFR, CKD, hemoglobin, gender, current smoking, baseline ejection fraction, and moderate to severe lung disease. Adjusted odds ratio (OR) were derived using multivariable logistic regression models. For all variables, a p value <0.05 was considered to be statistically significant. All p values are 2-sided. Data were analyzed using the statistical software package Stata 14.2 (Stata Corp, College Station, Texas).

Results

For the entire analyzed cohort of 1,497 patients, AKR was observed in 17.8% of patients and AKI was demonstrated in 5.1% of patients. The occurrence of AKR was strongly associated with baseline CKD: 8.9% for patients with GFR >60 as compared to 26.6% in patients with GFR <60, p <0.001; Figure 2). The greatest incidence of AKR was observed in patients at the highest risk for AKI: those with GFR ≤30 cc/min (Figure 3). Notably AKR was fourfold more frequent than AKI among these patients with the worst baseline renal dysfunction. Among the 755 patients with baseline CKD, approximately 1 in 4 (26.6%) developed AKR, 2 of 3 had no change in renal function, and 6% developed AKI before discharge.

The baseline clinical characteristics, laboratory data, and procedural information of patients with baseline CKD are summarized in Table 1. Approximately three-quarters of the patients were elderly (>75 years of age), and half of the patients were female. Diabetes mellitus was common and valve in valve procedures occurred in 10% of the population. The median STS risk score was 6.1% (interquartile range 4.1 to 9.1%). Approximately 4% of patients underwent percutaneous coronary intervention within 2 weeks before TAVI. Approximately 80% of patients underwent TAVI from a femoral approach and 80% were treated with an Edwards balloon expandable valve. Baseline left ventricular systolic dysfunction was present in 1 out of 4 patients. Patients with AKR were less likely to have diabetes mellitus and had a higher baseline mean aortic valve gradient. Patients who developed AKI had higher rates of diabetes mellitus (58% vs 34% in AKR group, $p = 0.002$). Baseline anemia was present in 72% of TAVI patients with CKD and was more common among patients with AKI than AKR (81.3 vs 64.2%, $p = 0.007$). Patients with AKR received less contrast volume than patients with AKI: 130 ± 84 ml versus 98 ± 52 ml in AKR group, $p = 0.003$).

In patients who developed AKR, mean eGFR increased from 41 ± 13 ml/min from baseline to 62.0 ± 16 ml/min at the time of discharge; serum creatinine decreased from

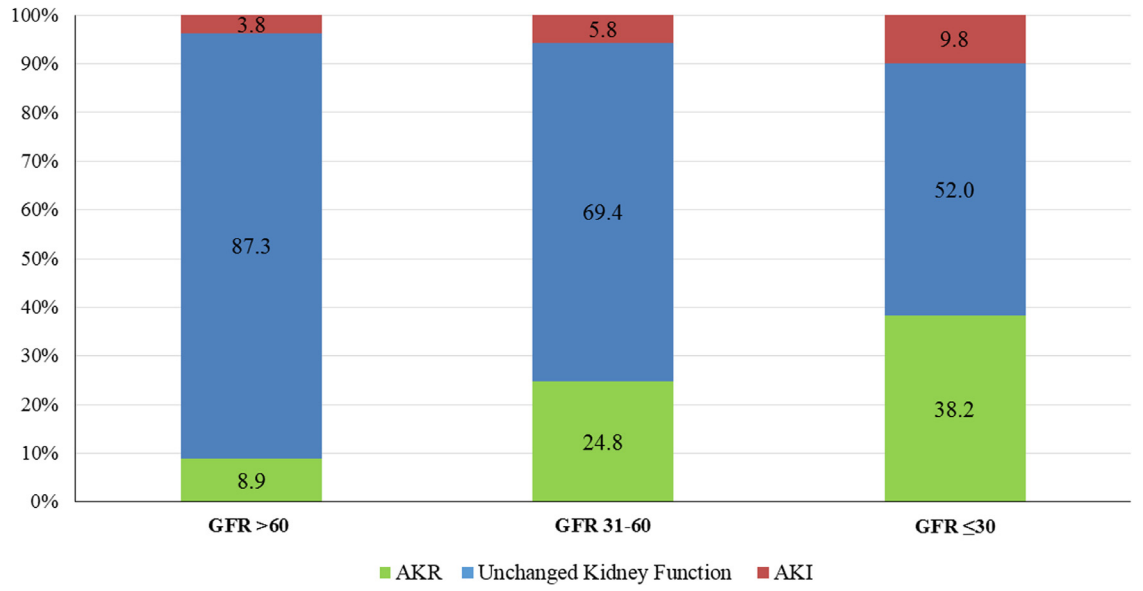

Figure 3. The interaction of AKR and baseline eGFR among 1,502 patients who underwent TAVI. AKI = acute kidney injury; AKR: = acute kidney recovery; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; TAVI = transcatheter aortic valve implantation.

Table 1
Baseline characteristics of patients with chronic kidney disease underwent TAVI

Variable	All subjects (n = 755)	AKR (n = 201)	Unchanged (n = 506)	AKI (n = 48)	p value
Age (years, mean)	81.5 ± 7.7	81.1 ± 8.1	81.8 ± 7.5	79.5 ± 7.7	0.08
Age > 75 years	77.6%	75.1%	78.7%	77.1%	0.594
Men	49.8%	45.8%	52.6%	37.5%	0.056
Body mass index (kg/m^2, mean)	29.3 ± 7.0	29.8 ± 8.5	28.8 ± 6.2	32.3 ± 7.0	0.002
Mean aortic valve gradient (mm Hg)	43.3 ± 13.3	45.0 ± 14.6	43.1 ± 12.9	39.4 ± 10.9	0.03
Diabetes mellitus	42.7%	33.8%	44.7%	58.3%	0.002
Current smoking	5.4%	6.5%	4.6%	10.4%	0.172
Peripheral arterial disease	29.9%	29.4%	30.4%	27.1%	0.87
Prior stroke or transient ischemic attack	20.5%	20.9%	20.0%	25.0%	0.703
Hypertension	89.7%	86.5%	90.9%	89.6%	0.223
Heart failure within 2 weeks	91.5%	94.5%	90.9%	85.4%	0.087
Chronic kidney disease stage 3*	86.5%	80.6%	89.5%	79.2%	0.001
Chronic kidney disease stage 4	11.9%	15.4%	9.9%	18.8%	0.001
Chronic kidney disease stage 5	1.6%	4.0%	0.6%	2.1%	0.001
Moderate to severe chronic lung disease	20.9%	25.4%	18.3%	29.2%	0.038
Prior aortic valve procedure	10.5%	16.4%	7.9%	12.5%	0.003
Anemia†	72.3%	64.2%	74.7%	81.3%	0.007
Baseline glomerular filtration rate (ml/min)	43.9 ± 11.6	41.2 ± 12.7	45.2 ± 10.7	40.5 ± 12.9	<0.001
Baseline creatinine (mg/dl)	1.47 ± 0.85	1.66 ± 1.34	1.38 ± 0.42	1.61 ± 1.17	<0.001
Ejection fraction (%, mean)	55.9 ± 12.0	54.2 ± 13.3	56.7 ± 11.5	54.6 ± 11.1	0.03
Ejection fraction <50%	23.1%	28.4%	20.8%	25.5%	0.093
Society of thoracic surgeons risk score, median (IQR)	6.1 (4.1-9.1)	6 (4.1-9.4)	6.1 (4.1-9.0)	8.1 (4.9-12.5)	0.07
Clinical presentation					
Elective	87.7%	85.6%	88.7%	85.4%	0.455
Urgent	12.2%	14.4%	11.3%	12.5%	0.509
Emergency	0.1%	0%	0%	2.1%	0.001
Trans-femoral access	79.3%	77.2%	80.4%	76.1%	0.86
Nonfemoral access	20.7%	22.8%	19.6%	23.9%	0.54
Contrast volume (ml)	105.7 ± 59.9	97.8 ± 52.0	106.6 ± 59.6	130.3 ± 83.7	0.003

* Chronic kidney disease (CKD) stage 3 defined as: estimated glomerular filtration rate (eGFR) of 31 to 60 ml/min/1.73 m^2; CKD stage 4 as eGFR of 15 to 30 ml/min/1.73 m^2 and stage 5 as eGFR ≤15 ml/min/1.73 m^2.

† Anemia defined as baseline hemoglobin of <13.5 g/dl in males and <12.0 g/dl in females.

Table 2
Hospital outcomes after TAVI stratified by dynamic changes in kidney function

Variable	All subjects (n = 755)	Acute kidney recovery (n = 201)	Unchanged (n = 506)	AKI (n = 48)	p value
Discharge glomerular filtration rate (ml/min, mean)	49.7 ± 16.7	62.0 ± 16.5	47.1 ± 12.8	24.3 ± 10.8	<0.001
Discharge creatinine (mg/dl)	1.36 ± 0.71	1.1 ± 0.33	1.35 ± 0.46	2.7 ± 1.77	<0.001
Post-TAVI length of stay (days)	4.7 ± 4.9	5.3 ± 6.7	4.0 ± 3.1	8.9 ± 8.3	<0.001
Pacemaker	8.9%	9%	7.3%	25%	<0.001
Major bleeding complication*	1.3%	1%	1.2%	4.2%	0.201
Any red blood cell transfusion	18.6%	22.5%	15%	39.6%	<0.001
Stroke or transient ischemic attack	2.4%	2.49%	1.98%	6.25%	0.178
Hospital mortality	1.85%	1%	0.59%	18.75%	<0.001
30-day mortality	4.37%	3.98%	2.77%	22.92%	<0.001

* Major bleeding complication defined as bleeding in a critical organ (i.e., intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome), bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery or bleeding with decrease in hemoglobin ≥3 g/dl or requiring transfusion of at least 2 or 3 units of packed red blood cells.

1.66 ± 1.34 mg/dl from baseline to 1.1 ± 0.33 mg/dl at the time of discharge (p <0.001; Table 2). Among the 201 CKD patients with AKR, the generalized shift of eGFR to the right is demonstrated in the histogram (Figure 4). Patients who developed AKI had significantly higher rates of hospital mortality: 19% versus less than 1% in other 2 groups, p <0.001. AKI was associated with other secondary adverse end points including a prolonged length of hospitalization. In contrast, hospital outcomes were similar between the AKR and no change in renal function groups.

In a multivariable logistic regression model of patients with baseline GFR ≤60 cc/min, patients were approximately 40% less likely to experience AKR following TAVI if they had diabetes mellitus or baseline anemia (Table 3). After adjusting for confounding variables, contrast volume dose less than the median was no longer predictive of AKR (OR 0.79, 95% confidence interval [CI] 0.55 to 1.13 p = 0.19). In contrast, lower baseline eGFR was highly predictive of AKR: patients with eGFR of <30 ml/min were over 3 times more likely to develop AKR (OR 3.27, 95% CI 1.84 to 5.82, p <0.001); patients with GFR 30 to 49 also were more likely to develop AKR than patients without renal dysfunction but the predictive value was less potent (OR 1.65, 95% CI 1.11 to 2.47, p = 0.01). The multivariable analysis was repeated to determine if more advanced age (age > 80) or severe LV dysfunction (EF < 30%) were independent predictors of AKR. Age > 80 years old was not a predictor of AKR (OR 1.05, CI 0.70 to 1.58, p = 0.82), similar to the original analysis. EF < 30% was a borderline predictor of AKR (OR 2.22, 95% CI 0.97 to 5.10, p = 0.06), similar to the results with EF <50% in the original model (p = 0.08). In both models, the independent predictors of AKR remained lack of diabetes mellitus, lack of anemia, more severe baseline renal

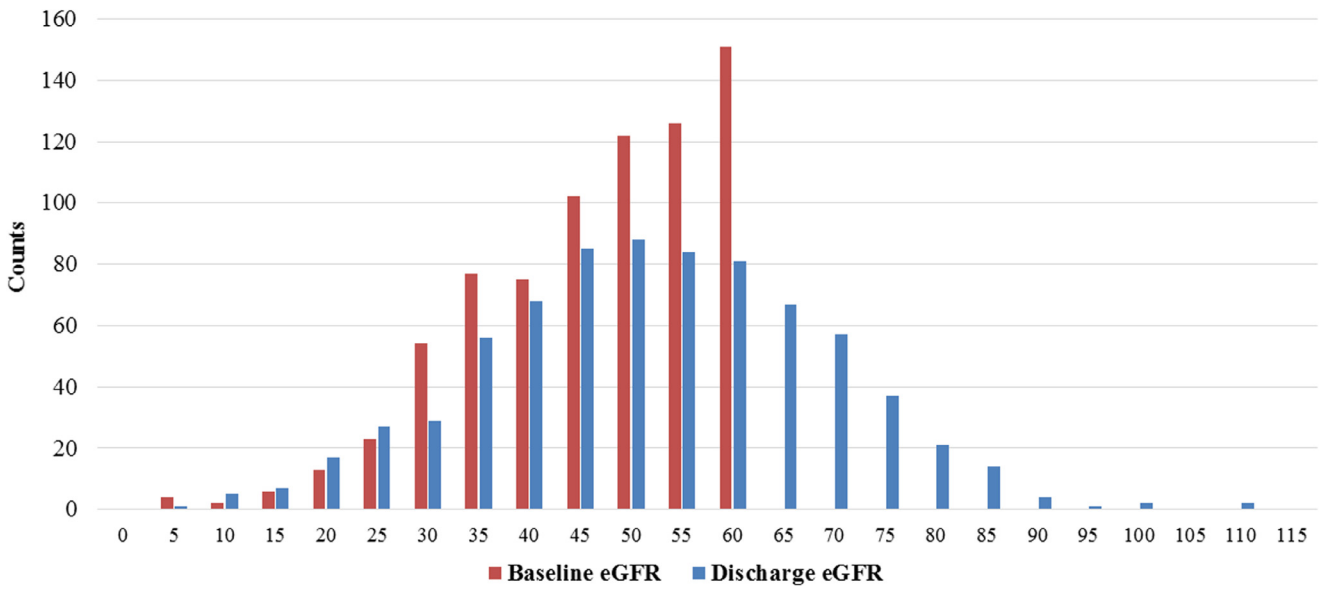

Figure 4. Discharge changes in eGFR among 755 patients with baseline CKD who underwent TAVI. CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; TAVI: Transcatheter aortic valve implantation.

Table 3
Predictors of acute kidney recovery after transcatheter aortic valve implantation

Acute kidney recovery	Odds ratio	95% Confidence interval	p value
Age >75 years	1.01	0.63−1.60	0.98
Female	1.23	0.85−1.79	0.27
Body mass index >30 (kg/m^2)	1.18	0.80−1.73	0.41
Left ventricular ejection fraction <50%	1.46	0.96−2.23	0.08
Diabetes mellitus	0.60	0.41−0.88	0.01
Prior heart failure in 2 weeks	1.81	0.88−3.70	0.11
Valve in valve TAVI*	2.42	1.39−4.20	0.01
Moderate to severe lung disease	1.54	1.01−2.35	0.05
Anemia	0.54	0.37-0.80	0.01
Aortic valve mean gradient (mm Hg)			
<25	1.00		
25-50	1.63	0.73−3.61	0.23
≥50	2.19	0.94−5.12	0.07
Baseline glomerular filtration rate (ml/min)			
≥50	1.00		
30-49	1.65	1.11−2.47	0.01
<30	3.27	1.84−5.82	<0.01
Society of thoracic surgeons risk score > 6.1% (median)	0.65	0.44−0.96	0.032
Urgent clinical presentation	1.16	0.68−1.98	0.591
Contrast volume > 94 ml (median)	0.79	0.55−1.13	0.193

* Valve in valve TAVI refers to implantation of a transcatheter aortic valve bioprosthesis inside a previously implanted surgical bioprosthetic aortic valve.

dysfunction, significant lung disease and lower STS risk score (Figure 5).

Discussion

In this multicenter prospective registry study, we confirm that AKR is a relatively frequent phenomena post-TAVI occurring in approximately 1 in 4 patients with baseline CKD. We found that (1) AKR defined as a 25% increase in eGFR at the time of discharge, occurs in approximately 4 times as many patients as AKI, (2) AKR is strongly predicted by lower baseline GFR, and (3) Patients with diabetes mellitus and baseline anemia were 40% less likely to develop AKR suggesting these clinical variables as possible markers of permanent kidney disease.

The lower rate of AKI (6%) observed in our study as compared to previous analyses is likely due to the use of discharge eGFR to assess injury.[9,10] We previously used an AKI definition of a 25% worsening in eGFR at 48 hours post-TAVI and reported an AKI incidence of 15%.[2] The diminishing incidence of AKI at discharge in our study is consistent with previous studies suggesting that acute worsening of renal function after TAVI is not sustained: in a recent study, AKI occurred in approximately 10% of patients early after TAVI, but persistent kidney injury was much less frequent.[11] Despite the lack of persistent kidney injury, AKI is associated with a significant increase in comorbid events.[9,12−15] Given the transient nature of AKI after TAVI, further study is warranted to determine the mechanism by which a temporary worsening of renal function is associated with enhanced risk.

We previously observed no significant difference in contrast use between the patients who developed AKI or AKR after TAVI.[2] The predictive value of contrast volume for

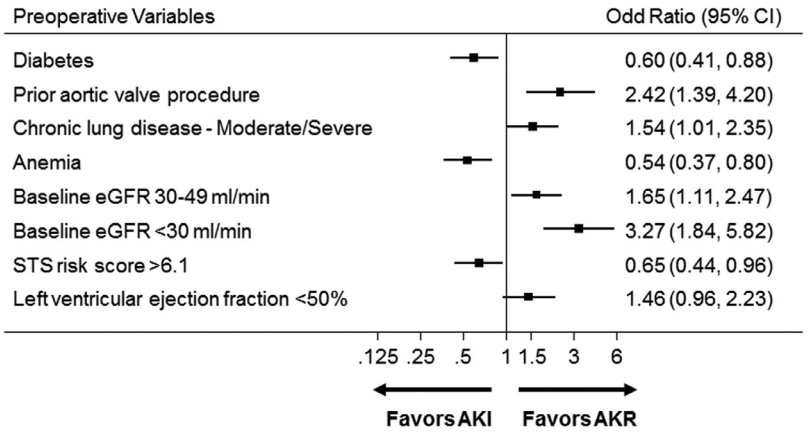

Figure 5. Forest plot demonstrating independent predictors of AKI and AKR after TAVI in Patients with baseline CKD. AKI = acute kidney injury; AKR = acute kidney recovery; CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; STS = Society of Thoracic Surgeons.

AKI after TAVI is controversial.[14,16] In a meta-analysis of over 3,800 patients post-TAVI, higher contrast use was not clearly associated with an enhanced risk of AKI (contrast volume difference 4.74 cc; 95% CI −2.33 to 11.81; p = 0.19).[9] Our multivariable analysis is consistent with this meta-analysis: contrast volume greater than the median dose was not associated with dynamic changes in kidney function.

AKR may be due to an acute improvement in cardiac output leading to better renal perfusion. Acute improvement in cardiac output after TAVI has been previously demonstrated: Voigtländer et al performed invasive hemodynamic measurements and showed that post-TAVI cardiac output significantly increased from 4.31 ± 1.36 l/min at baseline to 4.54 ± 1.49 l/min early after TAVI (p = 0.0001).[3] In our study, ejection fraction less than 50% was a borderline predictor of AKR in patients with baseline CKD (OR 1.46, 95% CI, p = 0.08) as was ejection fraction less than 30% (p = 0.06). This finding supports the concept that dynamic changes in left ventricular recovery[4,17] as well as cardiac output[3] occurring after TAVI may interact with renal recovery. A larger registry design with a higher prevalence of significant left ventricular dysfunction may be required to demonstrate the association between left ventricular recovery and AKR.

Our study found that 1 in 4 patients with baseline CKD developed AKR at the time of discharge. This rate of AKR is slightly lower than our previously published single center analysis, where 1 in 3 patients with baseline CKD developed AKR.[2] This is likely due to the difference in definition (48 hours vs discharge AKR). Our findings are consistent with a recent single center analysis by Nijenhuis et al demonstrating that AKR is persistent after TAVI (observed at both 48 hours and discharge time points) whereas AKI is a transient phenomena.[11] Importantly, our study demonstrated that patients with GFR ≤30 were more likely than any other group to develop AKR. Thus, clinical avoidance of TAVI in patients with severe renal dysfunction may not be warranted given the greatest potential for improvement in this high risk group.

In contrast, we identified 2 potential markers of irreversible kidney disease: diabetes mellitus and baseline anemia. AKR was 40% less likely in patients with these co-morbidities than those without these factors. The association between baseline anemia and poor outcomes has been previously described in patients with acute myocardial infarction,[18] PCI,[19] and TAVI.[9,20,21] Similarly, diabetes mellitus has been associated with increased risk for surgical aortic valve replacement and TAVI.[22,23] Our findings are consistent with these previous observations and suggest that persistent kidney dysfunction is more likely in these 2 groups. Although the NNECDSG is a prospective registry, the analysis of AKR was not prespecified; we do not have complete data on later changes in eGFR and thus cannot comment on the longer term persistence of AKR. The strength of the NNECDSG registry is the complete data set from the index hospitalization. Beohar et al, investigated the 30-day changes in eGFR and defined improved or worsening renal function as 10% increase or decrease from baseline renal function at 30 days.[6] They found that eGFR improved significantly in 42% of patients at 30 days consistent with the concept of AKR as a sustained phenomena. We did not study the impact of AKR on late mortality; a recent registry analysis suggested that improvement of kidney function after TAVI is associated with improved 2-year mortality.[11] In addition, we have identified significant clinical predictors of AKR but have not analyzed selected hemodynamic factors (such as pre-TAVI or post-TAVI stroke volume) which may predict AKR; further prospective study is warranted to determine hemodynamic determinants of AKR.

In conclusion, AKR is a frequent phenomena after TAVI and occurs in 1 of 4 of patients in our broadly inclusive registry. Patients with the worst renal dysfunction are more likely to experience recovery. In contrast, certain high risk groups (patients with anemia and diabetes mellitus) appear to have more irreversible renal dysfunction. The mechanism of AKR cannot be clearly associated with contrast dose alone and further exploration of associated improvement in cardiac output and left ventricular recovery is warranted.

Disclosures

Dr. Dauerman is currently a consultant to Edwards, Medtronic and Boston Scientific and has research grants from Medtronic and Edwards. None of the other authors have any relevant financial disclosures. Dr. Dauerman has no relevant conflicts of interest with the current study. All other authors have no relevant conflicts of interest.

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