A Within-Patient Analysis for Time-Varying Risk Factors of CKD Progression

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ABSTRACT

Recent data suggest that nonlinear GFR trajectories are common among patients with CKD, but the modifiable risk factors underlying these changes in CKD progression rate are unknown. Analyses relating baseline risk factors to subsequent GFR decline are suboptimal because these relationships often attenuate as follow-up time increases and these analyses do not account for temporal changes in risk factors. We identified 74 participants in the African American Study of Kidney Disease and Hypertension who had both a period of rapid GFR decline and an extended period of stability during a follow-up period of ≥12 years. We performed a within-patient comparison of time-varying risk factors measured during the periods of GFR decline and stability and identified several risk factors associated with faster GFR decline: more hospitalization episodes and hospitalization days per year; higher BP, serum phosphorus, and urine protein-to-creatinine ratio; lower serum albumin and urine sodium-to-potassium ratio; slower rate of decline of serum urea nitrogen, serum creatinine, serum uric acid, and serum phosphorus; and faster rate of decline of serum hematocrit and serum bicarbonate. By allowing each patient to serve as his or her own control, this novel, within-patient analytic approach holds considerable promise as a means to identify time-varying risk factors associated with stabilization of GFR or acceleration of GFR decline.

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Anecdotal observations of nephrologists have long suggested that the rate of GFR decline can be punctuated by episodes of rapid decline as well as periods of stability. However, until recently, most statistical analyses of GFR decline have relied on the assumption of linear rates of decline.[1,2] This analytic approach is used in part because of its simplicity and in part because the relatively brief follow-up times of most longitudinal studies of patients with CKD limited the ability to detect deviations from linearity. Recent analyses of CKD cohorts with extended duration of follow-up have provided rigorous statistical confirmation that nonlinear trajectories are in fact commonplace.[1,2] Using Bayesian analysis, we established that over a median follow-up of 9 years, 42% of the participants from the African American Study of Kidney Disease (AASK) had a ≥0.9 probability of having a nonlinear trajectory or a prolonged period of nonprogression.[1]

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The development of rigorous methods for identifying nonlinear trajectories provides intriguing new possibilities for epidemiologic investigation of the relationships between CKD progression and potential risk factors. In particular, if specific periods of stable GFR and rapidly declining GFR can be identified, then it would be possible to investigate which factors changed over time that may have led to changes in the rate of CKD progression. In this approach, risk factors would be compared between periods of rapidly declining GFR and periods of stable GFR in the same patients. Although observational in nature, such a within-patient approach would overcome three fundamental problems that hamper the current standard epidemiologic approaches in CKD cohort studies in which baseline (*i.e.*, time-invariant) risk factors are related to subsequent CKD progression. First, by relating the rate of progression in specific periods to measurements of risk factors in those same periods, the within-patient approach avoids the drawback seen with use of baseline risk factors: that the relationship between GFR decline and the baseline risk factors often attenuates as follow-up time increases. Second, by limiting assessment of the risk factor to a single measurement at baseline, the standard approach is unable to account for changes in risk factors occurring during the study that may lead to changes in rates of progression. Third, by comparing risk factors between periods of rapid progression and stable GFR in the same patients, each patient is used as his or her own control; thus, we can eliminate the effects of patient-specific confounders, both measured and unmeasured, that are often present in the standard cohort design when progression rates are related to risk factors across different patients with different characteristics.

In this study we use a novel within-patient crossover design and analytic approach to study time-varying risk factors of CKD progression. We previously identified 74 AASK participants whose estimated GFR (eGFR) trajectories had both a period of rapid decline and an extended period of stability, according to conservative prespecified criteria.[1] Using data from these participants, we compared time-varying risk factors measured during the decline and stable periods within each participant to identify potentially-modifiable risk factors associated with GFR decline.

RESULTS

Table 1 summarizes the baseline characteristics of the 74 AASK participants in this analysis, which includes 45 participants who had the stable period first (stable/decline) and 29 who had the decline period first (decline/stable). For the stable/decline group, the median eGFRs (interquartile range) for the stable and the decline periods were 53.6 (46.3–61.6) ml/min per 1.73 m^2 and 34.7 (29.5–52.8) ml/min per 1.73 m^2, respectively. For the decline/stable group, median eGFRs (interquartile range) for the decline and the stable periods were 52.6 (44.0–59.8) ml/min per 1.73 m^2 and 39.1 (28.4–46.2) ml/min per 1.73 m^2, respectively. Median duration, including all 74 participants, was 32 months for the decline periods and 50 months for the stable periods. Of note, the earlier period always had a higher mean eGFR, regardless of whether it was a stable or decline period, because the overall trend in this cohort was that the eGFR declined over time. Figure 1 illustrates the nonlinear eGFR trajectories for six individuals in our analysis.

Hospitalizations

Participants experienced more hospitalization episodes per year (0.25 versus 0.12; P=0.01) and higher total days of hospitalization per year (1.8 versus 0.6; P=0.03) during the decline period than the stable period; results remained similar after adjustment for early/late period and mean eGFR during these periods (Table 2). The adjusted odds ratio of having a hospitalization was 0.7 (95% confidence interval, 0.3 to 1.5; P=0.3) for the stable versus decline comparison (Table 2). This nonsignificant result may be partly due to lower statistical power with the binary outcome variable.

Because the sample size was small, we did not have enough statistical power for formal comparisons of specific hospitalization diagnoses. However, Supplemental Table A1 shows a trend toward more hospitalizations for cardiovascular (19 compared with 12), surgery (16 compared with 2), and cancer (6 compared with 2) diagnoses during the decline periods compared with the stable periods.

Medication

Self-reported medication use was generally similar between the stable and decline periods, with no significant differences in use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, lipid-lowering medications, nonsteroid anti-inflammatory drugs, uric acid–lowering medications, or other BP medications (Supplemental Table A2).

BP

After adjustment for early/late period and mean eGFR of each period, systolic BP was on average 3.8 mmHg higher during the decline period than during the stable period (P=0.02). Likewise, diastolic BP was 1.6 mmHg (P=0.06) higher, and mean arterial BP was 2.3 mmHg (P=0.03) higher during the decline period compared with the stable period (Table 3).

Biomarkers

Mean levels of serum phosphorus, urine protein, and urine protein-to-creatinine ratio were higher, and mean levels of albumin and urine sodium-to-potassium ratio were lower in the decline periods than the stable periods, after adjustment for early/late period and mean eGFR of each period (Table 4).

In addition to studying the relationship of GFR decline rate with the mean level of a biomarker, we also considered its relationship with the rate of change of the biomarker, which was quantified by the least-squares slope of the biomarker within each stable or decline period. Mean slopes of serum urea nitrogen, serum creatinine, serum uric acid, and serum

Table 1. Summary statistics of the study sample

Baseline Characteristics	Summary Statistics		
	Stable/Decline (*n*=45)	Decline/Stable (*n*=29)	All 74 Patients
Age at randomization (yr)	53.1 (45.6, 57.8)	54.9 (44.5, 62.1)	53.7 (45.5, 58.9)
Women	13 (28.9)	12 (41.4)	25 (33)
Baseline eGFR (ml/min per 1.73 m^2)[a]	49.7 (41.1, 57.3)	60.6 (55.4, 68.0)	55.8 (44.1, 61.8)
Baseline urine protein-to-creatinine ratio (g/g)	0.05 (0.02, 0.12)	0.05 (0.03, 0.11)	0.05 (0.02, 0.11)
Duration of stable periods (mo)	51 (41, 57)	49 (41, 58)	50 (41, 58)
Duration of decline periods (mo)	34 (24, 50)	28 (24, 41)	32 (24, 42)
AASK randomized intervention: mean arterial pressure goal			
≤92 mmHg	18 (40)	14 (48.3)	32 (43)
102–107 mmHg	27 (60)	15 (51.7)	42 (57)
AASK randomized intervention: antihypertensive drugs[b]			
Ramipril	19 (42.2)	10 (34.5)	29 (39)
Metoprolol	18 (40)	11 (37.9)	29 (39)
Amlodipine	8 (17.8)	8 (27.6)	16 (22)
Average eGFR on segments of estimated trajectory (ml/min per 1.73 m^2)			
On stable periods	53.6 (46.3, 61.6)	39.1 (28.4, 46.2)	48.5 (37.2, 58.0)
On decline periods	34.7 (29.5, 52.8)	52.6 (44.0, 59.8)	43.1 (31.8, 54.8)

Continuous variables were summarized by median (25th and 75th percentiles). Categorical variables were summarized by number (percentage).
[a]Averaged over two baseline values, <3 months apart.
[b]The randomized antihypertensive drugs were allocated in 2:2:1 ratio. Amlodipine was stopped 3 years after randomization.

phosphorus were higher, and mean slopes of serum hematocrit and bicarbonate were lower in the decline periods than the stable periods, after adjustment for early/late period and mean eGFR of each period (Table 5). Note that a higher slope (more positive or less negative) generally indicates faster rate of increase or slower rate of decline of a biomarker, while a lower slope (more negative or less positive) generally indicates slower rate of increase or faster rate of decline.

DISCUSSION

In this study comparing periods of stable GFR with periods of declining GFR in 74 individuals with hypertensive kidney disease, we illustrated how a novel, within-patient crossover design can be used to identify time-varying risk factors for GFR decline. This approach has many advantages. First, the design is conceptually simple and the analytic approach is intuitive and easy to interpret. Second, the selected subset of AASK participants, with clear-cut stable and decline periods, was most informative for the investigation of the association of contemporaneously measured time-varying risk factors with changes in the rate of GFR decline. Third, this design removes the confounding effects of all time-invariant (*e.g.*, baseline) risk factors, regardless of whether they are measured or unmeasured, because the stable and decline periods of each patient share the same time-invariant risk factors. Fourth, because risk factors are measured concurrently with eGFR in this design, there may be increased power to detect time-varying risk factors associated with periods of GFR decline compared with studies that use baseline risk factors, where the relationships between risk factors and the outcome attenuate over time. Fifth, our analytic approach can be used to study the association between CKD progression and both the level (Table 4) and rate (Table 5) of change in each time-varying risk factor.

This latter approach using data on rates of changes in biomarkers and other risk factors could help improve our understanding of CKD progression because risk factors often change over time as GFR declines. Moreover, this type of dynamic data may become increasingly available for clinicians and researchers alike with the widespread adoption of electronic medical records. Using this method, we identified serum phosphorus, bicarbonate, and uric acid as potentially modifiable risk factors, although we cannot prove causality. Most,[3–5] but not all,[6] traditional observational studies examining baseline risk factors have found that higher serum phosphorus levels are associated with rapid GFR decline and ESRD. Other researchers have also found an association between lower serum bicarbonate and CKD progression,[7,8] and small, randomized trials have found that bicarbonate supplementation slows the rate of CKD progression.[9,10] Some have suggested a pathogenic role of hyperuricemia in hypertension and renal injury,[11,12] although hyperuricemia has been associated with cardiovascular events and mortality, but not rapid renal progression or ESRD.[13,14]

Several studies have found an association between episodes of AKI and risk of rapid GFR decline and ESRD.[2,15,16] In our study, we found that the number of hospital episodes and hospitalization days per year were significantly greater in the decline periods than the stable periods. We did not have information beyond International Classification of Diseases, Ninth Revision, codes for primary and secondary diagnoses, so we cannot ascertain whether episodes of AKI occurred during these hospitalizations. Because AKI often

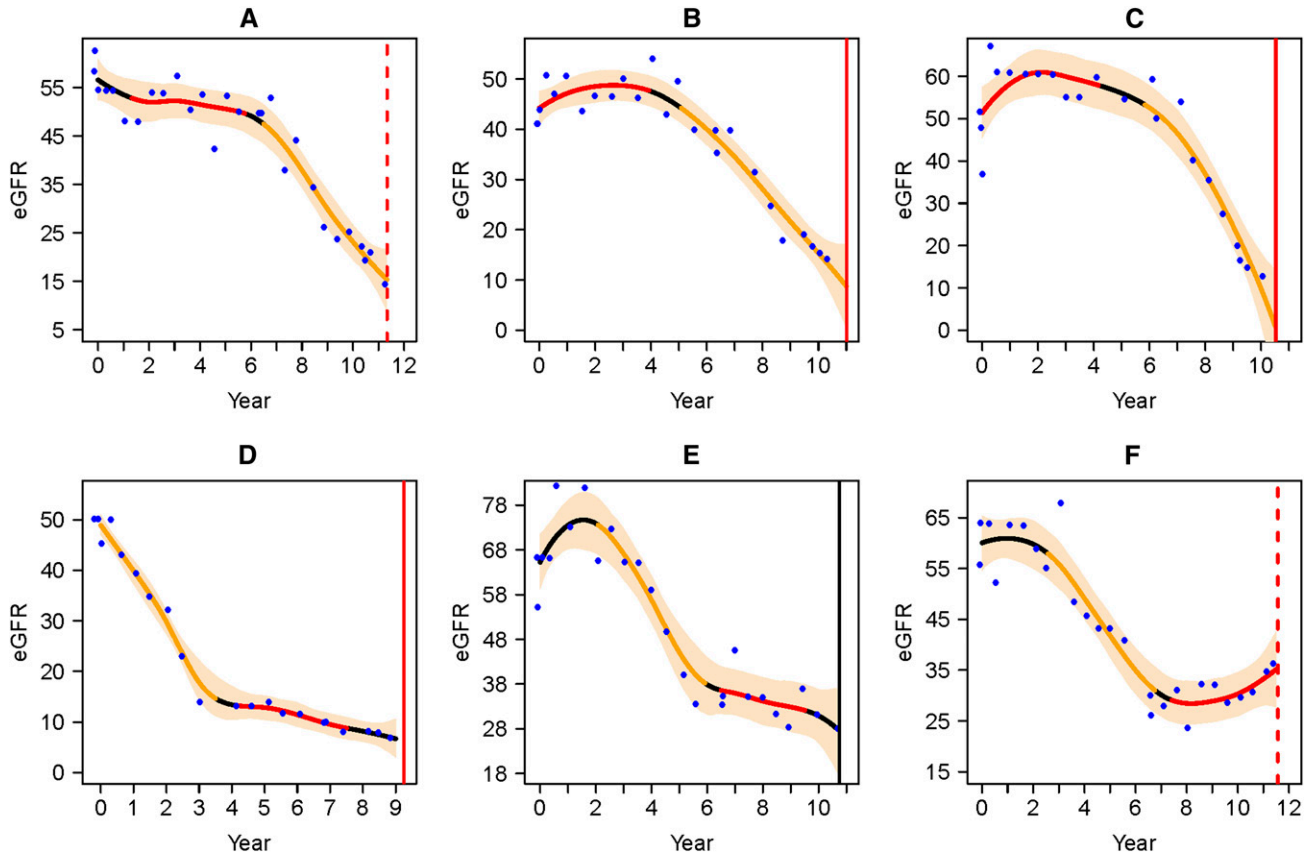

Figure 1. It can be seen that a patient's trajectory can have both a period of stability and a period of decline. The eGFR trajectories of six AASK patients in the analysis. On each plot, the horizontal axis is year since randomization, and the vertical axis is eGFR (ml/min per 1.73 m^2). The blue dots are eGFR data, and the black smooth curve is the estimated trajectory; the yellow segment represents the declining eGFR period, and the red segment represents the stable or increasing eGFR period. The bisque-colored band is the pointwise 95% Bayesian confidence intervals. The red vertical line represents time of censoring (dashed) or dialysis (solid). The black vertical line represents time of death. Plots a–c represent individuals who had the stable period first, and d–f represent individuals who had the decline period first.

Table 2. Comparison of three hospitalization metrics between the stable and decline periods

Hospitalization Metrics	Unadjusted Comparison				Adjusted for Early/Late Periods and Mean eGFR	
	Stable Periods	Decline Periods	Unadjusted Difference (Stable–Decline)	*P* Value	Adjusted Difference (Stable–Decline)	*P* Value
Periods with hospitalization (%)	31	41	OR, 0.63 (0.31 to 1.3)	0.21	OR, 0.66 (0.29 to 1.5)	0.31
Hospitalization episodes per year (*n*)	0.12	0.25	−0.13 (0.05)	0.013	−0.13 (0.06)	0.02
Total duration of hospitalizations per year (*d*)	0.61	1.8	−1.2 (0.55)	0.03	−1.1 (0.57)	0.05

For the first binary metric, the difference is expressed as odds ratio (OR) with 95% confidence intervals. For the other two continuous metrics, the differences are expressed as the mean differences with estimated SEMs.

occurs in the setting of cardiovascular, cancer, and surgery hospitalizations,[17,18] we speculate that episodes of AKI may have occurred, explaining the trend toward more hospitalizations for these diagnoses during periods of decline. However, it is also possible that the decline periods may simply represent worsening overall health, resulting in more hospitalizations.

Although this study design has many advantages, we still are unable to prove that these associations are causal in nature. For instance, mean slope of hematocrit was lower in the decline period than the stable period, a finding consistent with those of other showing that lower hemoglobin levels are associated with progression to ESRD.[19,20] However, randomized controlled trials treating anemia with erythropoietin-stimulating agents

Table 3. Comparison of the average BP between the stable and decline periods

Blood Pressure	Unadjusted Comparison				Adjusted for Early/Late and Mean eGFR	
	Mean of Stable Periods	Mean of Decline Periods	Unadjusted Mean Difference (Stable–Decline)	*P* Value	Adjusted Mean Difference (Stable–Decline)	*P* Value
Systolic (mmHg)	131.1 (107.1, 161.7)	134.0 (100.5, 169.8)	−2.8 (1.6)	0.08	−3.8 (1.6)	0.02
Diastolic (mmHg)	81.2 (54.6, 96.1)	81.2 (56.6, 111.3)	0 (1.1)	1.0	−1.6 (0.9)	0.06
Mean arterial pressure (mmHg)	98.0 (75.6, 114.2)	98.9 (72.6, 128.2)	−0.9 (1.3)	0.47	−2.3 (1.1)	0.03

The numbers in the parentheses are the range of BP or the SEM of the unadjusted or adjusted mean differences.

Table 4. Comparison of the average biomarker levels between the stable and decline periods

Biomarker	Unadjusted Comparison				Adjusted for Early/Late Periods and Mean eGFR	
	Mean of Stable Periods	Mean of Decline Periods	Unadjusted Mean Difference (Stable–Decline)	*P* Value	Adjusted Mean Difference (Stable–Decline)	*P* Value
Serum						
Albumin (g/dl)	4.16	4.03	0.13 (0.03)	<0.001	0.12 (0.03)	<0.001
Alkaline phosphatase (U/L)	93.2	97.4	−4.27 (2.45)	0.08	−1.93 (2.31)	0.38
Calcium (mg/dl)	9.34	9.44	−0.1 (0.07)	0.14	−0.01 (0.05)	0.87
Glucose (mg/dl)	100.9	100.6	0.32 (2.06)	0.88	1.74 (1.95)	0.35
Serum urea nitrogen (mg/dl)	26.5	31.4	−4.87 (2.26)	0.03	−0.89 (1.45)	0.50
Serum creatinine (mg/dl)	2.05	2.43	−0.38 (0.14)	0.005	−0.15 (0.09)	0.12
Serum urea nitrogen-to-creatinine ratio	13.09	13.06	0.03 (0.52)	0.95	0.5 (0.49)	0.30
eGFR (ml/min per 1.73 m^2)	47.5	43.2	4.36 (1.71)	0.010	0.67 (0.27)	0.02
Serum uric acid (mg/dl)	8.55	8.54	0.01 (0.23)	0.95	0.13 (0.24)	0.62
Serum phosphorus (mg/dl)	3.42	3.71	−0.29 (0.08)	<0.001	−0.18 (0.07)	0.005
Serum sodium (mmol/L)	138.4	139.0	−0.63 (0.35)	0.07	−0.27 (0.33)	0.45
Serum hematocrit (%)	39.3	38.3	1.05 (0.43)	0.01	0.55 (0.38)	0.13
Serum bicarbonate (mmol/L)	26.0	25.9	0.08 (0.35)	0.82	−0.16 (0.35)	0.61
Urine						
Urine urea nitrogen (g/d)	8.37	8.10	0.27 (0.28)	0.33	0.07 (0.28)	0.81
Urine protein (g/d)	0.36	1.01	−0.65 (0.15)	<0.001	−0.49 (0.14)	<0.001
Urine creatinine (g/d)	1.60	1.57	0.04 (0.05)	0.47	0 (0.05)	0.95
Urine protein/creatinine ratio (g/g)	0.21	0.69	−0.48 (0.12)	<0.001	−0.36 (0.11)	<0.001
Urine sodium (g/d)	4.02	3.72	0.3 (0.19)	0.11	0.27 (0.19)	0.12
Urine potassium (g/d)	2.06	2.05	0.01 (0.09)	0.94	−0.07 (0.09)	0.43
Urine sodium-to-potassium ratio (g/g)	2.29	2.10	0.19 (0.11)	0.07	0.26 (0.11)	0.02

The unadjusted or adjusted mean differences are expressed as the estimator (SEM).

have resulted in no difference in CKD progression, while one small study found no effect of iron supplementation on CKD progression.[21,22] Other studies have suggested potential renal risks with targeting higher hemoglobin goals with erythropoietin-stimulating agents.[23,24] Biomarkers, BP, and overall health may simply worsen as kidney function declines, so that difference in the rates of eGFR decline between the decline and stable periods may have influenced the studied time-varying risk factors rather than the converse. Creatinine-based eGFR does not account for some of the observed differences in biomarkers may reflect differences in kidney function.

Our design and analytic approach have some limitations. First, the design restricts the analysis to a subset of the AASK participants who had both a period of rapidly declining GFR and a period of stable GFR according to conservative prespecified criteria. The use of a focused subset of the full cohort is common to a variety of designs that are widely used in epidemiologic research, including matched case-control and case-crossover designs. The rationale for these designs is to facilitate robust

Table 5. Comparison of the rate of change (per year) of biomarkers between the stable and decline periods

Biomarker	Unadjusted Comparison				Adjusted for Early/Late Periods and Mean eGFR	
	Mean Slope of Stable Periods	Mean Slope of Decline Periods	Unadjusted Mean Slope Difference (Stable–Decline)	*P* Value	Adjusted Mean Slope Difference (Stable–Decline)	*P* Value
Serum						
Albumin (g/dl)	−0.01	0.034	−0.04 (0.05)	0.35	−0.01 (0.05)	0.74
Alkaline phosphatase (U/L)	1.38	1.00	0.38 (2.7)	0.89	−0.45 (2.9)	0.87
Calcium (mg/dl)	0.043	0.068	−0.03 (0.06)	0.69	−0.06 (0.07)	0.25
Glucose (mg/dl)	0.11	−1.30	1.4 (4.23)	0.74	1.6 (4.49)	0.71
Serum urea nitrogen (mg/dl)	−0.72	9.34	−10.1 (1.8)	<0.001	−9.44 (1.95)	<0.001
Serum creatinine (mg/dl)	−0.042	0.77	−0.81 (0.18)	<0.001	−0.71 (0.19)	<0.001
Serum urea nitrogen-to-creatinine ratio	0.044	0.44	−0.39 (0.46)	0.39	−0.45 (0.49)	0.37
eGFR (ml/min per 1.73 m^2)	1.49	−8.04	9.53 (1.74)	<0.001	9.21 (1.78)	<0.001
Serum uric acid (mg/dl)	−0.32	0.63	−0.95 (0.21)	<0.001	−1.12 (0.21)	<0.001
Serum phosphorus (mg/dl)	−0.012	0.24	−0.25 (0.08)	0.002	−0.2 (0.09)	0.004
Serum sodium (mmol/L)	−0.21	0.47	−0.68 (0.35)	0.050	−0.74 (0.37)	0.056
Serum hematocrit (%)	0.41	−1.48	1.88 (0.42)	<0.001	1.87 (0.44)	<0.001
Serum bicarbonate (mmol/L)	0.57	−0.53	1.1 (0.36)	0.002	0.87 (0.37)	0.007
Urine						
Urine urea nitrogen (g/d)	0.11	−0.20	0.31 (0.34)	0.36	0.31 (0.34)	0.32
Urine protein (g/d)	0.087	0.22	−0.13 (0.12)	0.25	−0.15 (0.12)	0.24
Urine creatinine (g/d)	0.016	−0.047	0.06 (0.04)	0.14	0.06 (0.04)	0.18
Urine protein/creatinine ratio (g/g)	0.049	0.12	−0.07 (0.07)	0.30	−0.06 (0.07)	0.34
Urine sodium (g/d)	0.23	0.026	0.2 (0.21)	0.33	0.2 (0.21)	0.31
Urine potassium (g/d)	0.046	−0.013	0.06 (0.11)	0.60	0.01 (0.12)	0.95
Urine sodium-to-potassium ratio (g/g)	0.12	0.018	0.1 (0.11)	0.35	0.16 (0.11)	0.17

The unadjusted or adjusted mean slope differences are expressed as the estimator (SEM).

analyses that minimize confounding and other forms of bias while focusing on the topics that are most informative for the research question under consideration. Although used in other lines of epidemiologic research, the case-crossover study design has not previously been used to examine risk factors for accelerated CKD progression. Second, we have considered time-varying risk factors one at a time and have not investigated the joint dependence of GFR decline on multiple risk factors. Future work is warranted to develop multivariable time-varying risk factor models that use multiple time-varying exposures. Third, although our design eliminates confounding from all time-invariant risk factors, both measured and unmeasured, there could still be residual confounding from other time-varying risk factors. However, because we incorporated covariate adjustment for the temporal ordering of the stable and decline periods, as well as the mean eGFR levels during the respective periods, our adjusted comparisons are unlikely to have been affected by confounding associated with time or the level of eGFR itself.

In summary, this novel, within-patient analytic approach holds considerable promise as a means to identify time-varying risk factors associated with stabilization of GFR or acceleration of GFR decline. Our analyses identified several modifiable factors (serum uric acid, serum phosphorus, and serum bicarbonate) that could be therapeutic targets in clinical trials.

CONCISE METHODS

Study Population

AASK was a multicenter, randomized clinical trial of 1094 African American patients aged 18–70 years with a baseline GFR between 20 and 65 ml/min per 1.73 m^2.[25] The participants were randomly assigned in a 3×2 factorial design to one of three antihypertensive drug regimens (ramipril, amlodipine, or metoprolol) and two levels of BP control (mean arterial pressure≤92 mmHg or 102–107 mmHg). At the completion of the trial, 787 participants were alive and not undergoing dialysis; of these, 691 were enrolled in the subsequent AASK Cohort Study.[25] The maximum follow-up of both trial and cohort phases was 12 years. Serum creatinine was measured twice at baseline, less than 3 months apart, and at follow-up months 3 and 6, and then every 6 months for the rest of the follow-up.

Previously,[1] we analyzed the combined trial and cohort phase data from 846 AASK participants with at least 3 years of follow-up and at least eight visits in which GFR could be estimated from serum creatinine measurements using the AASK equation[26]:

$$\text{eGFR} = 329 \times (\text{serum creatinine})^{-1.096} \times (\text{age})^{-0.294} \times (0.736 \text{ for female}).$$

Bayesian penalized splines were used to estimate the eGFR trajectory of each patient as a smooth curve, removing much of the noise, short-term variation, and measurement error in the eGFR and revealing the overall trend over time.

Definitions of Stable and Decline Periods

Using the eGFR trajectories, we defined a period of stable GFR to be a period of time that satisfied the following three conditions: (*1*) the period was at least 3 years; (*2*) the trajectory increased or declined slowly (*i.e.*, at a rate of <2 ml/min per 1.73 m^2 per year throughout); and (*3*) the total decrease in eGFR, if any, was no more than 4.5 ml/min per 1.73 m^2. We defined a period of rapidly declining GFR to be a period of time that satisfied the following two conditions: (*1*) the trajectory decreased at a rate of at least 4 ml/min per 1.73 m^2 per year during the entire period; and (*2*) the total decline was at least 8 ml/min per 1.73 m^2. It was found that 74 AASK participants had both a stable period and a decline period (1). Of the 74 patients, the stable period preceded the decline period in 45 participants, and the decline period preceded the stable period in 29 participants. The mean (minimum, maximum) length of the stable periods was 52 (36, 93) months, and that of the decline periods was 36 (13, 79) months.

The Within-Patient Crossover Design

We used data from these 74 participants with both stable and decline periods to determine whether time-varying risk factors were associated with eGFR decline. Essentially, a difference in a time-varying risk factor between the stable and decline periods implies that this time-varying risk factor may be associated with GFR decline. This approach allows us to study a large number of time-varying risk factors that are associated with GFR decline or stabilization without complicated modeling assumptions.

Statistical Analyses

We considered four classes of time-dependent risk factors for their association with the eGFR decline: hospitalizations, medications, BP levels, and biomarkers. Below we define clinically relevant metrics for each class.

Hospitalization

We used three metrics to quantify hospitalizations: (*1*) the percentage of patients with at least one hospitalization episode; (*2*) the number of hospitalization episodes per year; and (*3*) the total days of hospitalization per year. The primary and secondary International Classification of Diseases, Ninth Revision, codes of hospitalization were summarized and compared between the stable and decline periods by frequency tables.

Medication

The current medications taken by the patient were recorded at each follow-up visit. We made the simplifying assumption that if a patient was receiving a certain medication at a particular visit, this patient had been receiving that medication between that visit and the preceding visit. The proportion of time that a patient was receiving a certain medication was calculated for each patient's stable and decline periods and was used as a metric to quantify medication use.

BP

We calculated the mean BP (arterial, systolic, diastolic) within each patient's stable and decline periods.

Biomarkers

We used two different metrics to characterize the levels and the average rates of change of biomarkers during the stable and decline periods. First, we calculated the mean biomarker value for each patient's stable and decline periods. Second, we computed the least-squares slopes of separate linear regressions of the biomarker values versus time within each patient's stable and decline periods.

The general analytic strategy was to calculate the change in the aforementioned metrics of the time-varying risk factors between the stable and decline periods within the same patient and average the results across all 74 patients. The later period generally had lower eGFR than the earlier period, and on average the decline periods also had lower mean eGFR than the stable periods. Hence, we provide results both with and without adjusting for temporal confounding and for confounding by the level of GFR by including as covariates an indicator of early/late period and the mean eGFR level of each period. Time-varying risk factors exhibiting statistically significant differences between the stable and decline periods in the adjusted analysis were identified as being associated with GFR decline or stabilization, independent of the temporal ordering of the periods or the level of eGFR. We interpreted our analyses as representing the discovery phase of risk factor identification, and thus performed all hypothesis tests on a comparison-wise basis using a two-sided α=0.05, without adjustment for multiple comparisons. Details on the statistical models can be found in the Supplemental Materials.

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DISCLOSURES

None.

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Supplemental Materials for Online Archive

Title: A Within-Patient Analysis for Time-varying Risk Factors of CKD Progression

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Statistical Details

From a statistical perspective, there are two kinds of time-varying risk factors in this paper: binary and continuous. The first metric in the *hospitalization* category is binary (Table 2), and all others are continuous variables. For a binary time-varying risk factor, we used McNemar test for the unadjusted comparison, and used the following conditional logistic regression for the adjusted analysis:

$$\log it\left(Y_{ij} = 1\right) = \beta_0 + \beta_1 S_{ij} + \beta_2 Z_{ij} + \beta_3 W_{ij} + \alpha_i + \varepsilon_{ij},$$

where $i = 1,2,...,74$ is the index of the 74 patients in this analysis, and $j = 1,2$ index the early and late period. S_{ij} is an indicator that equals 0 if the j th period of patient i is a decline period and equals 1 if it is a stable period. Z_{ij} equals 0 if the period is an early period, and equals 1 if the period is a late period (i.e., $Z_{ij} = j - 1$). W_{ij} equals the mean eGFR of the j th period of patient i, as identified from the estimated trajectory. α_i is a patient-specific random intercept with mean zero that introduces within-patient correlation to Y. In this model, β_1, β_2 and β_3 quantify the odds ratios of the stable period, the late period, and the mean eGFR, respectively.

For a continuous time-varying risk factor, we used paired t-test for unadjusted analysis, and used the following linear model for the adjusted analysis:

$$Y_{ij} = \beta_0 + \beta_1 S_{ij} + \beta_2 Z_{ij} + \beta_3 W_{ij} + \alpha_i + \varepsilon_{ij}.$$

The syntax is similar to the conditional logistic regression model above, except that ε_{ij} is an independent residual noise term with mean zero. In this model, β_1, β_2 and β_3 quantify the effects of the stable period, the late period, and the mean eGFR, respectively, on the mean of Y. The model above implies that

$$Y_{i2} - Y_{i1} = \beta_1 \left(S_{i2} - S_{i1} \right) + \beta_2 \left(Z_{i2} - Z_{i1} \right) + \beta_3 \left(W_{i2} - W_{i1} \right) + \left(\varepsilon_{i2} - \varepsilon_{i1} \right) ,$$

which is a linear model without intercept and can be fit using standard software for linear models. We made no assumptions on the distributions of α and ε terms beyond zero mean, and used the sandwich method to derive the variance estimator in anticipation of some heterogeneity in the variance of $\varepsilon_{i2} - \varepsilon_{i1}$.

All analyses above were performed using R 2.12.2 (www.r-project.org). For statistical tests, the α level of 0.05 was used.

Table A1. Number of hospitalization episodes with the primary or secondary ICD-9 diagnosis codes

ICD-9 code	Composite ICD-9 code: either primary or secondary		Primary ICD-9 code		Secondary ICD-9 code	
	Decline periods	Stable periods	Decline periods	Stable periods	Decline periods	Stable periods
Cancer	6	2	5	2	2	0
Cardiovascular	19	12	16	9	9	6
Endocrine	4	0	3	0	1	0
Fluid	1	2	1	0	0	2
Hypertension	8	13	4	11	4	2
Infection	2	3	2	3	0	1
Other	12	17	10	10	3	10
Psychiatry	1	2	0	2	1	1
Pulmonary	2	1	1	0	1	1
Renal	1	1	1	1	0	0
Surgery	16	2	7	2	9	0
None	20	17	0	0	20	17

Table A2. Comparison of the average percentage of time that a patient is on a medication between the stable and decline periods. The unadjusted or adjusted mean differences are expressed as the estimator (standard error)

	Unadjusted comparison				Adjust for early/late and mean eGFR	
Medication	Mean of stable periods	Mean of decline periods	Unadjusted mean difference (stable – decline)	p-value	Adjusted mean difference (stable – decline)	p-value
ACE/ARB	67.1	71.3	-4.1(7.5)	0.58	6(5.7)	0.25
Acetaminophen	15.1	14.5	0.6(3.5)	0.87	3.2(3.4)	0.32
Alpha-1 Adrenergic Agent	42.5	46.1	-3.6(5.4)	0.51	-7.9(5.2)	0.12
Aminoglycoside	0.3	0.04	0.23 (0.27)	0.39	0.09(0.3)	0.56
Antiplatelet aspirin	18.9	21.7	-2.8(4.2)	0.50	-1.9(4.3)	0.63
Beta Blockers	41.4	47.6	-6.2 (6.2)	0.31	-2.8(6.2)	0.66
Central Adrenergic Agent	34.4	35.1	-0.7(4.6)	0.87	-0.5(4.8)	0.91
Di-hydropyridine Calcium Channel Blocker	31.3	37.1	-5.8(5.3)	0.27	-0.9(5.0)	0.86
Non-Di-Hydropyridine Calcium Channel Blocker	7.0	13.1	-6.2(4.0)	0.12	-4.3(3.9)	0.24
Distal Diuretic	15.4	17.6	-2.3(3.6)	0.52	-2.3(3.6)	0.52
Gout	29.7	27.4	2.3(3.7)	0.53	5.1(3.6)	0.20
HMG CoA Inhibitors	23.8	25.7	-1.9(6.1)	0.76	4.4(5.6)	0.44
Potassium-Sparing Diuretic	7.7	8.5	-0.9(2.7)	0.75	0.68(2.7)	0.81
Loop Diuretic	79.6	78.9	0.7(4.0)	0.87	2.9(4.1)	0.49
NSAID	7.0	7.8	-0.7(2.2)	0.74	-0.87(2.3)	0.74
Vasodilator	26.2	21	5.2(4.2)	0.21	2.9(4.2)	0.46
Miscellaneous	12.2	11.2	1.0(4.4)	0.82	1.7(4.6)	0.73
Mineral Supplements						
Iron (Fe)	6.9	10.6	-3.8(2.7)	0.16	-2.5(2.7)	0.40
Potassium (K)	26.5	28.8	-2.4(3.5)	0.49	-2.3(3.6)	0.51