Letter to the Editor

Urinary Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Acute Kidney Injury after Transcatheter Aortic Valve Implantation

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Acute kidney injury (AKI) can occur in 30-50% of patients after transcatheter aortic valve implantation (TAVI).[1] This may be due to a number of factors, such as administration of contrast media, occurrence of short periods of extreme hypotension (during rapid pacing, balloon valvuloplasty, and valve deployment), and manipulation of large catheters and sheaths in the aorta of patients with a high prevalence of diffuse atherosclerosis and thus at risk for cholesterol embolisation. AKI is associated with increased morbidity and mortality in this high-risk group of patients, despite significant advances in supportive care.[2] Only a few studies with relatively small sample sizes have analysed the incidence and predictors of AKI after TAVI.[3,4] Thus, the identification of biomarkers that can predict AKI in this high-risk population could potentially lead to improved clinical outcomes through earlier diagnosis and hence treatment. The currently used serum creatinine is a delayed indicator of AKI, as an increase in creatinine is a late indication of a decrease in glomerular filtration rate (GFR) – hours to days can lapse before decreased creatinine excretion is established and serum levels rise. Neutrophil gelatinase-associated lipocalin (NGAL) is emerging as a sensitive biomarker for AKI after acute nephrotoxic and ischaemic injury.[5] NGAL was originally identified as a 25 kDa protein covalently bound to matrix metalloproteinase-9 (MMP-9) by neutrophils. Although NGAL is expressed only at very low levels in several human tissues, it is markedly induced in injured epithelial cells, including the kidney. NGAL has been suggested as an excellent standalone structural biomarker in the plasma and urine for the early diagnosis of AKI and for the prediction of clinical outcomes (i.e. dialysis requirement, mortality) in several clinical scenarios.[6] The approach of using NGAL as a safety biomarker when using potentially nephrotoxic agents also seems promising.[7,8]

The objective of this study was to investigate the role of NGAL as a urinary biomarker for AKI after TAVI. Urinary NGAL from catheter samples was measured 4 hours after transfemoral TAVI in 34 consecutive patients. All patients provided informed consent for the procedure, subsequent data collection and analysis. The mean patient age was 79 ± 7.2 years and 53% of patients were female. The mean volume of contrast adminis-

tered during the TAVI procedure was 124 ± 65 mL (Table 1) and was significantly more in patients who developed AKI (177 ± 83 vs. 113 ± 55 mL, p=0.03). Baseline creatinine and estimated glomerular filtration rate (eGFR, as calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation) were 1.04 ± 0.3 mg/dL and 60.3 ± 21.4 mL/min, respectively. Serum creatinine was measured at 4, 24, 48 and 72 hours post-procedure. Peak creatinine was 1.16 ± 0.43 mg/dL (range 0.65-2.6) with an increase in creatinine of 0.14 ± 0.21 mg/dL (range 0-1.11). Valve Academic Research Consortium-defined AKI occurred in 17.7% of patients, all of them Stage 1.[9] The percentage changes from baseline in creatinine and eGFR in the patients with and without AKI are shown in Table 2. Urinary NGAL levels measured 4 hours after TAVI were 44.5 ± 72.5 ng/mL. No difference in urinary NGAL levels was noted in patients with AKI versus those without (41.6 ± 35.7 vs. 45.3 ± 38.7 ng/mL, p=0.57). There were also no differences between the two groups when the ratios NGAL:(percentage eGFR increase) or

Table 1. Baseline patient characteristics. Values are mean ± SD, unless otherwise stated

Patient characteristics	Entire cohort (n=34)	AKI (n=6)	No AKI (n=28)	p
Age (years)	79.0 ± 7.2	79.7 ± 5.9	78.9 ± 7.5	0.81
Male, n (%)	18 (53)	5 (83)	13 (46)	0.10
Height (cm)	165 ± 9	169 ± 7	164 ± 10	0.29
BMI (kg/m^2)	27.5 ± 5.5	27 ± 2.5	27.6 ± 5.9	0.78
BSA (m^2)	1.84 ± 0.20	1.85 ± 0.18	1.84 ± 0.20	0.92
NYHA class I, n (%)	5 (15)	1 (17)	4 (14)	0.89
NYHA class II, n (%)	5 (15)	0 (0)	5 (18)	
NYHA class III, n (%)	24 (70)	5 (83)	19 (68)	0.47
Previous cerebrovascular event, n (%)	8 (24)	2 (33)	6 (21)	0.55
Previous myocardial infarction, n (%)	4 (12)	1 (17)	3 (11)	0.69
Previous CABG, n (%)	6 (18)	3 (50)	3 (11)	0.02
Previous PCI, n (%)	5 (15)	2 (33)	3 (11)	0.17
Diabetes mellitus, n (%)	11 (32)	2 (33)	9 (32)	0.96
Hypertension, n (%)	34 (100)	6 (100)	28 (100)	
COPD, n (%)	12 (35)	2 (33)	10 (35)	0.92
Permanent pacemaker, n (%)	3 (9)	0 (0)	3 (11)	
Atrial fibrillation, n (%)	13 (38)	1 (17)	12 (43)	0.22
Logistic EuroSCORE (%), median (interquartile range)	15.2 (3.8-42.2)	16.6 (13.8-33.6)	14.7 (3.8-42.2)	0.21
STS score (%), median (range)	5.3 (1.5-36.1)	15.7 (2.7-25.4)	5.1 (1.5-36.1)	0.29
Mean aortic gradient	49 ± 12	59 ± 18	47 ± 9	0.02
Serum creatinine (mg/dL)	1.04 ± 0.30	1.11 ± 0.20	1.03 ± 0.32	0.57
Estimated glomerular filtration rate (ml/min/1.73 m^2)	60.3 ± 21.4	55.2 ± 15.4	61.5 ± 22.5	0.53
Contrast volume (mL)	124 ± 65	177 ± 83	113 ± 55	0.03
Mehran Score	13 ± 4	15 ± 4	12 ± 3	0.12
Risk of CIN	28.4 ± 14.5	34.5 ± 18.3	27.1 ± 13.7	0.27
Risk of dialysis	2.9 ± 4.6	4.8 ± 6	2.5 ± 4.2	0.27

AKI – acute kidney injury; BMI – body mass index; BSA – body surface area; CABG – coronary artery bypass graft; CIN – contrast-induced nephropathy; COPD – chronic obstructive pulmonary disease; NYHA – New York Heart Association; PCI – percutaneous coronary intervention; STS – Society of Thoracic Surgeons.

Table 2. Acute kidney injury and NGAL. Values are mean ± SD.

Renal function	AKI (n=6)	No AKI (n=28)	p
Peak serum creatinine (mg/dL)	1.58 ± 0.52	1.08 ± 0.37	<0.01
% increase in serum creatinine above baseline	40 ± 18	7 ± 9	<0.01
Peak glomerular filtration rate (ml/min/1.73 m^2)	39.7 ± 11.8	59.9 ± 24.1	0.06
% decrease in glomerular filtration rate below baseline	30 ± 8	8 ± 11	<0.01
Urinary NGAL (ng/mL) at 4-hour post-TAVI	41.6 ± 35.7	45.3 ± 38.7	0.57

AKI – acute kidney injury; NGAL – neutrophil gelatinase-associated lipocalin; TAVI – transcatheter aortic valve implantation.

NGAL:(percentage creatinine increase) were considered. There was no association between urinary NGAL levels and the peak change in creatinine (p=0.73) or the change in eGFR (p=0.37), irrespective of whether AKI developed.

To our knowledge, this is the first study to examine the role of NGAL in a population of patients who underwent TAVI. In this preliminary study, urinary NGAL did not appear to be a marker of AKI after TAVI, in contrast to other studies that investigated the role of NGAL as a predictive biomarker of contrast-induced nephrotoxicity. This finding may be due to several reasons, such the small patient population, the timing of the single NGAL measurement, and the fact that all AKI patients were only Stage 1, which may underestimate the entity of AKI in the whole TAVI population. Other potential contributing factors include the effect of age on NGAL's performance as an AKI predictor, with better predictive results in children (area under the receiver operating characteristic curve, AUC-ROC, overall 0.93) than in adults (AUC-ROC 0.78).[10] In addition, there are a number of limitations pertaining to the NGAL studies published thus far, as the majority of studies reported were from single centres that enrolled small numbers of patients. Despite the results of this study, the role of NGAL as a predictor of AKI in the TAVI population warrants further investigation in large multi-centre studies, given the high incidence of AKI in TAVI and its effect on morbidity and mortality on this already frail population.

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