Supplemental Materials: Table of Conetents

Supplemental Table 1. Causes of death (N = 5) by CKD primary diagnosis.

Non-Glomerular (N = 3)
Cerebrovascular
Drug Overdose (not due to suicide or street drugs)
Unknown
Glomerular (N = 2)
Septicemia
Septicemia

Supplemental Table 2. Reported alkali therapy treatment throughout follow-up by previous bicarbonate level among 511 children with non-glomerular disease contributing 2673 person-years of follow-up.

Previous visit Bicarbonate level	Person-years of follow-up, n (%)	Rate of Therapy Use	95% CI
Normal (CO_2>22)	1670 (63%)	23%	20%, 28%
Low (CO_2 19-22)	805 (30%)	41%	35%, 47%
Very low (CO_2≤18)	198 (7%)	71%	62%, 79%
Low/Very Low (CO_2≤22)	1003 (37%)	46%	41%, 52%

Supplemental Table 3. Reported alkali therapy treatment throughout follow-up by previous bicarbonate level among 213 children with glomerular disease contributing 808 person-years of follow-up.

Previous visit Bicarbonate level	Person-years of follow-up, n (%)	Rate of Therapy Use	95% CI
Normal (CO_2>22)	606 (75%)	7%	5%, 12%
Low ($CO_2$19-22)	193 (24%)	21%	14%, 30%
Very low (CO_2≤18)	9 (1%)	37%	19%, 59%
Low/Very Low (CO_2≤22)	202 (25%)	23%	16%, 31%

Supplemental Table 4. Hazard ratios (95% confidence intervals) for development of 50% decline in eGFR or kidney replacement therapy (KRT; transplant or dialysis) among all 858 children contributing 3481 person-years of follow-up and 280 composite events**.**

	Model 1	Model 2	Model 3	Model 4
Baseline Bicarbonate				
>22 mEq/L	1	1	1	1
19-22 mEq/L	**1.75 (1.35, 2.25)**	1.12 (0.86, 1.47)	1.09 (0.83, 1.42)	1.09 (0.83, 1.44)
≤18 mEq/L	**3.75 (2.61, 5.38)**	**1.49 (1.02, 2.18)**	1.24 (0.84, 1.82)	1.24 (0.84, 1.82**)**
Time-varying Bicarbonate*				
>22 mEq/L	1	1	1	1
19-22 mEq/L	**1.94 (1.49, 2.52)**	1.40 (1.07, 1.84)	1.12 (0.85, 1.47)	1.11 (0.84, 1.45)
≤18 mEq/L	**4.60 (3.31, 6.40)**	**2.21 (1.56, 3.14)**	**1.48 (1.04, 2.12)**	**1.46 (1.02, 2.08)**

Model 1: unadjusted model

Model 2: model 1 plus adjustment for glomerular diagnosis, baseline age (centered at 10), male sex, Caucasian race, baseline eGFR (<30, 30-45, 45-60, ≥60 ml/min/1.73 m^2), proteinuria (< 0.5, 0.5-2.0, ≥ 2.0 mg/mg)

Model 3: model 2 plus adjustment for anemia, phosphate (centered at 4.5mg/dL)

Model 4: model 3 plus adjustment for hypertension, alkali therapy use

Bold indicates significance.

Supplemental Table 5. Hazard ratios (95% confidence intervals) for development of a 50% decline in eGFR or kidney replacement therapy (KRT; transplant or dialysis).

	Non-glomerular (n=603) 2673 person-years of follow-up, 190 events		Glomerular (n=255) 808 person-years of follow-up, 90 events		Overall (n=858) 3481 person-years of follow-up, 280 events	
	Baseline*	Time-varying**	Baseline*	Time-varying**	Baseline*	Time-varying**
Bicarbonate, mEq/L						
>22	1	1	1	1	1	1
19-22	1.13 (0.80, 1.59)	0.91 (0.65, 1.26)	1.28 (0.80, 2.05)	**1.74 (1.07, 2.85)**	1.09 (0.83, 1.44)	1.11 (0.84, 1.45)
≤18	**1.95 (1.23, 3.09)**	1.28 (0.84, 1.94)	NE	**2.16 (1.05, 4.44)**	1.24 (0.84, 1.82)	**1.46 (1.02, 2.08)**
Baseline age, years	**1.09 (1.05, 1.13)**	**1.08 (1.04, 1.12)**	1.07 (0.99, 1.15)	**1.02 (0.95, 1.09)**	**1.09 (1.05, 1.12)**	**1.06 (1.03, 1.10)**
Male sex	1.23 (0.90, 1.69)	1.12 (0.81, 1.53)	0.89 (0.53, 1.48)	0.77 (0.47, 1.26)	1.08 (0.83, 1.39)	1.00 (0.77, 1.30)
Caucasian race	0.72 (0.52, 1.00)	0.79 (0.57, 1.11)	0.84 (0.51, 1.38)	0.89 (0.55, 1.44)	0.84 (0.65, 1.00)	0.86 (0.66, 1.12)
Baseline eGFR, ml/min/1.73 m^2						
≥60	1	1	1	1	1	1
≥45-60	**2.91 (1.39, 6.08)**	1.99 (0.94, 4.22)	**2.78 (1.48, 5.24)**	1.79 (0.94, 3.40)	**2.57 (1.65, 4.00)**	**1.92 (1.22, 3.02)**
≥30-45	**6.10 (2.94, 12.67)**	**2.29 (1.08, 4.87)**	**4.85 (2.56, 9.19)**	1.93 (0.98, 3.80)	**4.86 (3.16, 7.47)**	**2.18 (1.37, 3.46)**
<30	**15.11 (6.88, 33.20)**	**4.76 (2.16, 10.50)**	**7.48 (3.26, 17.16)**	**2.95 (1.30, 6.67)**	**10.48 (6.41, 17.14)**	**4.15 (2.50, 6.87)**
Protein/creatinine ratio, mg/mg						
< 0.5	1	1	1	1	1	1
0.5-2.0	**1.94 (1.40, 2.69)**	**2.99 (1.96, 4.54)**	**2.26 (1.17, 4.38)**	**2.31 (1.10, 4.87)**	**2.01 (1.51, 2.68)**	**2.75 (1.92, 3.94)**
≥ 2.0	**4.04 (2.53, 6.43)**	**8.83 (5.75, 13.58)**	**7.08 (3.71, 13.52)**	**9.79 (4.95, 19.37)**	**5.68 (4.03, 8.01)**	**9.26 (6.49, 13.25)**
Anemia	**1.66 (1.19, 2.31)**	**2.31 (1.67, 3.21)**	**2.23 (1.34, 3.71)**	**1.90 (1.14, 3.18)**	**1.70 (1.30, 2.21)**	**2.23 (1.80, 2.93)**
Hyperhosphatemia	1.04 (0.84, 1.29)	**1.46 (1.22, 1.75)**	**1.85 (1.33, 2.57)**	**1.40 (1.12, 1.74)**	**1.31 (1.10, 1.55)**	**1.45 (1.27, 1.66)**
Hypertension	1.00 (0.73, 1.37)	1.30 (0.97, 1.75)	1.00 (0.60, 1.66)	**1.63 (1.00, 2.64)**	0.98 (0.76, 1.27)	**1.36 (1.06, 1.75)**
Alkali therapy use	0.88 (0.63,	**1.47 (1.07,**	1.00 (0.50,	1.39 (0.80,	1.04 (0.78,	**1.45 (1.11,**

	1.22)	**2.02)**	2.01)	2.44)	1.38)	**1.91)**
Glomerular diagnosis	NI	NI	NI	NI	**1.80 (1.32, 2.44)**	**1.72 (1.26, 2.33)**

NE: not estimated due to small sample size (n=18, 8 events)

NI: not included

Note: Baseline glomerular model included 237 children with 82 composite events.

*Adjusted for baseline age (centered at 10), male sex, Caucasian race, baseline eGFR (<30, 30-45, 45-60, ≥60 ml/min/1.73 m^2), and time-fixed covariates including proteinuria (< 0.5, 0.5-2.0, ≥ 2.0 mg/mg), anemia, phosphate (centered at 4.5mg/dL), hypertension, alkali therapy use

**Adjusted for baseline age (centered at 10), male sex, Caucasian race, baseline eGFR (<30, 30-45, 45-60, ≥60 ml/min/1.73 m^2), and time-updated covariates including proteinuria (< 0.5, 0.5-2.0, ≥ 2.0 mg/mg), anemia, phosphate (centered at 4.5mg/dL), hypertension, alkali therapy use

Bold indicates significance.

Supplemental Table 6. Sensitivity analyses including adjustment for lagged bicarbonate (i.e., controlling for bicarbonate level from the previous year). Hazard ratios (95% confidence intervals) for development of 50% decline in eGFR or kidney replacement therapy (KRT; transplant or dialysis) among 724 children contributing at least 2 serum bicarbonate measurements across 2649 person-years of follow-up and 230 composite events.

	Sensitivity Model 1	Sensitivity Model 2	Sensitivity Model 3	Sensitivity Model 4
Non-glomerular (n=511, 2084 person-years of follow-up, 169 events)				
Time-varying Bicarbonate				
>22 mEq/L	1	1	1	1
19-22 mEq/L	**1.74 (1.23, 2.44)**	1.20 (0.84, 1.70)	1.00 (0.70, 1.43)	1.04 (0.73, 1.48)
≤18 mEq/L	**3.70 (2.44, 5.61)**	**1.70 (1.06, 2.72)**	1.35 (0.85, 2.14)	1.42 (0.89, 2.26)
P-value for trend	<0.001	0.09	0.41	0.33
Glomerular (n=213, 565 person-years of follow-up 61 events)				
Time-varying Bicarbonate				
>22 mEq/L	1	1	1	1
19-22 mEq/L	**3.32 (1.89, 5.83)**	**2.58 (1.40, 4.77)**	1.84 (0.96, 3.52)	1.80 (0.94, 3.44)
≤18 mEq/L	**8.37 (3.94, 17.77)**	**3.93 (1.68, 9.19)**	**2.66 (1.08, 6.54)**	**2.68 (1.07, 6.71)**
P-value for trend	<0.001	0.001	0.07	0.07
Overall (n=724, 2649 person-years of follow-up, 230 events)*				
Time-varying Bicarbonate				
>22 mEq/L	1	1	1	1
19-22 mEq/L	**2.01 (1.51, 2.68)**	**1.44 (1.06, 1.94)**	1.14 (0.84, 1.55)	1.17 (0.86, 1.58)
≤18 mEq/L	**4.23 (2.94, 6.07)**	**2.11 (1.40, 3.17)**	**1.57 (1.05, 2.37)**	**1.65 (1.10, 2.49)**
P-value for trend	<0.001	0.001	0.10	0.06

Model 1: unadjusted model

Model 2: model 1 plus adjustment for lagged bicarbonate (centered at 22), baseline age (centered at 10), male sex, Caucasian race, baseline eGFR (<30, 30-45, 45-60, ≥60 ml/min/1.73 m^2), proteinuria (< 0.5, 0.5-2.0, ≥ 2.0 mg/mg)

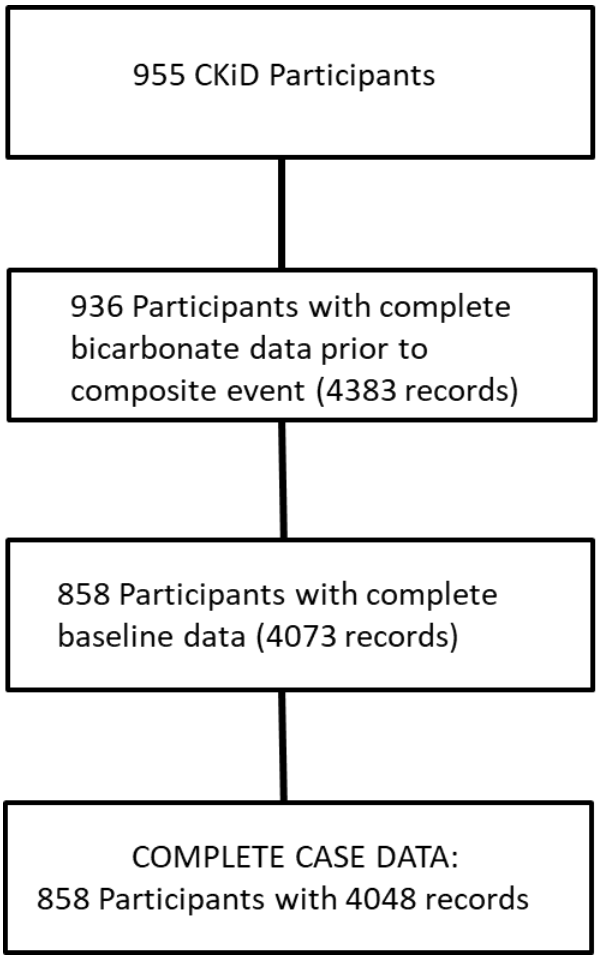
Model 3: model 2 plus adjustment for anemia, phosphate (centered at 4.5mg/dL)

Model 4: model 3 plus adjustment for hypertension, alkali therapy use

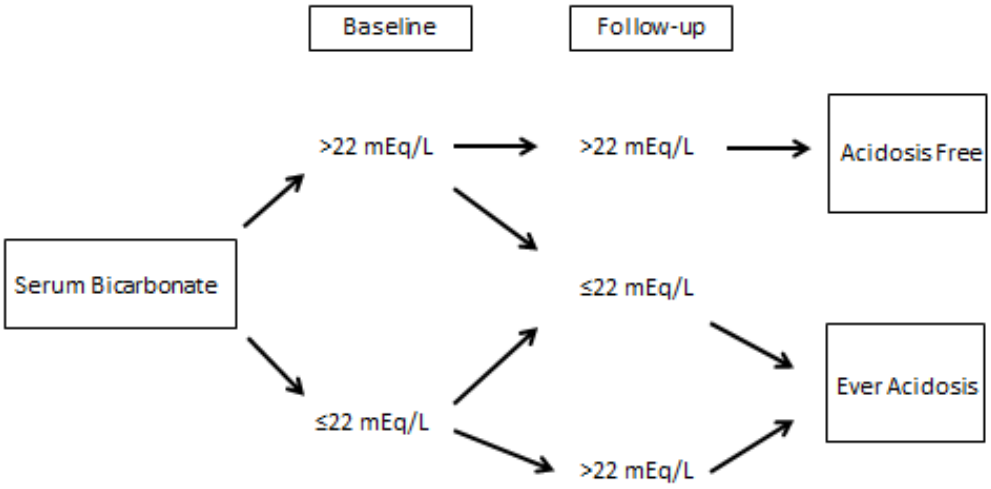
Bold indicates significance.

* Overall models 2, 3, and 4 additional adjusted for glomerular diagnosis

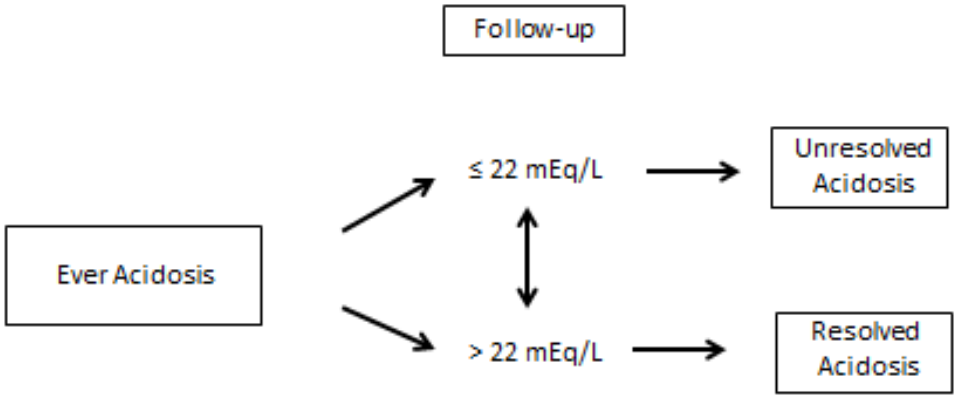
Supplemental Figure 1. Case Selection for Analysis.



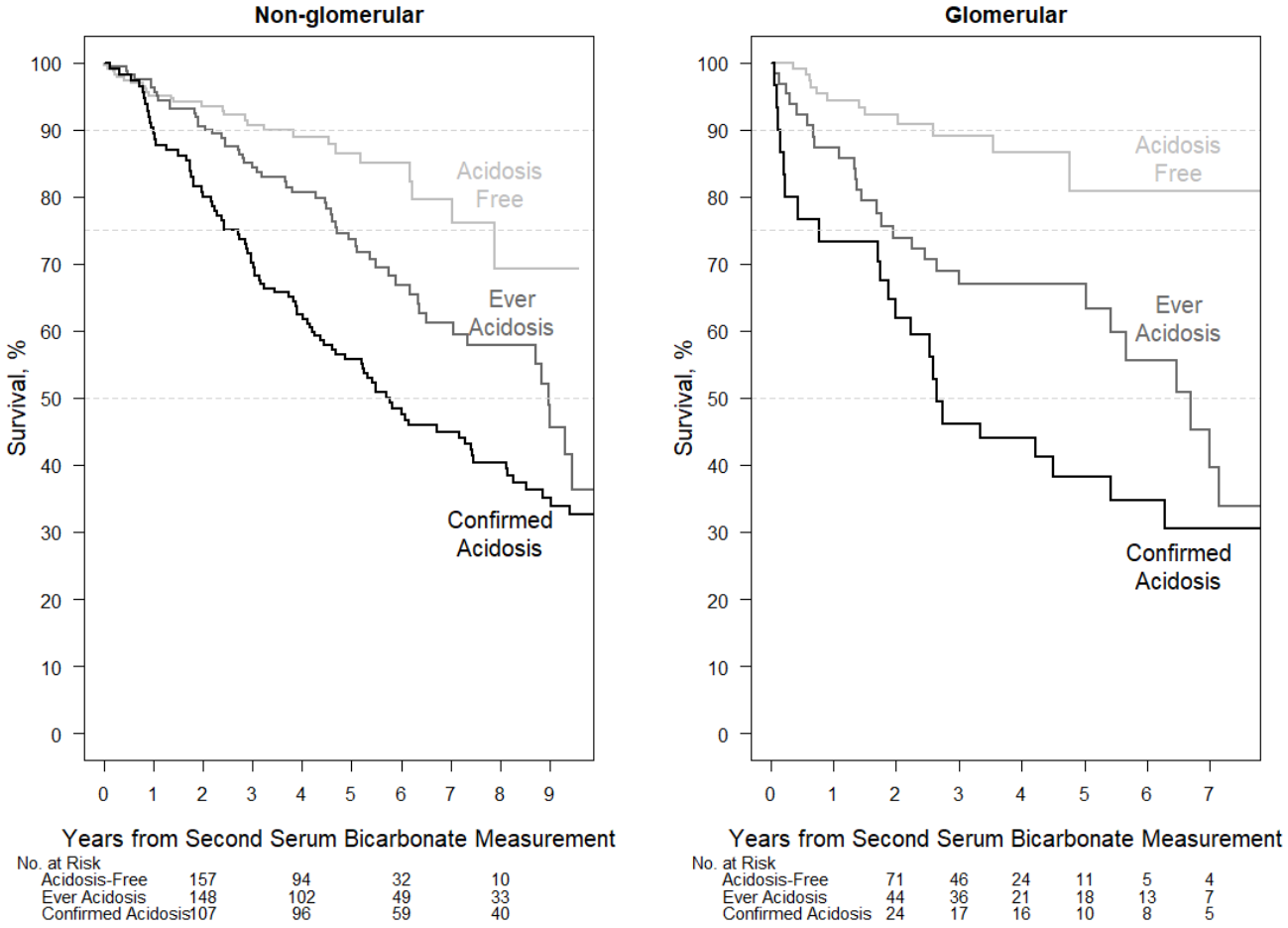
Supplemental Figure 2. "Acidosis Free" vs "Ever Acidosis". Participant categories were determined by serum bicarbonate measured at baseline and follow-up. Participants who maintained a serum bicarbonate of >22 mEq/L throughout the study period were characterized as "Acidosis Free" and contributed data to that group until the first serum bicarbonate ≤22 mEq/L, after which they contributed data to the "Ever Acidosis" group. Participants who enter the study with a serum bicarbonate of ≤22 mEq/L only contributed data to the "Ever Acidosis" group.



Supplemental Figure 3. Categorization of "Resolved" vs "Unresolved" Acidosis. All participants who had at least one serum bicarbonate ≤ 22 mEq/L ("Ever Acidosis") were included. During follow-up, when the participant's serum bicarbonate was ≤ 22 mEq/L, they contributed data to the "Unresolved Acidosis" group. When serum bicarbonate was > 22 mEq/L, they contributed data to the "Resolved Acidosis" group. Participants were allowed to contribute data to both groups throughout the follow-up period, depending on serum bicarbonate.



Supplemental Figure 4. Survival time to 50% decline in eGFR or kidney replacement therapy (KRT; transplant or dialysis) by "ever acidosis" following the second bicarbonate measurement among participants with at least two serum bicarbonate measurements. Panel (A) shows the 511 non-glomerular participants and (B) are the 213 glomerular participants. Gray lines depict acidosis-free (all serum bicarbonate measurements >22 mEq/L); dark gray lines represent "ever-acidosis" (at least one serum bicarbonate measurement ≤22 mEq/L); and black lines are confirmed acidosis (two consecutive serum bicarbonate measurements ≤22 mEq/L).



	Non-glomerular (n=511)			Glomerular (n=213)		
	Never Acidosis (n=141)	Ever Acidosis (n=170)	Confirmed Acidosis (n=200)	Never Acidosis (n=86)	Ever Acidosis (n=77)	Confirmed Acidosis (n=50)
Composite outcome, n (%)	27 (19)	56 (33)	86 (43)	12 (14)	27 (35)	22 (44)
50% reduction in eGFR	9 (33)	18 (32)	28 (33)	10 (83)	10 (29)	9 (41)
Kidney replacement therapy	18 (67)	38 (68)	58 (67)	2 (17)	17 (71)	13 (59)

Parametic Survival Model Selection. Parametric survival models were fit using the generalized gamma (GG) family to model the incidence of the composite event using maximum likelihood methods. Three parameters define the GG family of distributions and are denoted as GG(β, σ, κ). The Weibull and lognormal distributions, both of which are special cases of the GG family, correspond to $\kappa = 1$ and $\kappa = 0$, respectively. Models were systematically compared based on parsimony of parameters and model fit to the data using likelihood ratio tests.