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ORIGINAL RESEARCH

Metabolite Profiles Predict Acute Kidney Injury and Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement

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***Background*—**Acute kidney injury (AKI) occurs commonly after transcatheter aortic valve replacement (TAVR) and is associated with markedly increased postoperative mortality. We previously identified plasma metabolites predictive of incident chronic kidney disease, but whether metabolite profiles can identify those at risk of AKI is unknown.

***Methods and Results*—**We performed liquid chromatography–mass spectrometry–based metabolite profiling on plasma from patients undergoing TAVR and subjects from the community-based Framingham Heart Study (N=2164). AKI was defined by using the Valve Academic Research Consortium-2 criteria. Of 44 patients (mean age 82±9 years, 52% female) undergoing TAVR, 22 (50%) had chronic kidney disease and 9 (20%) developed AKI. Of 85 metabolites profiled, we detected markedly concordant cross-sectional metabolic changes associated with chronic kidney disease in the hospital-based TAVR and Framingham Heart Study cohorts. Baseline levels of 5-adenosylhomocysteine predicted AKI after TAVR, despite adjustment for baseline glomerular filtration rate (odds ratio per 1-SD increase 5.97, 95% CI 1.62–22.0; *P*=0.007). Of the patients who had AKI, 6 (66.7%) subsequently died, compared with 3 (8.6%) deaths among those patients who did not develop AKI (*P*=0.0008) over a median follow-up of 7.8 months. 5-adenosylhomocysteine was predictive of all-cause mortality after TAVR (hazard ratio per 1-SD increase 2.96, 95% CI 1.33–6.58; *P*=0.008), independent of baseline glomerular filtration rate.

***Conclusions*—**In an elderly population with severe aortic stenosis undergoing TAVR, metabolite profiling improves the prediction of AKI. Given the multifactorial nature of AKI after TAVR, metabolite profiles may identify those patients with reduced renal reserve.
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Key Words: aortic stenosis • kidney • metabolomics • mortality • transcatheter aortic valve implantation

Transcatheter aortic valve replacement (TAVR) is an emerging alternative to surgery for patients with severe aortic stenosis perceived to be at increased risk for perioperative mortality.[1–4] TAVR patients are universally elderly and often possess numerous comorbid conditions, many of which are known risk factors for acute kidney injury (AKI) after cardiac procedures.[5–8] The incidence of AKI after TAVR is consequently high, with AKI occurring in 8% to 42% of cases.[9–15] The precipitants of AKI after TAVR are diverse, including contrast, atheroemboli, medications, hypotension/hypoperfusion, and blood transfusions, among others. Consequently, the prediction of AKI after TAVR has consequently been difficult.[9] Because AKI is associated with markedly reduced short- and long-term survival after TAVR,[9–12,14,15] better predictors of AKI in these high-risk patients would be of clinical value to better gauge procedural risk and might facilitate the investigation and eventual implementation of preventative measures.

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/5/3/e002712/suppl/DC1

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Metabolomic profiling technologies provide high-throughput phenotyping of an individual's metabolic state. When applied to well-characterized cohorts, these techniques may identify novel disease biomarkers and provide insight into biological mechanisms.[16,17] Recent studies have identified subtle metabolic perturbations that predict incident chronic kidney disease (CKD) and diabetes up to 12 years before overt disease.[18–23] Whether metabolite profiles might ultimately be used to predict adverse events in hospital-based cohorts remains unknown. To begin to address this question, we performed metabolite profiling in a cohort of high-risk individuals undergoing TAVR, with the goals of assessing the utility of applying metabolomics profiling techniques to a cohort of complex TAVR patients, identifying biomarkers that are predictive of AKI and increased morbidity and, in turn, the high-risk patients most likely to benefit from preventative strategies.

Methods

Patients

We recruited 44 consecutive patients undergoing transfemoral TAVR at the Massachusetts General Hospital for severe aortic stenosis. Transapical and transaortic TAVR patients were excluded to avoid confounding caused by surgical trauma on plasma metabolites and potentially on the risk of subsequent AKI. A patient with end-stage renal failure was excluded from the analysis.

All patients provided written informed consent, and the study protocol was approved by the institutional review board.

Transcatheter Aortic Valve Replacement

The TAVR procedure was performed by using Edwards Sapien or Sapien XT transcatheter heart valves (Edwards Lifescience) according to standard techniques.[1,2] Briefly, femoral arterial access was obtain either percutaneously or by using open surgical cut-down. Procedures were performed under general anesthesia with the use of fluoroscopic and transesophageal echocardiographic guidance within a hybrid catheterization laboratory/operating room. After performance of balloon aortic valvuloplasty, the transcatheter heart valve was deployed during rapid right ventricular pacing. Supravalvular aortography was serially performed during the procedure to identify optimal camera angulation and to help guide valve positioning and deployment. Heparin was administered for all procedures.

Framingham Heart Study Cohort

The Framingham Offspring Study was initiated in 1971 and sought to enroll a sample of 5124 young adult offspring of the original Framingham Heart Study (FHS) cohort. Subjects attended quadrennial visits, during which physician-administered physical examination, medical history, and routine laboratory tests were administered. The presence of CKD was ascertained at the fifth examination, which occurred between 1991 and 1995.[24] As previously described, we performed metabolite profiling of plasma samples from 2164 subjects collected during the fifth examination, of whom 139 (6%) had prevalent CKD defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2.[21]

Metabolite Profiling

Fasting venous blood samples were collected into EDTA-treated tubes after femoral vascular access was obtained. The samples were immediately placed on ice and then processed within 30 minutes. Samples were centrifuged at 2000*g* for 10 minutes. The supernatant plasma was stored at −80°C, and aliquots were thawed for analyses. Amino acids, amino acid derivatives, urea cycle intermediates, nucleotides, and other positively charged polar metabolites were profiled by using liquid chromatography–mass spectrometry (LC-MS)–based metabolite profiling as previously described.[18,21,23] Multiquant software (version 1.0; Applied Biosystem/Sciex) was used for automated peak integration, and all metabolite peaks were manually reviewed for quality of integration.

Statistical Analyses and Definitions

We examined the association between plasma metabolites immediately before TAVR and incident AKI. AKI was defined by using the Valve Academic Research Consortium-2 criteria.[25] Specifically, patients with an increase in plasma creatinine to 150% to 199% of baseline or an increase of ≥0.3 mg/dL within 7 days of TAVR were considered to have AKI. Change in creatinine (Δcreatinine) was defined as the absolute difference between baseline and peak in-hospital creatinine. Estimated glomerular filtration rate (eGFR) was calculated by using the Modification of Diet in Renal Disease formula.[26] Metabolites that did not distribute normally on visual assessment of kurtosis and skew were log transformed. Continuous clinical variables and metabolite levels were then depicted as mean±SD, and comparisons were made by using the Student *t* test. Categorical parameters were presented as frequencies and distributions were compared using the Fisher exact test. Robust linear regression was used to model the relationship between plasma metabolites and continuous end points, specifically Δcreatinine, hospital length of stay, and intensive care unit hours. Relative risk regression was used to model prevalence ratios assessing relationships between plasma metabolites and prevalent chronic kidney disease.

Relative risk regression was performed by using proc genmod in SAS with log link with a Poisson distribution. Logistic regression models were generated to identify predictors of AKI. Multivariable logistic regression models were constructed to establish the relationship between metabolite levels and incident AKI, adjusting for baseline eGFR. We used a Bonferroni-corrected *P* value threshold of 5.8E–4 (0.05/85) for biomarker discovery.

Results

Patient Characteristics

Baseline characteristics of the TAVR study cohort are presented in Table 1. Patients were elderly (mean age 82±9 years) and evenly balanced between genders (52% female). Mean left ventricular ejection fraction was 56.7±17.1% and mean peak and mean aortic valve gradients were 84.8±29.1 and 50.5±18.6 mm Hg, respectively. Baseline creatinine was 1.14±0.37 mg/dL and mean estimated eGFR was 58.1±18.2 mL/min/1.73 m^2. CKD was prevalent in 50% of patients. Of the 44 enrolled patients, 9 (20%) developed AKI after TAVR.

Given the complexities of hospital patients, we first compared our findings to metabolite profiles among 139 (6%) individuals with CKD from Exam 5 of the FHS offspring cohort. Subjects (N=2164) in the community-based cohort were younger (55.4±9.9 years) and less likely to possess comorbid conditions (Table S1).

Metabolites Associated With Prevalent Kidney Disease

In the TAVR patients, plasma metabolite profiling identified 6 of 85 metabolites, 5-adenosylhomocysteine, xanthosine, and trimethylamine-*N*-oxide (TMNO), cysteamine, C4-butyryl

Table 1. Baseline Patient Characteristics

Clinical Characteristics	All Patients (N=44)	No AKI (n=35)	AKI (n=9)	*P* Value
Age, y	81.9±8.5	81.9±11.5	82.0±7.2	0.96
Female	23 (52)	19 (54)	4 (44)	0.71
Weight, kg	82.3±27.9	79.0±19.8	94.8±48.0	0.36
Height, cm	158.8±25.7	160.8±24.2	151.4±31.4	0.34
BSA, m^2	1.8±0.3	1.8±0.3	1.8±0.3	0.96
Diabetes mellitus	16 (36)	12 (33)	4 (50)	0.61
IDDM	2 (5)	2 (6)	0 (0)	
NIDDM	14 (33)	10 (29)	4 (50)	
Hypertension	36 (84)	29 (83)	7 (88)	>0.99
Hyperlipidemia	25 (58)	20 (57)	5 (63)	>0.99
Smoking	22 (51)	16 (46)	6 (75)	0.24
Prior MI	4 (9)	3 (9)	1 (13)	>0.99
Prior PCI	17 (40)	15 (43)	2 (25)	0.45
Prior CABG	10 (23)	8 (23)	2 (25)	>0.99
Prior chronic kidney disease	22 (50)	16 (46)	6 (67)	0.46
Baseline creatinine	1.14±0.37	1.07±0.3	1.42±0.5	0.009
eGFR (MDRD), mL/min/1.73 m^2	58.1±18.2	61.0±17.5	46.9±17.0	0.04
Echocardiographic parameters				
LVEF, %	56.7±17.1	58.4±15.3	50.2±22.8	0.20
Peak AVG, mm Hg	84.8±29.1	86.8±28.9	77.1±30.2	0.38
Mean AVG, mm Hg	50.5±18.6	51.5±19.0	46.4±17.0	0.47
AVA, cm^2	0.65±0.16	0.64±0.16	0.71±0.16	0.24

AVA indicates aortic valve area; AVG, aortic valve gradient; BSA, body surface area; CABG, coronary artery bypass grafting surgery; IDDM, insulin-dependent diabetes mellitus; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; NIDDM, non–insulin-dependent diabetes mellitus; PCI, percutaneous coronary intervention.

Table 2. Correlation of Plasma Metabolites With Estimated Glomerular Filtration Rate

Metabolite	Pearson Correlation Coefficient	*P* Value	Metabolite	Pearson Correlation Coefficient	*P* Value
5-Adenosylhomocysteine	−0.61	<0.0001	C14-carnitine	−0.15	0.32
TMNO	−0.61	<0.0001	Anserine	−0.15	0.33
Xanthosine*	−0.56	<0.0001	5-HIAA*	−0.15	0.33
Cysteamine*	−0.55	0.0002	α-Glycerophosphocholine	0.15	0.34
C4-butyryl carnitine	−0.52	0.0003	Isoleucine	−0.14	0.37
C4-methylmalonyl carnitine	−0.50	0.0005	Threonine	0.13	0.41
C3 carnitine	−0.49	0.0006	Glutamate	−0.12	0.43
Kynurenic acid	−0.50	0.0006	Proline	−0.12	0.44
C5-valeryl carnitine	−0.48	0.001	Alanine	−0.12	0.44
Kynurenine	−0.48	0.001	Aspartate	−0.11	0.49
ADMA/SDMA	−0.46	0.002	Methionine	−0.10	0.51
Choline	−0.47	0.002	Tryptophan	−0.10	0.52
C2 carnitine	−0.46	0.002	Creatine	0.09	0.55
Taurine	−0.44	0.003	Phosphoethanolamine	0.08	0.60
C8-carnitine*	−0.41	0.006	Methionine sulfoximine	0.07	0.64
C5-glutaryl carnitine*	−0.38	0.01	Glycine	−0.07	0.64
Anthranilic_acid	−0.36	0.02	C26-carnitine	0.07	0.66
cis/trans-Hydroxyproline	−0.35	0.02	Histidine	0.07	0.66
C3-malonyl carnitine*	−0.33	0.03	C18-carnitine*	−0.06	0.72
Betaine	−0.33	0.03	Valine	−0.05	0.74
C10-carnitine	−0.32	0.03	Deoxycytidine	−0.06	0.75
C12-carnitine	−0.32	0.04	Cytidine*	0.05	0.76
Carnitine	−0.30	0.05	C16-carnitine	−0.05	0.77
C6-carnitine	−0.28	0.07	C18:2-carnitine	−0.04	0.78
Serine	0.27	0.08	C18:1-carnitine	−0.04	0.79
Anandamide	−0.27	0.08	Spermidine	0.04	0.81
Phenylalanine	−0.27	0.08	3-Hydroxyanthranilic acid	−0.03	0.84
Citrulline	−0.26	0.08	Cobalamin	0.03	0.86
Arginosuccinate	0.29	0.09	Asparagine	−0.03	0.86
C9-carnitine*	−0.25	0.10	Xanthine	−0.03	0.87
NMMA	−0.25	0.10	Beta-alanine*	0.02	0.88
C7-carnitine	−0.24	0.11	Thiamine	−0.02	0.88
Glucose	−0.23	0.14	Glutamine	0.02	0.89
Homocysteine	0.22	0.14	Glycerol	−0.02	0.90
Dimethyl-2-oxoglutarate	−0.24	0.15	Xanthurenate	0.02	0.90
Niacinamide	−0.22	0.15	Arginine	0.02	0.90
Cystamine*	−0.22	0.16	Uridine	−0.02	0.91
Cystine	−0.21	0.18	Lysine	0.02	0.91
Thymidine	−0.21	0.18	GABA	−0.02	0.91
Thyroxine	−0.20	0.20	Phosphocholine	0.01	0.95
Tyrosine	−0.20	0.20	Leucine	−0.01	0.97
Aminoisobutyric acid	−0.17	0.29	Acetylcholine	0.00	0.99
Ornithine	−0.16	0.31			

*Denotes log-transformed metabolite. ADMA/SDMA indicates asymmetric/symmetric dimethylarginine; GABA, Gama-aminobutyric acid; NMMA, NG-monomethyl-L-arginine; TMNO, trimethylamine-N-oxide.

carnitine, and C4-methylmalonyl carnitine demonstrated significant negative correlations with baseline eGFR after Bonferroni adjustment. A complete listing of metabolites is included in Table 2. Similarly, numerous metabolites were differentially detected in TAVR patients with CKD. Among these, kynurenic acid, xanthosine, TMNO, taurine, asymmetric/symmetric dimethylarginine, 5-adenosylhomocysteine, cysteamine, and the short-chain acyl carnitines were most strongly associated with CKD (Table 3). Metabolite profiles of individuals with CKD versus controls from exam 5 of the Framingham Offspring Study revealed consistent associations between key metabolites and renal function. Thus, the profiling of TAVR patients confirmed associations with established kidney disease and identified novel metabolomic signatures that might be expected given the differences in size and clinical characteristics of the 2 cohorts.

Metabolites Predictive of AKI

The findings from the cross-sectional analyses of metabolites with renal function motivated us to test whether plasma metabolites might identify TAVR patients most susceptible to acute kidney injury. Of 44 TAVR patients, 9 (20%) developed AKI within 7 days of TAVR. Male sex, diabetes mellitus, hypertension, hyperlipidemia, and smoking were more prevalent in patients that developed AKI after TAVR, although none of these imbalances reached statistical significance (Table 1). Only baseline creatinine and eGFR significantly differed between patients that developed and did not develop AKI after TAVR. Baseline creatinine was 1.42±0.5 mg/dL in patients who developed AKI compared to 1.07±0.3 mg/dL in those who did not (P=0.009), and eGFR was 46.9±17.0 mL/min/1.73 m^2 in AKI cases and 61.0±17.5 mL/min in those without AKI (P=0.04).

Median Δcreatinine was 0.08 mg/dL [IQR −0.05 to 0.24] in the entire study cohort and 0.63 mg/dL [IQR 0.44–1.11] in those that developed AKI. Only 5-adenosylhomocysteine was significantly associated with Δcreatinine on univariable analysis (β-coefficient per 1-SD 0.11, 95% CI 0.05–0.17; P=0.0005). In addition, 5-adenosylhomocysteine remained a significant predictor of Δcreatinine despite adjustment for baseline eGFR (β-coefficient per 1-SD 0.12, 95% CI 0.04–0.20; P=0.002).

Similarly, only 5-adenosylhomocysteine was differentially detected in patients that went on to developed AKI (Figure 1). Also, 5-adenosylhomocysteine was predictive of AKI after adjustment for eGFR (5-adenosylhomocysteine: odds ratio per 1-SD increase=5.97, 95% CI, 1.62–22.0; P=0.007; Table 4). 5-adenosylhomocysteine supplanted eGFR on multivariable modeling of AKI. The probability of developing AKI after TAVR significantly increased with increasing tertile of baseline plasma 5-adenosylhomocysteine, such that none of those in the lowest tertile developed AKI compared to 50% of patients in the highest tertile (Figure 2).

Table 3. Unadjusted Relationships of Metabolite Levels With Prevalent CKD

Plasma Metabolite	TAVR Cohort PR (95% CI)	*P* Value	FHS Cohort PR (95% CI)	*P* Value
Xanthosine*	1.79 (1.44–2.22)	1.90E–7	1.47 (1.38–1.56)	2.07E–31
TMNO	1.58 (1.32–1.93)	1.17E–6	1.30 (1.21–1.40)	8.45E–12
ADMA/SDMA	1.49 (1.25–1.77)	9.16E–6	1.31 (1.20–1.43)†	2.04E–9
Taurine	1.59 (1.29–1.95)	1.09E–5	1.29 (1.14–1.47)	7.59E–5
5-Adenosylhomocysteine	1.53 (1.24–1.88)	6.10E–5	1.35 (1.21–1.48)	3.11E–9
Kynurenine	1.54 (1.23–1.92)	1.00E–4	1.65 (1.48–1.83)	1.50E–20
Kynurenic acid	1.64 (1.28–2.13)	1.00E–4	1.14 (1.09–1.19)	2.80E–9
Choline	1.55 (1.24–1.96)	2.00E–4	1.39 (1.27–1.52)	2.30E–13
Cysteamine*	1.82 (1.39–2.38)	1.18E–5	N/A	
C2-carnitine	1.49 (1.21–1.83)	1.00E–4	N/A	
C3-carnitine	1.53 (1.23–1.91)	2.00E–4	N/A	
C4-butyryl carnitine	1.92 (1.50–2.45)	1.60E–7	N/A	
C4-methylmalonyl carnitine	1.53 (1.26–1.85)	1.80E–5	N/A	
C5-valeryl carnitine	1.53 (1.25–1.86)	3.72E–5	N/A	

Twenty-two (55%) and 139 (6.4%) of patients within the TAVR and FHS cohorts, respectively, had CKD. ADMA/SDMA indicates asymmetric/symmetric dimethylarginine; CKD, chronic kidney disease; FHS, Framingham Heart Study; N/A indicates not available; metabolite not quantified within FHS on earlier platform; PR, prevalence ratio; TAVR, transcatheter aortic valve replacement; TMNO, trimethylamine-Noxide.

*Denotes log-transformed metabolite.

†SDMA quantified individually within the FHS.

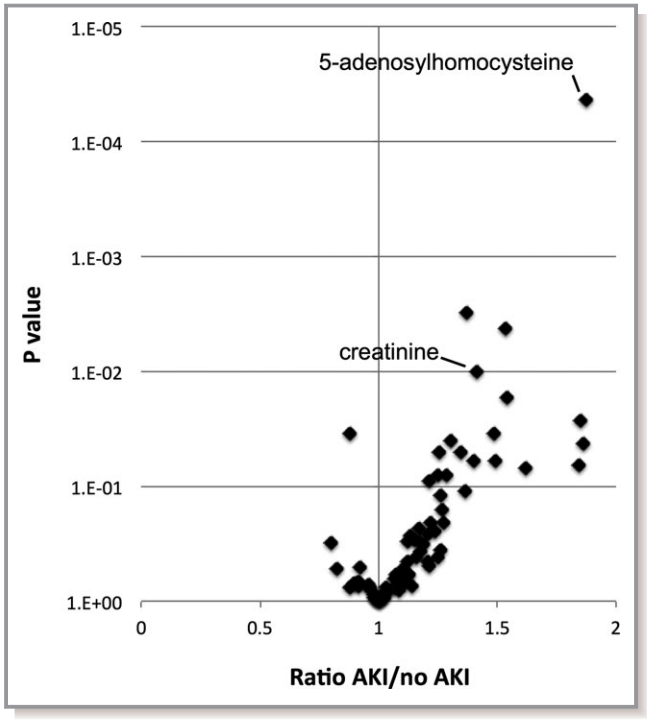

Figure 1. Mean metabolite ratios in those that do and do not develop AKI. Mean ratio of all metabolites for AKI cases relative to those that do not develop AKI in fasting pre-TAVR samples. AKI indicates acute kidney injury.

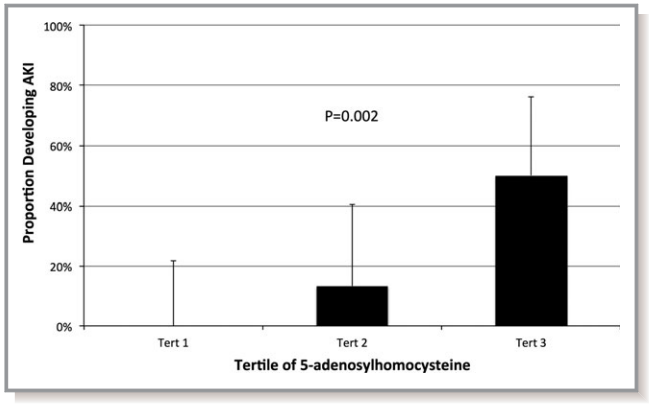

Figure 2. Acute kidney injury (AKI) by tertile of 5-adenosylhomocysteine. The proportion of patients developing AKI after TAVR significantly increased with increasing tertile of baseline plasma 5-adenosylhomocysteine, such that none of those in the lowest tertile developed AKI compared to 50% of patients in the highest tertile (*P*=0.002). Error bars represent upper bounds of the 95% confidence interval. TAVR indicates transcatheter aortic valve replacement.

Clinical Outcomes

Hospital length of stay was significantly prolonged in patients that experienced AKI after TAVR (median [IQR] 6 [4–9] versus 15 [12–24] days; *P*=0.03). The number of hours in an intensive care unit after TAVR was also longer in patients that developed AKI than in those that did not (median [IQR] 27 [24–50] versus 61 [48–204]; *P*=0.01). Length of stay (β-coefficient per 1-SD increase 1.3 days, 95% CI −0.0 to 2.7; *P*=0.058) and hours in the intensive care unit (β-coefficient per 1-SD increase 7.5 hours, 95% CI 1.3–13.8; *P*=0.02) were prolonged in patients with higher baseline 5-adenosylhomocysteine.

Over a median follow-up time of 7.8 (IQR 1.3–12.4) months, 9 (20.5%) patients died. Of the 9 patients who had AKI after TAVR, 6 (66.7%) subsequently died, compared to 3 (8.6%) deaths among those patients that did not develop AKI (*P*=0.0008; Figure 3A). Pre-TAVR eGFR possessed a borderline association with survival (HR per 1-SD decrease 2.44, 95% CI 0.96–6.25; *P*=0.06; Figure 3B). Baseline 5-adenosylhomocysteine was significantly higher (ratio 1.70; *P*=0.001) in patients that subsequently died than in survivors. Also, 5-adenosylhomocysteine (HR per 1-SD increase 2.96, 95% CI 1.33–6.58; *P*=0.008) was predictive of mortality despite adjustment for baseline glomerular filtration rate. Increasing tertile of plasma 5-adenosylhomocysteine was similarly associated with progressively reduced survival (Figure 3C).

Discussion

Using an LC-MS–based metabolite profiling techniques, we have identified metabolic perturbations that associate with chronic kidney disease both in a hospitalized cohort of TAVR patients as well as in participants with CKD in the Framingham Offspring Study cohort. In addition, we found 5-adenosylhomocysteine, a precursor to homocysteine and adenosine, to be highly predictive of AKI after TAVR. The

Table 4. Baseline Plasma Metabolites Predictive of AKI

	Unadjusted		Multivariable	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
5-Adenosylhomocysteine	6.06 (1.85–19.83)	0.003	5.97 (1.62–22.0)	0.007
eGFR	0.95 (0.90–1.00)	0.04	1.00 (0.94–1.06)	0.96

Odds ratio (OR) per 1-SD increase in 5-adenosylhomocysteine. Multivariable model includes eGFR and 5-adenosylhomocysteine. AKI indicates acute kidney injury; eGFR, estimated glomerular filtration rate.

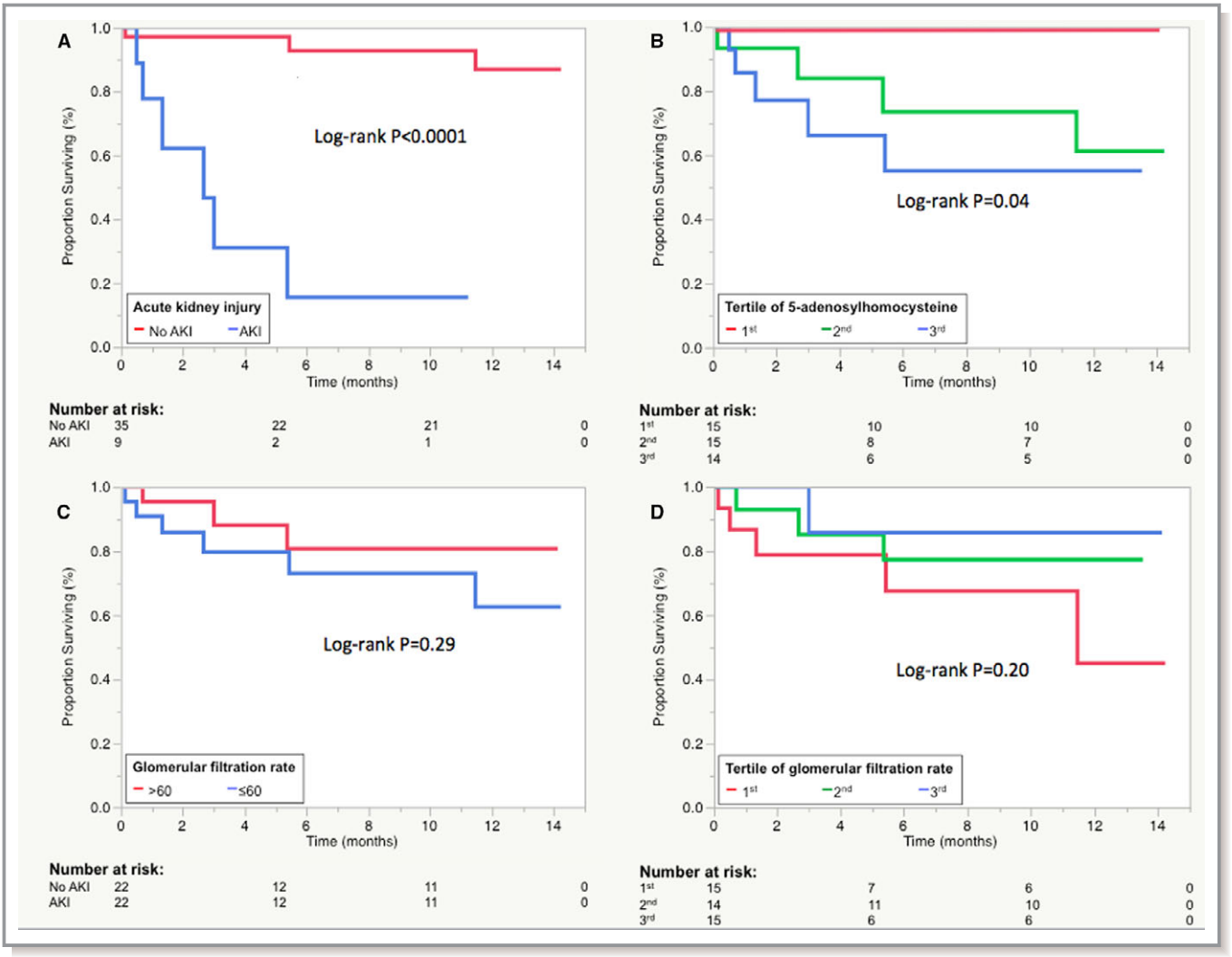

Figure 3. Kaplan–Meier curves of survival. Over a median follow-up time of 7.8 (IQR1.3, 12.4) months, 9 (20.5%) patients died. A, Acute kidney injury after TAVR is associated with markedly increased mortality (Log-rank $P<0.0001$). B, Baseline serum 5-adenosylhomocysteine predicted mortality after TAVR (Log-rank $P=0.04$); whereas baseline eGFR stratified around 60 mL/min per 1.73 m^2 (Log-rank $P=0.29$; C) and by tertile (Log-rank $P=0.20$; D) did not. AKI indicates acute kidney injury; TAVR, transcatheter aortic valve replacement.

metabolite not only provided more robust prediction of AKI than baseline eGFR, but it was also significantly predictive of post-TAVR survival and possessed a borderline association with hospital length of stay. Our study reiterates prior observations of the tremendous adverse impact of AKI on survival after TAVR.

Currently, clinical assessment of kidney function and the risk of AKI rely primarily on measurement of plasma creatinine levels. Creatinine is used to noninvasively estimate glomerular filtration because it is freely filtered by the glomerulus, is not reabsorbed, and undergoes only limited tubular secretion.[27] In current clinical practice, several equations that rely heavily on eGFR have been developed to predict the risk of AKI after cardiac catheterization and cardiac surgery[5,28]; however, to our knowledge, none of these have been applied to TAVR patients and none incorporate other axes of kidney function beyond filtration.

We have previously used LC-MS–based metabolite profiling techniques to identify a broad set of metabolites associated with and predictive of CKD.[21,23] Within the FHS, the addition of metabolomic profiling to clinical data allowed for the prediction of incident CKD 8 years before its occurrence.[21] These metabolic biomarkers may reflect axes of renal function orthogonal to glomerular filtration, such as tubular secretion and intraorgan metabolism, and consequently providing a more complete picture of renal health and prognosis. Here, we build on our prior experience by identifying metabolic perturbations that presage incident AKI after TAVR, demonstrating that baseline 5-adenosylhomocysteine levels are robust predictors of subsequent AKI, in fact supplanting

eGFR in multivariable models predicting AKI. Notably, the fractional excretion of 5-adenosylhomocysteine has previously been shown to be twice that of creatinine, reflecting filtration as well as active metabolism and/or secretion within the kidney.[29] Thus, 5-adenosylhomocysteine may serve as a sensitive indicator of subclinical renal dysfunction or of poor renal reserve. Alternatively, alterations in 5-adenosylhomocysteine may play a direct causal role in acute renal injury as 5-adenosylhomocysteine is a powerful inhibitor of DNA methylation and thereby impacts epigenetic regulation of a wide array of proteins and disease processes, including atherosclerosis, endothelial dysfunction, and cancer.[29–32]

TAVR is an alternative to surgery for high-risk patients with symptomatic severe aortic stenosis. Candidates for this invasive procedure are consequently elderly and often possess numerous comorbid conditions including heart failure, diabetes mellitus, hypertension, advanced vascular disease, and CKD, each of which conveys an increased risk of kidney injury.[1–3] During TAVR, these high-risk patients are exposed to significant physiologic stresses such as iodinated contrast, a myriad of potentially nephrotoxic medications, periods of hypotension and hypoperfusion, and frequently atheroembolic events and blood transfusions. It is therefore not surprising, as demonstrated here, that AKI occurs in 8% to 42% of cases and that AKI is in turn associated with markedly increased short- and long-term mortality after TAVR.[9–15] Studies attempting to predict AKI using routine clinical and laboratory parameters to date have resulted in varied and inconsistent predictors.[9] There is therefore an unmet clinical need to identify patients at increased risk of AKI after TAVR. The accurate prediction of AKI risk would inform conversations with patients regarding postprocedure recovery and allow for the targeted evaluation and eventual implementation of preventative measures including potentially the limitation of iodinated contrast use, shortening of rapid pacing runs and periods of hypotension/hypoperfusion, application of conservative blood transfusion thresholds, hydration, and hydration with matched diuresis.[33] The addition of metabolic biomarkers to clinical data is therefore a novel approach that may ultimately improve renal risk prediction and the management of high-risk patients.

Limitations of the current study warrant attention. The sample size of this study was limited and did not allow for validation of our findings. Additional plasma metabolites, beyond those identified here, may therefore be valuable in predicting renal risk. While false discovery is possible with a small sample, the marked consistency of the identified metabolites with the FHS cohort and with prior observations in independent cohorts supports the validity of our findings.[21,23,29] In addition, the small number of patients limits the use of extensive multivariable regression analysis to adjust for potential confounding. Nevertheless, elevations in the identified plasma metabolites denote increased clinical risk and motivate validation in additional cohorts in future studies. Finally, patient death may impact the relationship between metabolite levels and hospital and intensive care unit lengths of stay. Given that higher 5-adenosylhomocystine was associated with both death and prolonged length of stay, death in fact attenuates the true relationship between the metabolite and length of stay.

In summary, the novel application of LC-MS–based metabolite profiling techniques to TAVR patients has identified metabolic perturbations that strongly predict not only AKI but also mortality after transfemoral TAVR. Future efforts are required to validate novel metabolic markers identified in this study in larger TAVR cohorts, to explore the mechanistic pathways by which these biomarkers confer risk, and to develop preventative clinical measures in patients at extreme risk of periprocedural kidney injury.

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Disclosures

None.

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