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ORIGINAL ARTICLE

The Extent of Aortic Atherosclerosis Predicts the Occurrence, Severity, and Recovery of Acute Kidney Injury After Transcatheter Aortic Valve Replacement

A Volumetric Multislice Computed Tomography Analysis

See Editorial by Devireddy and Hiremath

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BACKGROUND: Acute kidney injury (AKI) can be a major complication of transcatheter aortic valve replacement (TAVR). Atheroembolization of debris during catheter manipulation has been considered as a potential factor causing AKI. This study investigates the impact of aortic atheroma burden on AKI post-TAVR and evaluates the potential of preoperative multislice computed tomographic (MSCT) imaging for the assessment of AKI in these patients.

METHODS AND RESULTS: Preoperative multislice computed tomographic images were analyzed in 278 patients with symptomatic severe aortic stenosis who underwent TAVR. AKI was defined as an absolute increase in serum creatinine ≥0.3 mg/dL. Aorta vessel and lumen areas in each 1-mm cross-sectional image were measured. Percent atheroma volume above ($PAV_{above\ renal\ arteries}$) and below ($PAV_{below\ renal\ arteries}$) renal arteries were calculated by the following formula: PAV={Σ (vessel area−lumen area)/Σ(vessel area)}×100. AKI occurred in 92 patients (33.1%) after TAVR. AKI was associated with a greater PAV above (30.4±8.2 versus 21.3±5.8%; *P*=0.02) but not below (28.9±7.7 versus 25.8±6.1%; *P*=0.41) the renal arteries. Greater $PAV_{above\ renal\ arteries}$ was associated directly with AKI severity (*P*=0.008) and inversely with recovery in serum creatinine level from peak to discharge (*r*=0.78; *P*=0.002). Multivariate analysis demonstrated that $PAV_{above\ renal\ arteries}$ was a significant predictor of AKI (*P*=0.02). Receiver-operating curve analysis identified $PAV_{above\ renal\ arteries}$ >29.5% as an optimal threshold to predict AKI.

CONCLUSIONS: Suprarenal aortic atheroma burden is associated with the occurrence, severity, and recovery of AKI after TAVR. This highlights the utility of preoperative assessment of aortic atherosclerosis on multislice computed tomography to identify patients at high-risk for AKI.

Key Words: acute kidney injury ■ aorta ■ atherosclerosis ■ renal artery ■ transcatheter aortic valve replacement

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WHAT IS KNOWN

- Acute kidney injury (AKI) is one of major complications associated with worse clinical outcomes after transcatheter aortic valve replacement.
- Atherothrombotic embolism in the aorta because of catheter manipulation has been considered as a potential factor causing AKI.

WHAT THE STUDY ADDS

- Suprarenal aortic atheroma burden predicts recovery of renal function post procedure and thereby the occurrence of AKI post procedure.
- Infrarenal aortic atherosclerosis has no association with AKI.
- Preoperative CT imaging of aortic atherosclerosis could be used to evaluate the risk of atherothromboembolism triggering AKI after transcatheter aortic valve replacement.

Randomized clinical trials have demonstrated the clinical efficacy of transcatheter aortic valve replacement (TAVR) in patients with symptomatic severe aortic stenosis who are inoperable or at intermediate to high-risk for surgical aortic valve replacement.[1–4] Despite its favorable efficacy, several TAVR-related complications influence clinical outcomes. Depending on definition used, acute kidney injury (AKI) occurs in 10% to 30% of patients with symptomatic severe aortic stenosis.[5–7] The occurrence of AKI associates with greater rates of early and 1-year mortality.[8] These findings suggest the need to establish preoperative risk stratification of AKI after the procedure.

Atherothrombotic embolism, because of catheter manipulation, is one of potential factors associated with the occurrence of AKI. In a previous study, scraping of aortic plaques by catheters was observed in >50% of subjects receiving percutaneous coronary intervention.[9] In particular, this phenomenon was more frequently observed when larger size of catheters was used. This observation raises the concern that the TAVR procedure using larger caliber devices may be more likely to scrape atheromatous debris from the aortic vessel wall, potentially traveling to renal arteries and, thus, causing AKI. We hypothesized that the degree of atheroma burden in the aortic root might predict the occurrence of AKI after TAVR. We have previously reported the methodology for quantitative evaluation of aortic atheroma burden using multislice computed tomography (MSCT) and its utility in predicting cerebrovascular events during TAVR.[10] In the current study, we sought to evaluate the association of atheroma burden on MSCT with AKI risks in patients undergoing TAVR.

METHODS

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

This is a retrospective study of 278 patients with symptomatic severe aortic valve stenosis who underwent TAVR at the Royal Adelaide Hospital from August 2009 to July 2015. Eligibility of TAVR was discussed by the multidisciplinary team, including interventional cardiologists, cardiac surgeons, anesthesiologists, and physicians. This study was approved by the Human Research and Ethics Committee at the Royal Adelaide Hospital. All patients gave informed consent with regard to the performance and analysis of the computed tomography data set before TAVR.

Preoperative MSCT Imaging

A 128-detector MSCT (Siemens Definition AS+; Siemens Medical Solutions, Erlangen, Germany) was used to evaluate aortic root in the current study subjects. The scan of the thorax, abdomen, and pelvis was acquired during the injection of 90 to 150 mL nonionic iodinated contrast agent (Ultravist 370; Bayer Healthcare LLC, Whippany, NJ). Retrospectively, ECG-gated data acquisition was conducted with 128×0.6 mm collimation, scan pitch of 0.18, and a gantry rotation time of 300 ms. Exposure parameters included 120 kVp tube voltage and 280 to 320 effective mAs. Image reconstruction parameters included 180° cardiac-gated B26 (medium smooth advanced smoothing algorithm) reconstruction algorithm and a temporal resolution of 150 ms. Ten cardiac phases (each 10% of RR-interval) were reconstructed with a slice thickness between 0.6 and 2 mm.

Measurements of Atheroma Burden Within Aorta

A commercially available software (3-mensio, Structural Heart version 5.1; PIE medical imaging BV, Maastricht, the Netherlands) was used to analyze images of the aorta on MSCT imaging. The acquisition and analysis of MSCT images have been described in detail previously.[10] In brief, this software automatically segments the entire aortic root from ascending aorta to abdominal aorta (from the sino-tubular junction to the iliac bifurcation) and then draws a centerline across the aortic lumen. Following a manually adjusting centerline for accurate measurement, the short-axis views of the entire aorta were analyzed. Window settings were optimized to differentiate lumen from vessel wall and minimize calcium blooming artifact. The leading edges of luminal and outer wall boundaries were manually traced at 1-mm interval. The plaque area was defined as the difference in area occupied by the lumen (lumen area) and outer wall boundaries (vessel area).

The entire length of the aorta from the sino-tubular junction to the iliac bifurcation was divided into the following 2 segments according to the level of the right renal artery: (1) aortic segment above the right renal artery and (2) aortic segment below the right renal artery (Figure 1). In these 2 segments, total atheroma volume (TAV) was

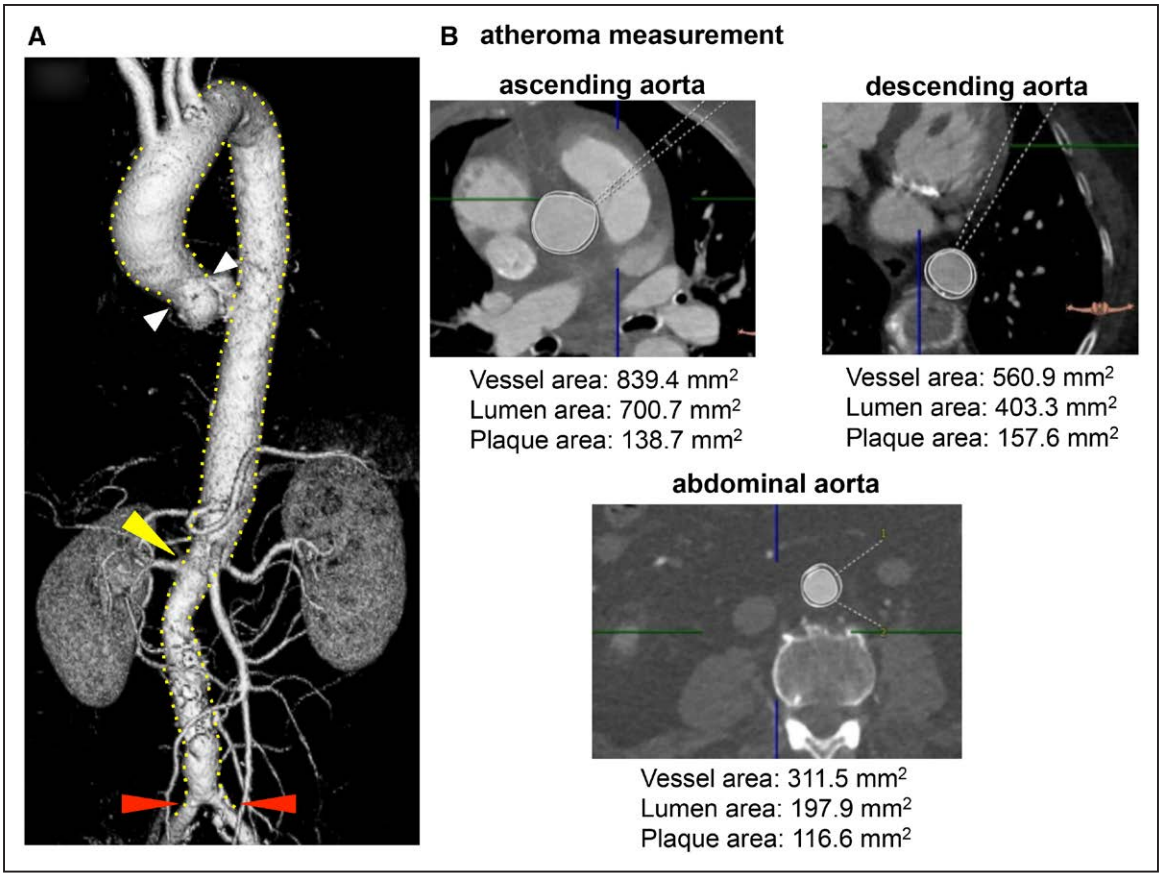

Figure 1. Quantitative measurements of aorta atheroma volume on multislice computed tomography.
A, The imaged aorta was stratified into 2 segments: (1) from the ascending aorta to abdominal aorta above the right renal artery (between white and yellow arrow heads) and (2) the abdominal aorta below the right renal artery and above the bifurcation of the common iliac artery (between yellow and red arrow heads. **B**, Lumen and vessel wall boundaries were manually traced in every 1-mm cross-sectional frame in each 2 aorta segments. Representative measured images are presented.

calculated by summation of the plaque area and subsequently normalized to account for differences in segment length between subjects:

$$\text{TAV},\text{cm}^3 = \frac{\sum(\text{vessel area} - \text{lumen area})}{\text{Number of images in segment}} \times \text{Median number of images in segment of study subjects}$$

Percent atheroma volume (PAV) was calculated as the proportion of vessel wall volume occupied by plaque:

$$\text{PAV},\% = \frac{\sum(\text{vessel area} - \text{lumen area})}{\sum(\text{vessel area})} \times 100$$

Vessel and lumen volumes were calculated by the summation of their respective areas in each measured image and then normalized similar to the TAV measurement. In all patients, PAV and TAV above and below renal arteries, ($PAV_{\text{above renal arteries}}$, $PAV_{\text{below renal arteries}}$, $TAV_{\text{above renal arteries}}$, $TAV_{\text{below renal arteries}}$) were calculated respectively, to assess the relationship between atherosclerotic burden and AKI.

TAVR PROCEDURES

TAVR procedures have been described previously.[11,12] In brief, under general anesthesia or conscious sedation, balloon dilatation of aortic valve was performed with a 20 to 23 mm balloon catheter under rapid right ventricular pacing. The deployment of balloon-expandable or self-expandable prostheses was performed as previously described.[11,12] One of the following 4 TAVR systems was utilized during the study period: CoreValve (Medtronic, Minneapolis, MN), SAPIEN XT (Edwards Lifesciences, Irvine, CA), Lotus (Boston Scientific, Natick, MA), or Portico (St Jude Medical, St Paul, MN). All patients received aspirin (100 mg) and clopidogrel (75 mg) before the procedure. Intravenous infusion of isotonic saline at a dose of 1 mL/kg per hour was used for 12 hours before TAVR in all subjects. Metformin was discontinued 48 hours before TAVR. During the procedure, intravenous unfractionated heparin was used to achieve an activated clotting time >250 s. After the completion of TAVR, aspirin was continued indefinitely. Clopidogrel was discontinued after 6 months. Intravenous infusion of isotonic saline was continued for 12 hours after the procedure. Metformin was commenced again 48 hours after TAVR.

Acute Kidney Injury

According to the definition of the Valve Academic Research Consortium-2, the following AKI stages were

defined: AKI stage 1=an increase in serum creatinine to 150% to 199% or an increase of ≥0.3 mg/dL, AKI stage 2=an increase in serum creatinine to 200% to 299%, AKI stage 3=an increase in serum creatinine to ≥300% or serum creatinine of ≥4.0 mg/dL with an acute increase of at least 0.5 mg/dL.[13] For the definition of AKI in this study, we not only took an inclusive approach encompassing all stages but also looked at the various stages of AKI individually. Serum creatinine level was measured a day before TAVR, and it was

Table 1. Baseline Clinical Characteristics

	AKI (–), n=186	AKI (+), n=92	*P* Value
Age, y	82.9±0.5	83.8±0.4	0.16
Females, n (%)	83 (44.6)	34 (36.9)	0.26
BMI, kg/m^2	27.4±0.6	28.2±0.5	0.35
Hypertension, n (%)	101 (54.3)	64 (69.5)	0.04
Diabetes mellitus, n (%)	76 (40.9)	45 (48.9)	0.07
Dyslipidemia, n (%)	83 (44.6)	33 (35.9)	0.35
NYHA functional class	2.6±0.5	2.5±0.5	0.59
STS score,* %	5.1 (4.2–10.1)	10.2 (6.6–17.3)	0.03
Time interval between CT and TAVR, d	16.8±7.4	13.2±6.1	0.33
Concomitant disease			
Chronic atrial fibrillation, n (%)	63 (33.9)	33 (35.9)	0.62
Coronary artery disease, n (%)	120 (64.5)	66 (71.7)	0.55
Prior PCI, n (%)	110 (59.1)	60 (65.2)	0.50
Prior cerebrovascular event, n (%)	30 (16.1)	11 (11.9)	0.54
Peripheral artery disease, n (%)	16 (8.6)	18 (19.6)	0.03
COPD, n (%)	76 (40.9)	36 (39.1)	0.68
Renal function			
Creatinine, mg/dL	1.1±0.3	1.6±0.5	0.01
eGFR, mL/min per 1.73 meter^2	58.3±11.6	45.9±8.1	0.009
Other biochemistry data			
Hemoglobin, g/dL	11.3±1.9	10.2±1.0	0.04
LDL-C, mg/dL	2.2±0.4	2.3±0.5	0.41
HbA1c, %	5.9±0.9	6.4±1.2	0.08
Echocardiographic parameters			
Mean aortic gradient, mm Hg	49.9±0.9	48.0±1.3	0.22
Aortic valve area, cm^2	0.66±0.21	0.71±0.28	0.27
Aortic annulus diameter, mm	24.6±0.4	25.3±0.3	0.53
LVEF, %	56.9±1.3	59.1±0.9	0.17
Medication use			
Aspirin, n (%)	162 (83.1)	72 (82.4)	0.79
Clopidogrel, n (%)	139 (80.7)	61 (77.2)	0.48
Warfarin, n (%)	38 (16.1)	25 (23.3)	0.35
Statin, n (%)	129 (73.2)	76 (72.0)	0.74
High-intensity statin, n (%)	4 (2.2)	1 (1.1)	0.83
β-blocker, n (%)	7 (3.8)	2 (2.2)	0.80
ACE-I/ARB, n (%)	62 (33.3)	26 (28.3)	0.50
Calcium antagonist, n (%)	110 (59.1)	60 (65.2)	0.47

ACE-I indicates angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic pulmonary obstructive disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

*Median (interquartile range).

evaluated again 1, 2, 3, and 7 days after the procedure. Isotope dilution mass spectroscopy was used to measure creatinine level, and estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.

Statistical Analysis

Continuous variables are expressed as mean±SD and categorical variables as percentage. The χ^2 test was used to test for differences in categorical variables between groups, and continuous data were compared using unpaired *t* tests. Variables with a value of $P<0.10$ in the univariable analysis were entered into a logistic regression analysis to determine the independent predictors of AKI after TAVR. To examine the ability of MSCT-derived $PAV_{\text{above renal arteries}}$ to predict AKI, receiver-operating characteristic analyses and calculations of sensitivity, specificity, and positive and negative predictive values were performed. The best cutoff value of $PAV_{\text{above renal arteries}}$ was determined by using the Youden index method. In AKI subjects, percent change in serum creatinine and eGFR from its peak to discharge was examined using ANCOVA, with age, female, and AKI stage ≥II as covariates and grouping variable ($PAV_{\text{above renal arteries}}$ < or ≥30.6%) as a factor. A value of $P<0.05$ was considered significant. All statistical analyses were performed using JMP software, version 11.0.1 (SAS Institute, Cary, NC).

RESULTS

Clinical Demographics

Some form of AKI was identified in 92 patients (33.1%). Baseline clinical characteristics are summarized in Table 1. Patients with AKI were more likely to have a history of hypertension (69.5% versus 54.3%; $P=0.04$) and peripheral artery disease (19.6% versus 8.6%; $P=0.03$) and exhibit a higher Society of Thoracic Surgeons score (10.2 versus 5.1; $P=0.03$). AKI patients also demonstrated a higher creatinine (1.6±0.5 versus 1.1±0.3 mg/dL; $P=0.01$) and lower estimated glomerular filtration rate (eGFR, 45.9±8.1 versus 58.3±11.6 mL/

Table 2. Procedural Characteristics

	No AKI, n=186	AKI, n=92	*P* Value
Procedure time, min	81.1±14.6	78.4±12.3	0.36
Contrast medium use, mL	81.2±13.8	98.1±17.7	0.17
Activated clotting time, s	259.1±4.1	253.8±3.6	0.79
Approach			0.30
Transfemoral, n (%)	139 (74.7)	75 (81.5)	
Transapical, n (%)	14 (7.5)	6 (6.5)	
Subclavian, n (%)	33 (17.7)	11 (11.9)	
Prosthesis type			0.48
Core Valve, n (%)	85 (45.6)	37 (40.3)	
Sapien XT, n (%)	58 (31.2)	30 (32.6)	
Lotus, n (%)	20 (10.8)	16 (17.3)	
Portico, n (%)	23 (12.3)	9 (9.8)	
Prosthesis diameter			0.19
23 mm, n (%)	21 (11.3)	17 (18.5)	
26 mm, n (%)	76 (40.9)	21 (22.8)	
27 mm, n (%)	10 (5.4)	5 (5.4)	
29 mm, n (%)	72 (38.7)	46 (50.0)	
31 mm, (%)	7 (3.8)	3 (3.3)	
Ratio of prosthesis to annulus size	1.23±0.36	1.21±0.21	0.85
Balloon postdilation, n (%)	15 (8.1)	9 (9.8)	0.73
New-onset atrial fibrillation, n (%)	15 (8.1)	10 (10.9)	0.61
Intra-aortic balloon pump, n (%)	7 (3.7)	4 (4.3)	0.82
Permanent pacemaker insertion, n (%)	42 (22.6)	14 (15.2)	0.27
Valve embolization, n (%)	1 (0.5)	1 (1.1)	0.81

AKI indicates acute kidney injury.

Table 3. Serial Changes in Renal Functions

	AKI (–), n=186	AKI Stage I, n=58	AKI Stage II, n=17	AKI Stage III, n=17	*P* Value
Baseline					
Creatinine, mg/dL	1.1±0.3	1.4±0.3	1.4±0.4	1.9±0.4	0.006
eGFR, mL/min per 1.73 meter^2	58.3±11.6	51.3±6.2	46.2±4.1	38.1±3.2	0.003
Serial change					
Absolute change					
Creatinine, mg/dL	…	+0.9±0.3	+1.6±0.5	+4.8±0.9	<0.001
eGFR, mL/min per 1.73 meter^2	…	–8.1±3.7	–13.2±4.0	–22.7±5.3	<0.001
Percent change					
Creatinine, mg/dL	…	+167.5±15.1	+213.1±17.2	+357.3±23.6	<0.001
eGFR, mL/min per 1.73 meter^2	…	–15.7±10.2	–29.2±10.8	–54.8±13.9	<0.001
Postoperative renal failure requiring dialysis, n (%)	0 (0)	0 (0)	0 (0)	8 (47.1)	0.001

AKI indicates acute kidney injury; and eGFR, estimated glomerular filtration rate.

min per 1.73 meter^2; *P*=0.009) at baseline (Table 1). A lower level of hemoglobin (10.2±1.0 versus 11.3±1.9 g/dL; *P*=0.04) and a higher level of glycohemoglobin (6.4±1.2% versus 5.9±0.9%) were observed in AKI patients, although the latter comparison was of borderline significance (*P*=0.08). Aortic valve area before TAVR did not differ between those with AKI and those without (0.71±0.28 versus 0.66±0.21 cm^2; *P*=0.27). Other echocardiographic data and medication use were comparable in patients with and without AKI (Table 1).

Table 2 shows a comparison of procedural characteristics in the 2 groups. Patients with AKI were more likely to use a larger amount of contrast medium, but this comparison failed to meet statistical significance (98.1±17.7 versus 81.2±13.6 mL; *P*=0.17). Most of the study subjects received TAVR via femoral access (81.5% versus 74.7%; *P*=0.30). CoreValve was the predominant valve type deployed, with no relationship between valve type and risk of AKI (Table 2). Other procedural characteristics were also similar between 2 groups (Table 2).

Changes in Renal Function After TAVR

Table 3 summarizes baseline and serial change in renal functional data in patients stratified according to the stage of AKI. In patients with AKI (n=92), the proportion of patients with AKI stage I, II, and III was 63.0%, 18.5%, and 18.5%, respectively. Predictably, patients with AKI stage III were more likely to exhibit a higher serum creatinine level (*P*=0.006) and a lower eGFR level at baseline (*P*=0.003) with greater changes in these measures after the procedure (Table 3). Furthermore, the prevalence of those who required temporary hemodialysis after TAVR was highest in patients with AKI stage III (0% versus 0% versus 47.1%; *P*=0.001).

Volumetric Analysis of Aorta Atheroma Burden

MSCT-derived aorta atheroma measures are summarized in Table 4. On volumetric analysis, greater aorta atheroma volume above the renal arteries was observed in patients with AKI ($PAV_{above\ renal\ arteries}$, 30.4±8.2% versus 21.3±5.8%, *P*=0.02; $TAV_{above\ renal\ arteries}$, 62.8±18.2 versus 41.1±12.8 cm^3, *P*=0.02). Vessel and lumen volumes were comparable in the 2 groups (vessel volume, 204.3±29.5 versus 192.8±31.4 cm^3, *P*=0.48; lumen volume, 148.3±23.7 versus 154.3±26.5 cm^3, *P*=0.49). In contrast, the degree of aorta atheroma burden below renal arteries was not significantly different in patients with and without AKI ($PAV_{below\ renal\ arteries}$, 28.9±7.7% versus 25.8±6.1%, *P*=0.41; $TAV_{below\ renal\ arteries}$, 9.4±0.5 versus 8.0±0.3 cm^3, *P*=0.68). Atheroma measures in patients stratified according to severity of AKI are illustrated in Figure 2. Greater $PAV_{above\ renal\ arteries}$ and $TAV_{above\ renal\ arteries}$ associated with AKI severity ($PAV_{above\ renal\ arteries}$, *P*=0.008; $TAV_{above\ renal\ arteries}$, *P*=0.005), whereas there were no significant differences in $PAV_{below\ renal\ arteries}$ (*P*=0.73) and $TAV_{below\ renal\ arteries}$ (*P*=0.68) across AKI stages.

Table 4. Atheroma Volume in Patients With and Without AKI After TAVR

	AKI (–), n=186	AKI (+), n=92	*P* Value
CT measures of aorta above renal arteries			
$PAV_{above\ renal\ arteries}$, %	21.3±5.8	30.4±8.2	0.02
$TAV_{above\ renal\ arteries}$, cm^3	41.1±12.8	62.8±18.2	0.02
Vessel volume, cm^3	192.8±31.4	204.3±29.5	0.48
Lumen volume, cm^3	154.3±26.5	148.3±23.7	0.49
Analysed length, cm	34.5±21.1	34.2±19.6	0.88
CT measures of aorta below renal arteries			
$PAV_{below\ renal\ arteries}$, %	25.8±6.1	28.9±7.7	0.41
$TAV_{below\ renal\ arteries}$, cm^3	8.0±2.8	9.4±3.1	0.68
Vessel volume, cm^3	31.1±8.1	32.6±9.0	0.41
Lumen volume, cm^3	24.7±5.2	23.6±4.5	0.71
Analysed length, cm	10.1±6.1	10.5±7.2	0.67

AKI indicates acute kidney injury; CT, computed tomography; PAV, percent atheroma volume; TAV, total atheroma volume; and TAVR, transcatheter aortic valve replacement.

Predictors of AKI After TAVR

Factors associated with AKI on univariable and multivariate analysis are shown in Table 5. Univariable analysis identified eGFR <60 mg/min per 1.73 meter^2 (odds ratio, 1.48; 95% CI, 1.21–1.84; *P*=0.008), hemoglobin <10.0 g/dL (odds ratio, 1.16; 95% CI, 1.09–1.43; *P*=0.01), Society of Thoracic Surgeons score (odds ratio, 1.15; 95% CI, 1.06–1.29; *P*=0.04), $PAV_{above\ renal\ arteries}$ (odds ratio, 1.60, 95% CI, 1.16–2.37; *P*=0.009), and $TAV_{above\ renal\ arteries}$ (odds ratio, 1.98; 95% CI, 1.38–2.96; *P*=0.002) significantly associated with AKI after TAVR. On multivariate analysis, eGFR <60 mg/min per 1.73 meter^2, hemoglobin <10.0 g/dL, $PAV_{above\ renal\ arteries}$, and $TAV_{above\ renal\ arteries}$ still continued to associate with the occurrence of AKI in patients receiving TAVR (eGFR <60 mg/min per 1.73 meter^2, *P*=0.03; hemoglobin <10.0 g/dL, *P*=0.04; $PAV_{above\ renal\ arteries}$, *P*=0.02; $TAV_{above\ renal\ arteries}$, *P*=0.02; Table 5). Receiver-operating curve analysis identified $PAV_{above\ renal\ arteries}$ >29.5% predicted the occurrence of AKI accurately (area under the curve, 0.87; sensitivity, 90.1%; specificity, 85.6%; positive and negative predictive values, 85.7 and 89.4%, respectively; Figure 3).

Atheroma Burden and Recovery of Renal Function After AKI

In patients with AKI (n=92), the association of $PAV_{above\ renal\ arteries}$ with percent change in renal functional measures from its peak to discharge was analyzed. As shown in Figure 4A, greater atheroma burden in the entire aorta above the renal arteries was also associated

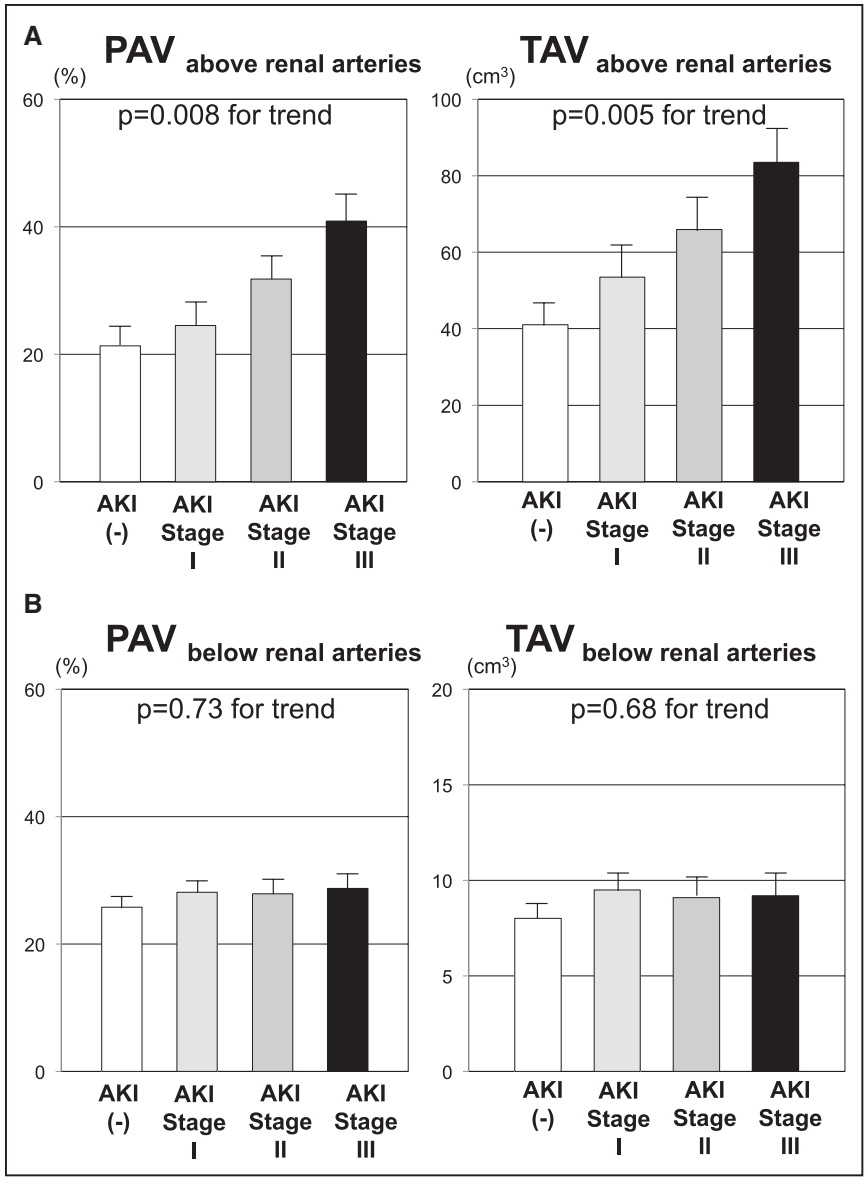

Figure 2. Comparison of percent atheroma volume (PAV) and total atheroma volume (TAV) in subjects stratified according to the severity of acute kidney injury (AKI). **A**, $PAV_{above\ renal\ arteries}$ and $TAV_{above\ renal\ arteries}$. **B**, $PAV_{below\ renal\ arteries}$ and $TAV_{below\ renal\ arteries}$.

with an attenuated recovery of serum creatinine level (r=0.78; P=0.002). Similarly, larger $PAV_{above\ renal\ arteries}$ predicted a smaller improvement in eGFR from peak to discharge (r=–0.80; P=0.001; Figure 4B).

The degree of renal functions' recovery was compared in AKI subjects stratified into 2 groups according to median $PAV_{above\ renal\ arteries}$=30.6% (Table 6). AKI patients with $PAV_{above\ renal\ arteries}$ ≥30.6% were more likely to exhibit a higher frequency of AKI stage ≥II (P=0.009) and less recovery of creatinine (P=0.01) and eGFR levels (P=0.01). Even after adjusting for age, sex (female), and AKI stage ≥II, a diminished recovery of creatinine and eGFR was still observed in AKI patients with $PAV_{above\ renal\ arteries}$ ≥30.6% (P=0.03 and 0.02, respectively).

DISCUSSION

The occurrence of AKI after TAVR has been shown to worsen clinical outcomes, suggesting an opportunity exists for preoperative risk assessment to establish appropriate risk mitigation strategies. In our MSCT volumetric analysis, patients with AKI harbored greater atheroma volume in different levels of the aorta above the renal arteries. Furthermore, the degree of atheroma in the aorta proximal to the renal arteries was associated with the severity of AKI and its recovery. These findings highlight that the evaluation of aortic atheroma could be an important risk stratification tool for AKI after TAVR.

The current MSCT findings provide mechanistic insights into AKI after TAVR. Atheroembolization has been considered as a potential cause of AKI after invasive procedures. This is supported by previous studies which demonstrated that atherosclerosis in the ascending aorta predicted deterioration of renal function in patients undergoing cardiac surgery.[14,15] In another study, the use of larger-sized catheters for percutaneous coronary intervention substantially dislodged plaques in the aorta.[16] These data indicate that invasive procedures

Table 5. Uni- and Multivariate Analysis for Predictor of AKI

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	1.10 (0.91–1.16)	0.45	…	…
Females	1.02 (0.94–1.06)	0.32	…	…
Hypertension	1.05 (0.81–1.12)	0.39		
Dyslipidemia	1.03 (0.74–1.21)	0.85		
BMI	1.09 (0.86–1.47)	0.50		
Diabetes mellitus	1.23 (0.89–1.38)	0.36	…	…
Chronic AF	0.97 (0.88–1.12)	0.21	…	…
eGFR <60 mL/min per 1.73 meter^2	1.48 (1.21–1.84)	0.008	1.21 (1.02–1.63)	0.03
Hemoglobin <10.0 g/dL	1.16 (1.09–1.43)	0.01	1.08 (1.02–1.39)	0.04
HbA1c	1.34 (0.89–1.54)	0.09	1.18 (0.84–1.20)	0.35
LDL-C	1.02 (0.75–1.34)	0.80		
Aortic valve area	1.01 (0.94–1.29)	0.73	…	…
LVEF <40%	1.02 (0.96–1.05)	0.95	…	…
Transfemoral approach	1.20 (0.91–1.38)	0.07	1.09 (0.87–1.20)	0.33
STS score	1.15 (1.06–1.29)	0.04	1.08 (0.96–1.10)	0.15
Amount of contrast medium	1.12 (1.00–1.16)	0.05	1.05 (0.96–1.09)	0.17
CT measures				
$PAV_{above\ renal\ arteries}$	1.60 (1.16–2.37)	0.009	1.46 (1.10–2.18)	0.02
$PAV_{below\ renal\ arteries}$	1.05 (0.74–1.19)	0.72	…	…
$TAV_{above\ renal\ arteries}$	1.98 (1.38–2.96)	0.002	1.74 (1.21–2.54)	0.02
$TAV_{below\ renal\ arteries}$	1.11 (0.97–1.23)	0.58	…	…

AF indicates atrial fibrillation; AKI, acute coronary injury; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycohemoglobin; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; OR, odds ratio; PAV, percent atheroma volume; STS, Society of Thoracic Surgeons; and TAV, total atheroma volume.

could detach plaque from the aorta, which potentially travels into other vascular beds, including renal arteries. The current study identified that the extent of aortic atheroma above renal arteries was associated with the occurrence of AKI, whereas this TAVR-related complication did not have any relationships with aortic atheroma below the renal arteries. van Rosendael et al[17] also reported a higher frequency of AKI in patients receiving TAVR who had atherosclerotic plaque on cross-sectional images. Anatomically, atheroma in the aorta proximal to the renal arteries could travel into the arterial microvasculature supplying the kidney. We do not have any direct evidence showing this phenomenon in this study; however, the accumulating observational evidence and current findings suggest that atheroembolization is an important potential cause of AKI.

The extent of aortic atheroma burden above the renal arteries predicted both the severity of AKI and its recovery after the procedure. In particular, more than a 2-fold increase in aortic atheroma burden above the renal arteries was observed in subjects with AKI stage III compared with those who did not have AKI. This provides further evidence that the use of the bulky delivery systems, such as those required in the TAVR procedures, in particular, those traversing the aortic arch, would be more likely to dislodge a larger amount of atheroma,

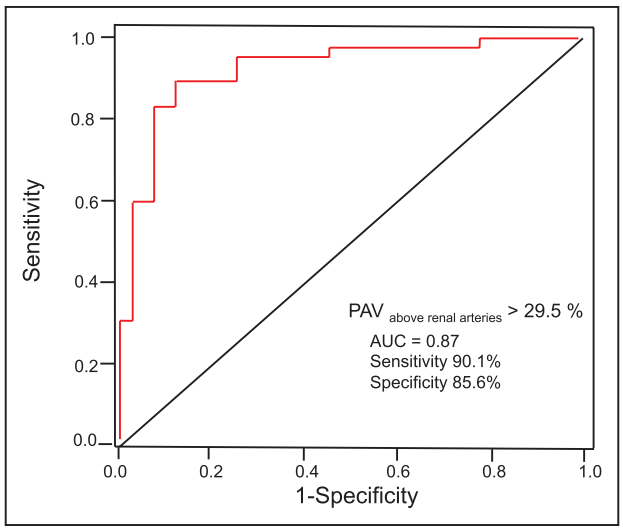

Figure 3. Receiver-operating curve analysis of percent atheroma volume (PAV) above renal arteries for the prediction of acute kidney injury.
AUC indicates area under the curve.

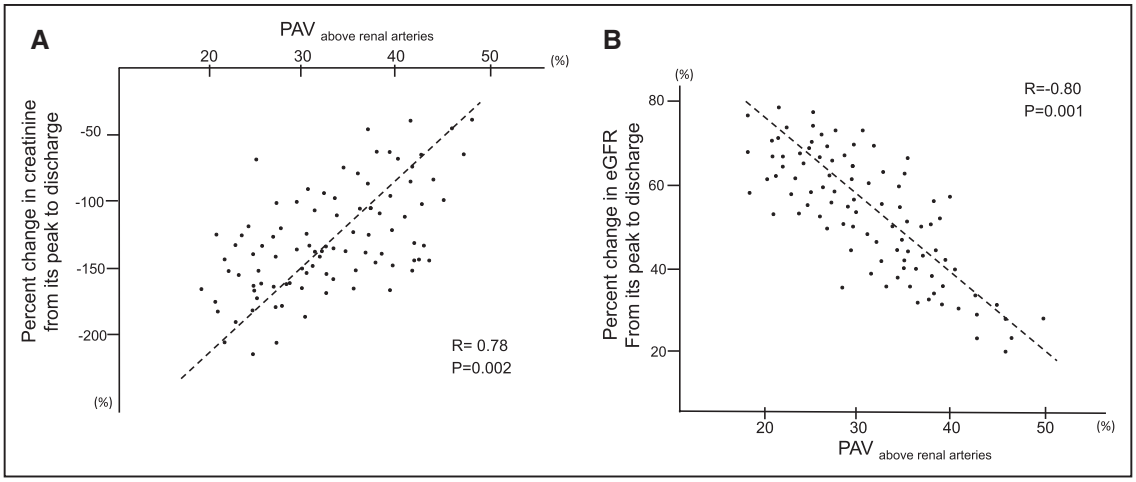

Figure 4. Percent atheroma volume (PAV) above renal arteries and recovery of renal function in patients with acute kidney injury (n=92). **A**, Change in creatinine level. **B**, Change in estimated glomerular filtration rate (eGFR).

which travels downstream to occlude the highly dense renal capillary vessels. These potential mechanisms could account for the association of PAV with severity of AKI and frequency of renal recovery in our study.

Our MSCT findings highlight the need for optimal management of atherosclerosis to help mitigate the risk of AKI in symptomatic severe aortic stenosis subjects who have larger atheroma burden within the aorta. Aortic valve stenosis has been considered an atherosclerotic disease caused by lipoprotein deposition, chronic inflammation, and active leaflet calcification.[18,19] Given that these atherogenic stimuli also contributes to the formation and progression of aortic atheroma, pharmacological agents, such as a statin which has the ability to modulate atherogenic lipids and inflammation, would be effective to reduce the risk of AKI.[20–22] In the

Table 6. $PAV_{above\ renal\ arteries}$ and Recovery of Renal Functions in AKI Subjects

	$PAV_{above\ renal\ arteries}$ <30.6% (Median; n=46)	$PAV_{above\ renal\ arteries}$ ≥30.6% (Median; n=46)	*P* Value
Age, y	83.0±0.2	84.9±0.3	0.58
Female, n (%)	18 (39.1)	16 (34.7)	0.82
Hypertension, n (%)	30 (65.2)	34 (73.9)	0.70
Diabetes mellitus, n (%)	19 (41.3)	26 (56.5)	0.48
Dyslipidemia, n (%)	15 (32.6)	18 (39.1)	0.76
Baseline renal function			
Creatinine, mg/dL	1.5±0.3	1.7±0.4	0.23
eGFR, mL/min per 1.73 meter^2	49.6±5.1	40.1±4.5	0.20
AKI stage, n (%)			
AKI stage I	40 (86.9)	18 (39.1)	0.01
AKI stage II	4 (8.8)	13 (28.3)	
AKI stage III	2 (4.3)	15 (32.6)	
AKI stage ≥ II	6 (13.0)	28 (60.8)	0.009
Recovery of renal function			
Percent change in creatinine from its peak to discharge, %	−154.8±38.8	−101.2±32.1	0.01
Adjusted value,* %	−147.4±20.6	−110.7±18.8	0.03
Percent change in eGFR from its peak to discharge (%)	+67.4±10.3	+41.7±6.9	0.01
Adjusted value,* %	+61.8±8.5	+48.8±4.8	0.02

AKI indicates acute kidney injury; eGFR, estimated glomerular filtration rate; and PAV, percent atheroma volume.

*Adjusted for age, female and AKI stage ≥II.

current study, only 2% of subjects received high-intensity statin. Whether more frequent use of this therapeutic regimen would reduce AKI after TAVR requires further investigation.

Several caveats should be noted. First, this is an observational study at a single center that currently conducts >100 TAVR procedures every year. Therefore, the possibility of selection bias cannot be excluded, although consecutive subjects were included in the current analysis. Second, the preoperative and postoperative management was according to each physicians' discretion. This might affect the prevalence of AKI and its stages after TAVR. Third, calcium blooming artifacts effect quantification of atheroma burden on MSCT. This potentially leads to the underestimation of atheroma volume.

In conclusion, the extent of atherosclerotic plaque burden in the aorta proximal to the renal arteries was associated with the occurrence of AKI in patients undergoing TAVR. This atheroma measure also predicted stages of AKI and its recovery after the procedure. Our findings show, for the first time, the potential utility of preoperative assessment of aortic atherosclerosis on MSCT for the prediction of AKI in patients with symptomatic severe aortic stenosis who underwent TAVR. That said, further studies are required to address the exact role of PAV measurement as a predictor of AKI post-TAVR and as an indicator for optimal management of atherosclerosis.

ARTICLE INFORMATION

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