SUPPLEMENTAL MATERIAL AND APPENDIX

Supplemental table 1. Distribution of causes of acute kidney injury among sickle cell trait and sickle cell disease patients.

Cause of AKI	Sickle cell trait AKI N = 133	Sickle cell disease AKI N = 52
Hemodynamic	86 (65%)	20 (38%)
Nephrotoxic	19 (14%)	7 (13%)
Obstructive	3 (2%)	1 (2%)
Pain crisis/Acute chest syndrome	0	19 (37%)
Undetermined	25 (19%)	5 (10%)

Supplemental table 2. Risk factors for incident acute kidney injury among patients with sickle cell trait and sickle cell disease.

*Risk factor	Reference (HR, 95% CI)	Sickle Cell Trait (HR, 95% CI)	Sickle Cell Disease (HR, 95% CI)
Age (per 10-year older age)	1.09 (1.01 to 1.17)	1.03 (0.88 to 1.22)	1.09 (0.81 to 1.48)
Males	1.49 (1.23 to 1.79)	1.12 (0.78 to 1.62)	1.60 (0.92 to 2.81)
Hypertension	1.57 (1.28 to 1.94)	1.21 (0.77 to 1.89)	1.28 (0.59 to 2.76)
Diabetes Mellitus	1.61 (1.34 to 1.94)	1.80 (1.19 to 2.70)	0.75 (0.29 to 1.94)
Cardiovascular disease	2.60 (2.15 to 3.15)	1.77 (1.19 to 2.63)	2.60 (1.48 to 4.57)
Baseline eGFR < 60 mL/min/1.73 m^2	2.81 (2.23 to 3.54)	1.95 (1.21 to 3.15)	4.96 (1.87 to 13.13)
Hydroxyurea	-	-	2.13 (1.05 to 4.31)
Baseline hemoglobin (per 2 g/dL higher)	0.78 (0.71 to 0.87)	0.72 (0.57 to 0.91)	0.61 (0.44 to 0.84)
Hemoglobin A_2 > 3.5%	-	0.70 (0.47 to 1.04)	-
Hemoglobin F > 0.4%	-	0.92 (0.56 to 1.51)	-
Hemoglobin S > 35%	-	1.05 (0.73 to 1.53)	-

*This table was generated by separate models by sickle cell trait/disease status. Each risk factor was adjusted for the following covariates: age, sex, hypertension, diabetes mellitus, cardiovascular disease and baseline eGFR < 60 mL/min/1.73 m^2. Hemoglobin electrophoresis indication was included in the sickle cell trait and reference models. Where the covariate was the risk factor of interest, the covariate was excluded from adjusted analysis.

Supplemental table 3. Risks for incident acute kidney injury by hemoglobin phenotype among patients with a baseline estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2.

	Acute kidney injury	Severe acute kidney injury	Sustained acute kidney injury
Number of events			
Normal hemoglobin phenotype (N = 8,681)	486	270	240

Sickle cell trait (N = 1,202)	103	55	66
Sickle cell disease (N = 240)	44	26	20
Incidence rate (per 1,000 person-years)			
Normal hemoglobin phenotype (N = 8,681)	7.46	4.14	3.68
Sickle cell trait (N = 1,202)	11.34	6.03	7.24
Sickle cell disease (N = 240)	27.67	16.21	12.48
Unadjusted relative risk of time to first event (HR, 95% CI)			
Normal hemoglobin phenotype (N = 8,681)	1 (reference)	1 (reference)	1 (reference)
Sickle cell trait (N = 1,202)	1.51 (1.22 to 1.86)	1.44 (1.08 to 1.92)	1.94 (1.48 to 2.55)
Sickle cell disease (N = 240)	3.72 (2.73 to 5.06)	3.93 (2.63 to 5.88)	3.37 (2.14 to 5.32)
Adjusted* relative risk of time to first event (HR, 95% CI)			
Normal hemoglobin phenotype (N = 8,681)	1 (reference)	1 (reference)	1 (reference)
Sickle cell trait (N = 1,202)	1.21 (0.95 to 1.53)	1.09 (0.80 to 1.47)	1.88 (1.39 to 2.52)
Sickle cell disease (N = 240)	3.33 (2.39 to 4.63)	2.48 (1.60 to 3.84)	2.90 (1.78 to 4.73)

*Adjusted for age, sex, hypertension, diabetes mellitus, cardiovascular disease, and prevalent use of renin angiotensin aldosterone system inhibitors. For violations of the proportional hazard assumption, specific covariates were fitted with time interactions. Hemoglobin electrophoresis indication was included in the sickle cell trait model.

Supplemental table 4. Risks for incident acute kidney injury by hemoglobin phenotype among patients with a baseline estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

	Acute kidney injury	**Severe acute kidney injury**	**Sustained acute kidney injury**
Number of events			
Normal hemoglobin phenotype	125	84	93

(N = 287)			
Sickle cell trait (N = 77)	30	23	25
Sickle cell disease (N = 14)	8	8	8
Incidence rate (per 1,000 person-years)			
Normal hemoglobin phenotype (N = 287)	69.30	45.18	50.40
Sickle cell trait (N = 77)	57.95	44.28	47.72
Sickle cell disease (N = 14)	180.00	172.73	179.15
Unadjusted relative risk of time to first event (HR, 95% CI)			
Normal hemoglobin phenotype (N = 287)	1 (reference)	1 (reference)	1 (reference)
Sickle cell trait (N = 77)	0.83 (0.55 to 1.24)	0.95 (0.60 to 1.53)	0.93 (0.59 to 1.45)
Sickle cell disease (N = 14)	2.16 (1.05 to 4.44)	3.18 (1.53 to 6.61)	2.99 (1.44 to 6.21)
Adjusted* relative risk of time to first event (HR, 95% CI)			
Normal hemoglobin phenotype (N = 287)	1 (reference)	1 (reference)	1 (reference)
Sickle cell trait (N = 77)	0.96 (0.63 to 1.48)	1.08 (0.66 to 1.77)	1.08 (0.68 to 1.74)
Sickle cell disease (N = 14)	2.41 (1.16 to 4.99)	3.26 (1.55 to 6.86)	3.37 (1.61 to 7.08)

*Adjusted for age, sex, hypertension, diabetes mellitus, cardiovascular disease, and prevalent use of renin angiotensin aldosterone system inhibitors. For violations of the proportional hazard assumption, specific covariates were fitted with time interactions. Hemoglobin electrophoresis indication was included in the sickle cell trait model.

Supplemental table 5. Sickle cell disease genotypes

Sickle cell disease genotype	N (%)
SS	153 (60%)
S-beta thalassemia zero	3 (1%)
SC	82 (32%)
S-beta thalassemia trait	14 (6%)
SG	2 (1%)

Severe phenotypes: SS and S-beta thalassemia zero (N = 156)
Non-severe phenotypes: SC, S-beta thalassemia trait and SG (N = 98).

Supplemental table 6. Risks for incident acute kidney injury by severity of sickle cell disease phenotype.

	Acute kidney injury	**Severe acute kidney injury**	**Sustained acute kidney injury**
Number of events			
Normal hemoglobin phenotype (N = 8,968)	611	354	333
Severe sickle cell disease phenotype (N = 156)	38	25	19
Non-severe sickle cell disease phenotypes (N = 98)	14	9	9
Incidence rate (per 1,000 person-years)			
Normal hemoglobin phenotype (N = 8,968)	9.13	5.27	4.96
Severe sickle cell disease phenotype (N = 156)	40.76	26.44	20.12
Non-severe sickle cell disease phenotypes (N = 98)	19.93	12.78	12.81
Unadjusted relative risk of time to first event (HR, 95% CI)			
Normal hemoglobin phenotype (N = 8,968)	1 (reference)	1 (reference)	1 (reference)
Severe sickle cell disease phenotype (N = 156)	4.49 (3.23 to 6.23)	5.05 (3.37 to 7.58)	4.05 (2.55 to 6.43)
Non-severe sickle cell disease phenotypes (N = 98)	2.17 (1.28 to 3.69)	2.38 (1.23 to 4.62)	2.53 (1.31 to 4.91)

Adjusted* relative risk of time to first event (HR, 95% CI)			
Normal hemoglobin phenotype (N = 8,968)	1 (reference)	1 (reference)	1 (reference)
Severe sickle cell disease phenotype (N = 156)	4.11 (2.89 to 5.83)	2.91 (1.89 to 4.49)	2.36 (1.45 to 3.84)
Non-severe sickle cell disease phenotypes (N = 98)	2.42 (1.42 to 4.12)	1.81 (0.93 to 3.52)	1.96 (1.01 to 3.81)

*Adjusted for age, sex, hypertension, diabetes mellitus, cardiovascular disease, and prevalent use of renin angiotensin aldosterone system inhibitors. For violations of the proportional hazard assumption, specific covariates were fitted with time interactions.

APPENDIX

Proportional hazards assumption test for main outcomes in Table 2.

Model	Sickle cell trait proportional hazard test global p value / covariates p value	Sickle cell disease proportional hazard test global p value / covariate p value
AKI, unadjusted	0.5521	0.5458
AKI adjusted	0.0008	0.0243
AKI adjusted model covariates which required interaction term with Time	diabetes mellitus (0.0253) and baseline CKD (0.0005)	diabetes mellitus (0.0414) and baseline CKD (0.0136)
Severe AKI, unadjusted	0.3803	0.3160
Severe AKI, adjusted	0.0005	0.0003
Severe AKI adjusted model covariates which required interaction term with Time	diabetes mellitus (0.0029) and RAAS inhibitors (0.0006)	Hypertension (0.0174), diabetes mellitus (0.0024) and RAAS inhibitors (0.0043)
Sustained AKI, unadjusted	0.9197	0.5478
Sustained AKI, adjusted	0.0015	0.0044
Sustained AKI adjusted model covariates which required interaction term with Time	Baseline age (0.0124), diabetes mellitus (0.0102), baseline CKD (0.0057) and RAAS inhibitors (0.0025)	Diabetes mellitus (0.0151), baseline CKD (0.007) and RAAS inhibitors (0.0074)

Algorithms for adjudicating covariates using ICD codes

Cardiovascular disease: coronary artery disease

The presence of at least 2 diagnosis codes during follow-up was required. We used the following codes: 410.x, 411.x, I20.0, I21.x, I24.x, I25.1x, I25.7x. These codes were evaluated on a subset of African 696 American CKD patients from the Partners RPDR database with coronary artery disease confirmed on chart review (using results of cardiac catheterizations, stress tests and/or physician documentation of a myocardial infarction).

Sensitivity: 81%, Specificity: 81%, negative predictive value (NPV): 93%, positive predictive value (PPV): 57%

Cardiovascular disease: stroke

The presence of at least 2 diagnosis codes during follow-up was required. We used the following codes: 362.30, 362.31, 362.32, 362.33, 362.34, 433.x, 434.x, 435.x, 436.x, 431.x, G45.x, H34.1x, I63.x, I65.x, I61.x. These codes were evaluated on a subset of 696 African American CKD patients from the Partners RPDR database with stroke confirmed on chart review (using brain imaging radiology reports and/or physician documentation of hemorrhagic or embolic stroke).

Sensitivity: 87%, Specificity: 88%, NPV: 97%, PPV: 59%

Hypertension

The presence of at least 15 diagnosis codes at different times during follow-up was required. We used the following codes: 997.91, 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.91, 402.90, 403.01, 403.00, 404.01, 404.03, 404.91, 404.92, 404.93, 404.11, 404.13, 404.12, 404.10, 402.11, 403.11, 403.10, I10.x, I11.x, I12.x, I13.x, I15.x. These codes were evaluated on a subset of 696 African American CKD patients from the Partners RPDR database with hypertension confirmed on chart review (using multiple physician notes).

Sensitivity: 80%, Specificity: 76%, NPV: 36%, PPV: 96%

Diabetes mellitus

The presence of at least 5 diagnosis codes at different times during follow-up was required. We used the following codes: 250.x, E10.x, E11.x, E12.x, E13.x, E14.x. These codes were evaluated on a subset of 696 African American CKD patients from the Partners RPDR database with diabetes mellitus confirmed on chart review (using multiple physician notes).

Sensitivity: 98%, Specificity: 82%, NPV: 97%, PPV: 86%